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Asymmetric synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines through rearrangement of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines

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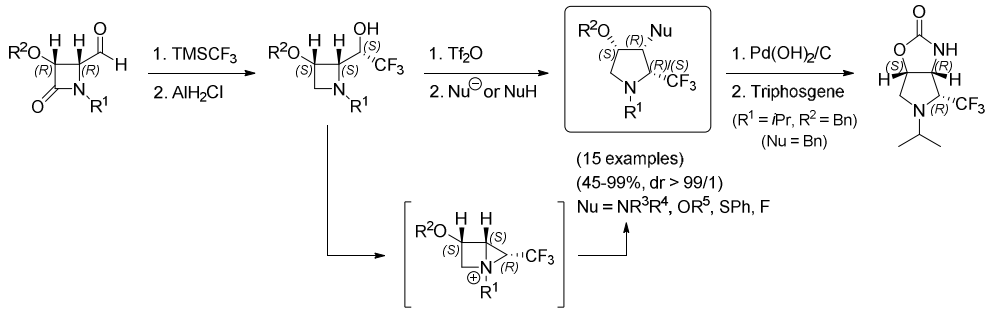
ABSTRACT

Enantiopure 4-formyl-β-lactams were deployed as synthons for the diastereoselective formation of chiral 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines via trifluoromethylation through aldehyde modification followed by reductive removal of the β-lactam carbonyl moiety. Subsequent treatment of the (*in situ*) activated 2-trifluoroethylated azetidines with a variety of nitrogen, oxygen, sulfur and fluorine nucleophiles afforded chiral 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines in good to excellent yields (45-99%) and high diastereoselectivities (dr > 99/1, ^{1}H NMR) via interception of bicyclic aziridinium intermediates. Furthermore, representative pyrrolidines were *N*,*O*-debenzylated in a selective way and used for further synthetic elaboration to produce e.g. a CF_3-substituted 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one system.

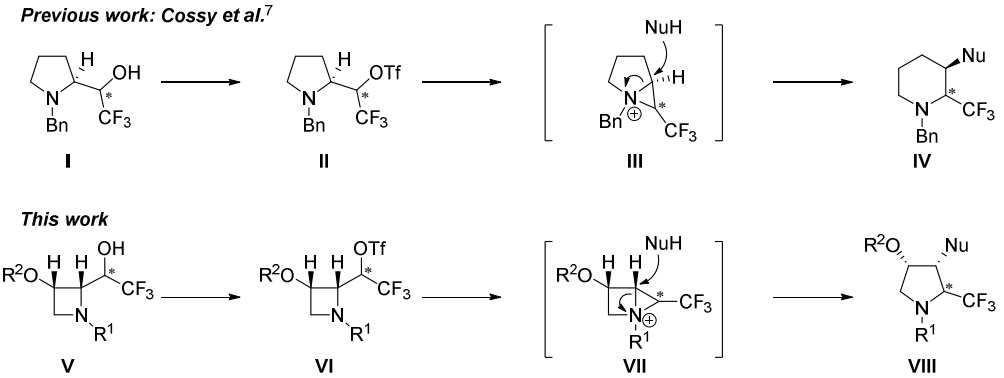


INTRODUCTION

In recent years, the search for synthetic strategies enabling the incorporation of a trifluoromethyl group in organic molecules has been expanded considerably, as the presence of this entity is known to provoke a pronounced impact on the physical and chemical properties of the resulting compounds.[1] In particular, hydrogen-by-fluorine replacement has been shown to induce an enhancement of the metabolic stability and a change in lipophilicity of the involved molecules.[2] Furthermore, the introduction of fluorine can have a significant effect on the acidity or basicity of proximal functional groups.[3] As a consequence, fluorine chemistry plays a pivotal role in pharmaceutical research nowadays, which is reflected in the fact that nearly 25% of new drugs contains at least one fluorine atom in their structure.[3-4]

Although many protocols toward fluorinated target compounds have been developed in the chemical literature, the preparation of enantiopure representatives still remains an important challenge and, as a consequence, novel routes toward these products are highly desirable.[5] Within the range of methods to access enantioenriched fluorinated azaheterocycles, ring enlargements of smaller-ring homologs cover very useful reactions because they can provide a straightforward and efficient access to different nitrogen-containing target molecules in a stereoselective way. Among them, ring-expansion reactions associated with strained bicyclic aziridinium intermediates have attracted considerable attention bearing in mind the extent and scope of the involved transformations.[6] In that respect, Cossy et al. have studied the ring enlargement of enantiopure trifluoromethylated prolinols toward 3-substituted 2-(trifluoromethyl)piperidines **IV** via bicyclic aziridinium intermediates **III** (Scheme 1).[7] It was shown that enantiopure piperidines **IV** could be prepared via regioselective ring expansion of 2-(hydroxymethyl)pyrrolidines **I** bearing a CF_3 group at the C1' position. Analogously, we proposed to pursue the synthesis of enantiopure 2-(trifluoromethyl)pyrrolidines **VIII** via ring enlargement of azetidines **V** (this work). Activation of the hydroxyl motif in azetidines **V** and subsequent heating might lead to the formation of bicyclic aziridinium intermediates **VII**, and interception by an appropriate nucleophile at the bridgehead carbon atom is then expected to afford pyrrolidine scaffolds **VIII** in a selective way. Generation and utilization of analogous 1-azoniabicyclo[2.1.0]pentane intermediates **VII** (starting from azetidine substrates with a leaving group attached to the α-carbon of the C2 side chain) toward the preparation of polysubstituted pyrrolidines, has been the topic of many research activities.[8] The synthesis of pyrrolidines **VIII** might also be of biological relevance, as a lot of bioactive compounds are accommodated with a (trifluoromethylated) pyrrolidine scaffold (Figure 1).[9]

Scheme 1. Synthesis of 3-substituted 2-(trifluoromethyl)piperidines and -pyrrolidines via ring expansion of the corresponding pyrrolidines and azetidines, respectively.



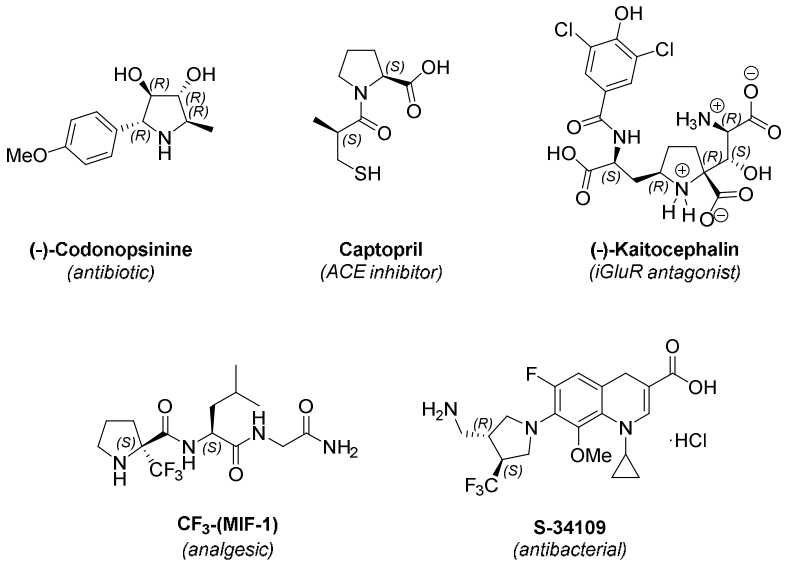
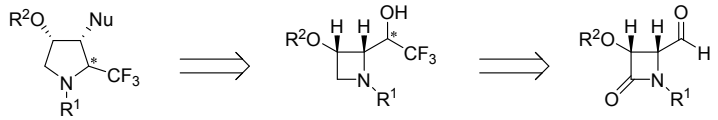


Figure 1. Bioactive compounds with a (trifluoromethylated) pyrrolidine scaffold.

From a retrosynthetic point of view, enantiopure pyrrolidines **VIII** will thus be prepared via ring expansion of trifluoromethylated 2-(hydroxymethyl)azetidines **V** through the intermediacy of bicyclic aziridinium ions **VII**. The synthesis of azetidines **V** will be performed starting from 4-formyl-β-lactams **IX** (Scheme 2), relying on a trifluoromethylation of the aldehyde moiety by the Ruppert-Prakash reagent ($TMSCF_3$)[10] and subsequent reduction of the β-lactam unit by *in situ* prepared monochloroalane (AlH_2Cl). It is worth mentioning that the class of 4-formyl-β-lactams has already proven to include versatile synthetic intermediates toward a broad range of substances of biological interest, which is reflected by the large amount of reactivity studies concerning the deployment of

these synthons in the preparation of amino sugars, bi- and polycyclic β-lactams, γ-lactams and γ-lactons, amino acids and complex natural products.[11]

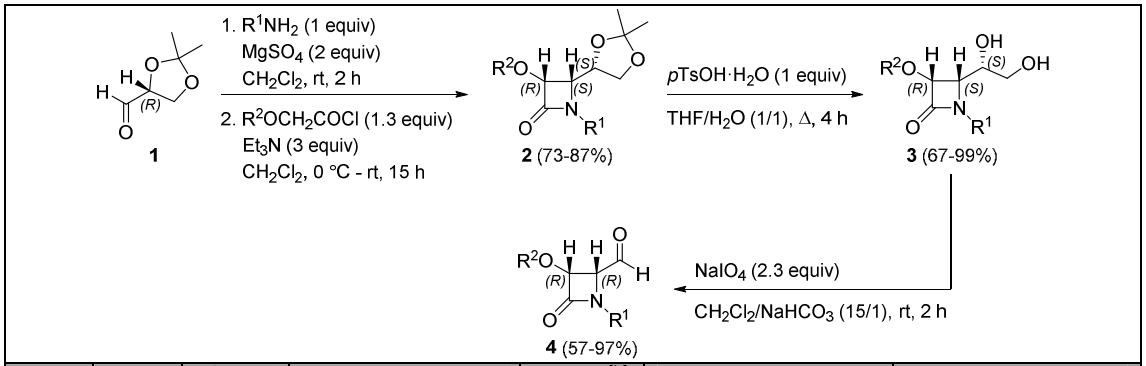
Scheme 2. Retrosynthetic approach for the synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines.



RESULTS AND DISCUSSION

The synthesis of 4-formyl-β-lactams **4** was performed according to a well-known four-step protocol[11b,11d,12] and was initiated by the imination of (*R*)-glyceraldehyde acetonide **1** upon treatment with a variety of alkylamines in the presence of $MgSO_4$ (Table 1). The corresponding chiral imines were immediately and as such treated with phenoxy- or benzyloxyacetyl chloride in the presence of triethylamine in CH_2Cl_2, affording *cis*-β-lactams **2** in an overall yield of 73-87% after column chromatography or recrystallization. Furthermore, it should be mentioned that these azetidine-2-ones **2** were obtained with high *cis*-diastereoselectivity (diastereomeric ratios of 91-99/1-9, determined by NMR, $CDCl_3$). This *cis*-diastereoselectivity could be determined by means of ^{1}H NMR spectroscopy, as typical coupling constants of 5.0-5.2 Hz ($CDCl_3$) between the 3H and 4H protons on the β-lactam ring indicate a *cis* configuration according to the literature.[12] Subsequently, acetal hydrolysis in the latter compounds **2** was performed in THF/H_2O (1/1) upon stirring with an equimolar amount of *p*-toluenesulfonic acid during four hours under reflux and afforded 4-(1,2-dihydroxyethyl)-β-lactams **3** in good to excellent yields (67-99%). A final $NaIO_4$-mediated Malaprade-type oxidation of the 1,2-dihydroxy moiety in β-lactams **3** furnished the desired 4-formyl-β-lactams **4** in 57-97% yield.

Table 1. Synthesis of 4-(2,2-dimethyl-1,3-dioxolanyl)-β-lactams 2, 4-(1,2-dihydroxyethyl)-β-lactams 3 and 4-formyl-β-lactams 4.



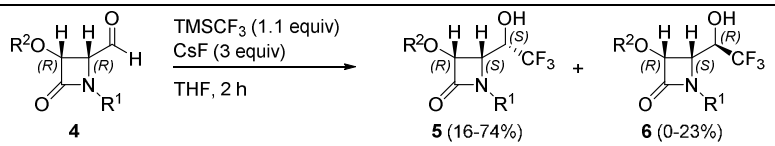
Entry	R^1	R^2	Compound **2** (yield [%])[a]	d.r. (**2**)[b]	Compound **3** (yield [%])	Compound **4** (yield [%])
1	*i*Pr	Ph	**2a** (73)	93/7	**3a** (99)	**4a** (94)
2	*n*Pr	Ph	**2b** (81)	95/5	**3b** (95)	**4b** (80)
3	*c*Hex	Ph	**2c** (87)	99/1	**3c** (99)	**4c** (78)
4	Bn	Ph	**2d** (74)	91/9	**3d** (99)	**4d** (81)
5	*i*Pr	Bn	**2e** (80)	93/7	**3e** (67)	**4e** (86)
6	*n*Pr	Bn	**2f** (87)	94/6	**3f** (76)	**4f** (97)
7	Bn	Bn	**2g** (74)	91/9	**3g** (98)	**4g** (57)[c]

[a] After column chromatography (SiO_2) or recrystallization from EtOH.
[b] Determined by ^1H NMR spectroscopy ($CDCl_3$) of the crude reaction mixture.
[c] After recrystallization from EtOAc/hexane (15/1).

Due to the presence of the aldehyde moiety in 4-formyl-β-lactams **4**, the introduction of the trifluoromethyl group could take place upon reaction with a nucleophilic CF_3 source. To that end, 4-formyl-β-lactams **4a,b** were converted into the corresponding 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5a,b** and **6a,b** in a diastereomeric ratio of 72-74/26-28 using slightly adapted reaction conditions as compared to those employed for the synthesis of prolinols **I**,[7] i.e. a reduced amount of $TMSCF_3$ (1.1 instead of 1.5 equiv) and CsF (3 instead of 5.3 equiv) was used in this study to obtain the adducts **5a,b** and **6a,b** in 88-95% yield after 2 hours at room temperature (Entry 1 and 3, Table 2). Importantly, lowering the reaction temperature at which the reagents are added, from room temperature to -78 °C, resulted in an improvement of the diastereomeric ratio in favor of β-lactams **5** (diastereomeric ratio of 90-93/7-10, Entry 2 and 4, Table 2). Having the optimal reaction conditions for the diastereoselective introduction of the CF_3 group across the aldehyde moiety in hand, the other 4-formyl-β-lactams **4c-g** were also deployed as substrates, affording diastereomers **5c-g** and **6c-g** in a 64-77/23-36 ratio (Entry 5-9, Table 2) and in 63-93% yield after work-up. The isolation of pure diastereoisomers out of the diastereomeric mixtures **5**/**6** appeared to be highly dependent on the substitution pattern of the obtained 4-(trifluoroethyl)azetidin-2-ones. In particular, purification of derivatives **a-c**,**e** via either recrystallization or column chromatography furnished the

major isomers **5a-c,e** exclusively in variable yields of 16-74% (Entry 1-5, 7, Table 2). For compounds **5d,f** and **6f**, only minor amounts (< 2%) could be obtained for spectroscopic analysis and, as a consequence, the involved diastereomeric mixtures **5/6d,f** were used as such in the next step. Fortunately, column chromatographic purification of **5g** and **6g** afforded the pure enantiomers in a yield of 35% and 23%, respectively. The absolute stereochemistry of the major 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5** was unequivocally established by means of a single-crystal X-ray analysis of compounds **5a** and **5e** (see Supporting Information). Although 4-formyl-β-lactams **4** are known to provoke a diastereoselective control upon reaction with a nucleophile,[11a,11c] the number of literature procedures involving a catalyst-free enantioselective introduction of a CF_3 group across carbonyl moieties is rather limited,[5b] and for that reason, the above-described trifluoromethylation procedure should be considered as relevant.

Table 2. Synthesis of 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones 5 and 6.



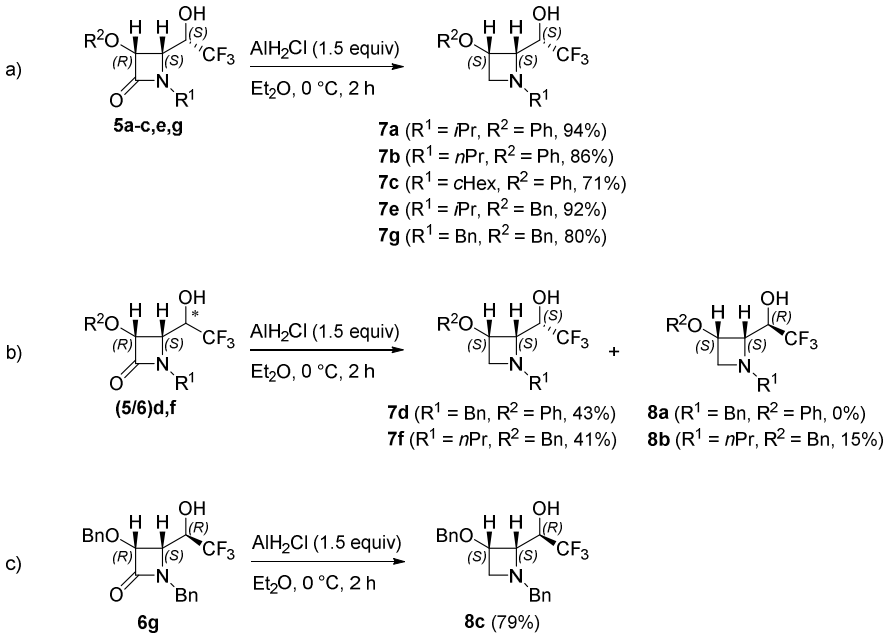
Entry	R^1	R^2	Reaction temp.	Compound **5** + **6** (yield [%])[a]	d.r. (**5**/**6**)[b]	Compound **5** (yield [%])[c]	Compound **6** (yield [%])[c]
1	*i*Pr	Ph	rt	95	74/26	**5a** (65)	**6a** (-)
2	*i*Pr	Ph	-78 °C – rt	92	93/7	**5a** (74)	**6a** (-)
3	*n*Pr	Ph	rt	88	72/28	**5b** (18)	**6b** (-)
4	*n*Pr	Ph	-78 °C – rt	64	90/10	**5b** (29)	**6b** (-)
5	*c*Hex	Ph	-78 °C – rt	63	77/23	**5c** (16)	**6c** (-)
6	Bn	Ph	-78 °C – rt	93	70/30	**5d** (-)[d]	**6d** (-)
7	*i*Pr	Bn	-78 °C – rt	93	67/33	**5e** (50)	**6e** (-)
8	*n*Pr	Bn	-78 °C – rt	92	71/29	**5f** (-)[d]	**6f** (-)[d]
9	Bn	Bn	-78 °C – rt	91	64/36	**5g** (35)	**6g** (23)

[a] After work-up.
[b] Determined by ^{1}H NMR spectroscopy ($CDCl_3$) of the crude reaction mixture.
[c] After column chromatography (SiO_2) or recrystallization from EtOAc/hexane (5-15/1).
[d] Only minor amounts (< 2%) could be obtained for spectroscopic analysis.

In the next step, the obtained 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5** and **6** were reduced toward the corresponding azetidines through selective carbonyl removal without affecting the sensitive ring system. To that end, azetidin-2-ones (3*R*,4*S*,1'*S*)-**5a-c,e,g** were subjected to 1.5 equiv of monochloroalane (*in situ* prepared from $AlCl_3$ and $LiAlH_4$)[13] and stirred during 2 hours at 0 °C, affording the corresponding azetidines **7** in good to excellent yields (71-94%) (Scheme 3a).[14] Azetidine **7e** appeared to be unstable upon purification on silica gel and, as a consequence, was used as such in the next step. The same reaction conditions were applied for the selective reduction of the carbonyl moiety in diastereomeric β-lactam mixtures **5/6d,f**, and, fortunately, subsequent column

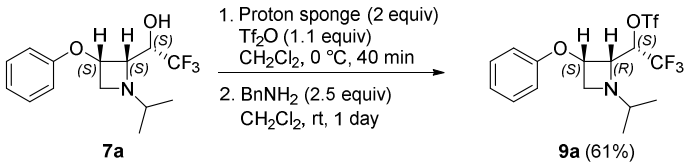
chromatographic purification enabled the separation of the major azetidines **7d,f** from the minor isomers **8a,b**, although in the case of minor compound **8a**, no pure azetidine could be obtained (Scheme 3b). Finally, treatment of (3*R*,4*S*,1'*R*)-azetidin-2-one **6g** with 1.5 equiv of AlH_2Cl afforded the corresponding azetidine **8c** in 79% yield (Scheme 3c). The isolation of azetidines **8b,c** as the 1'-epimers of azetidines **7** is important in order to be able to assess the influence of this stereocenter on their further ring-rearrangement aptitude. Also in this stage of the reaction sequence, the absolute stereochemistry of azetidines **7** was confirmed by means of a single-crystal X-ray analysis of compounds **7a,b** (see Supporting Information).

Scheme 3. Synthesis of 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines 7 and 8.



In accordance with the work performed on the ring expansion of prolinols **I** as the higher homologs of azetidines **7** (Scheme 1),[7] azetidine **7a** was treated with *N*,*N*,*N*',*N*'-tetramethylnaphthalene-1,8-diamine (Proton sponge, 2 equiv) and triflic anhydride (Tf_2O, 1.1 equiv) at 0 °C in CH_2Cl_2. Surprisingly, no ring-expansion product was detected after addition of benzylamine and, instead, triflate **9a** was isolated from the reaction mixture in 61% yield (Scheme 4).

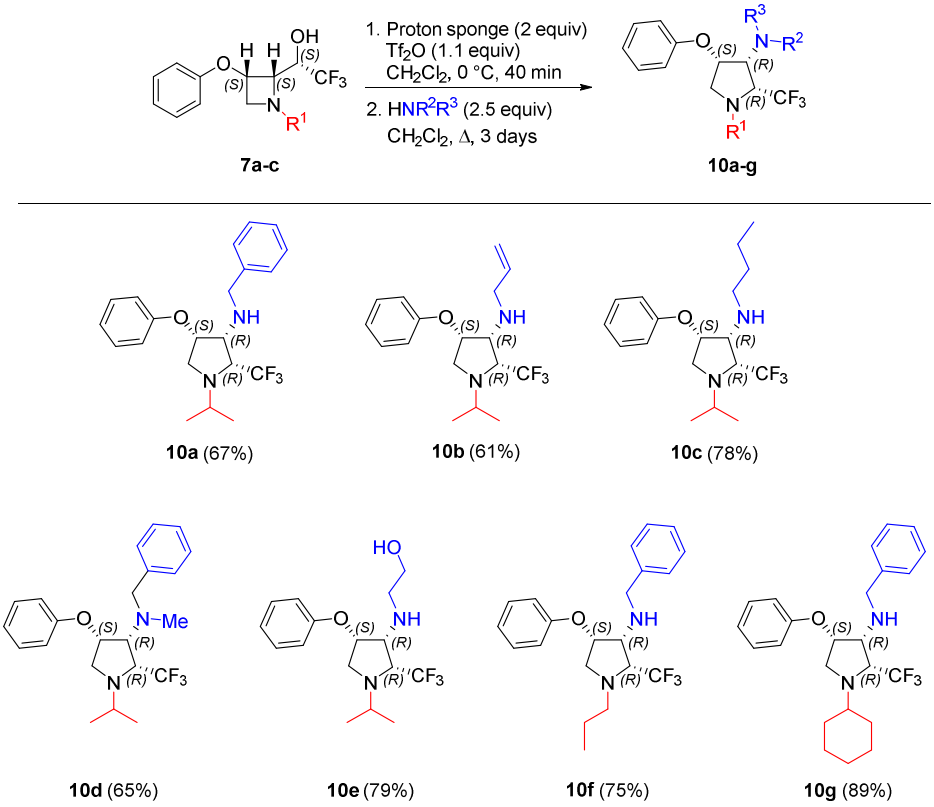
Scheme 4. Synthesis of triflate 9a.



7a **9a** (61%)

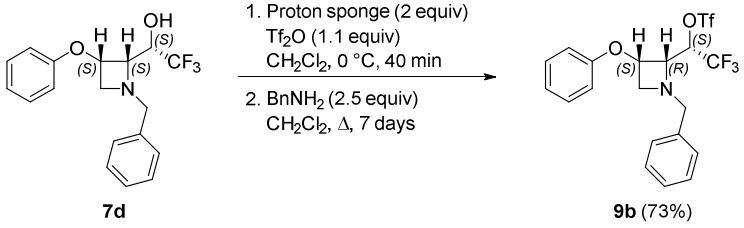
In order to effect the premised azetidine-to-pyrrolidine ring transformation, the reaction temperature was increased and finally, after 3 days stirring at reflux conditions, the desired 3,4-disubstituted pyrrolidine **10a** was produced in a good yield (67%) and with excellent diastereoselectivity (dr > 99/1, determined by NMR, $CDCl_3$) (Scheme 5). The requirement of applying a higher temperature and a prolonged reaction time to realize the formation of the bicyclic aziridinium intermediates **VII** can be explained by the fact that generation of 1-azoniabicyclo[2.1.0]pentanes might energetically be more difficult as compared to the production of less-constrained 1-azoniabicyclo[3.1.0]hexanes.[6a] Extension of the scope of the observed diastereoselective azetidine-to-pyrrolidine rearrangement was then accomplished through variation of the azetidine substrate and/or the applied nitrogen nucleophile. In the case of azetidines **7a-c**, reaction with different alkylamines (benzylamine, allylamine, butylamine, benzyl(methyl)amine and ethanolamine) afforded a broad range of novel enantiopure 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **10a-g** in good yields (61-89%) and with an excellent diastereoselectivity (dr > 99/1, determined by NMR, $CDCl_3$) (Scheme 5).

Scheme 5. Scope for the synthesis of 3-amino-substituted 2-(trifluoromethyl)pyrrolidines 10a-g starting from 4-(1-hydroxyethyl)azetidines 7a-c.



However, the deployment of 1-benzylazetidine **7d** as a substrate did not yield the anticipated pyrrolidine scaffold upon treatment with benzylamine, even after 7 days at reflux temperature and, instead, the corresponding triflate **9b** was isolated from the reaction mixture in 73% yield (Scheme 6). This discrepancy in reactivity might be attributable to the less electron-donating properties of a benzyl group in contrast to an alkyl group, hampering the generation of the corresponding bicyclic aziridinium intermediate.

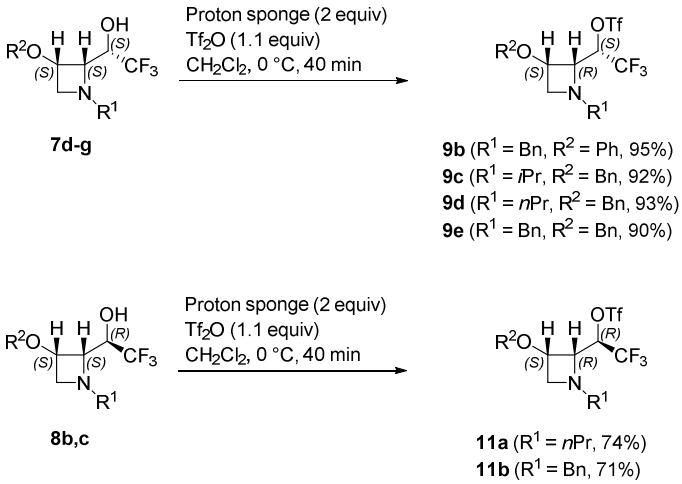
Scheme 6. Synthesis of triflate 9b.



To overcome this problem, the above-described one-pot reaction was modified to a two-step approach, involving sulfonylation of the hydroxyl moiety in azetidine **7d** followed by ring expansion

toward the corresponding 2-(trifluoromethyl)pyrrolidine skeleton in another solvent. To that end, treatment of azetidine **7d** with Tf_2O in the presence of proton sponge afforded azetidine **9b** in an excellent yield of 95% after 40 minutes at 0 °C (Scheme 7). Analogously, the other azetidines **7e-g** and **8b,c** were converted into their triflate-activated derivatives **9c-e** and **11a,b**. Triflate **9c** appeared to be unstable upon silica gel purification and, as a consequence, was used as such in the next step. Remarkably, triflates **9b-e** were obtained in higher yields (90-95%) as compared to their diastereomeric counterparts **11a,b** (71-74%).

Scheme 7. Synthesis of triflates 9b-e and 11a,b.

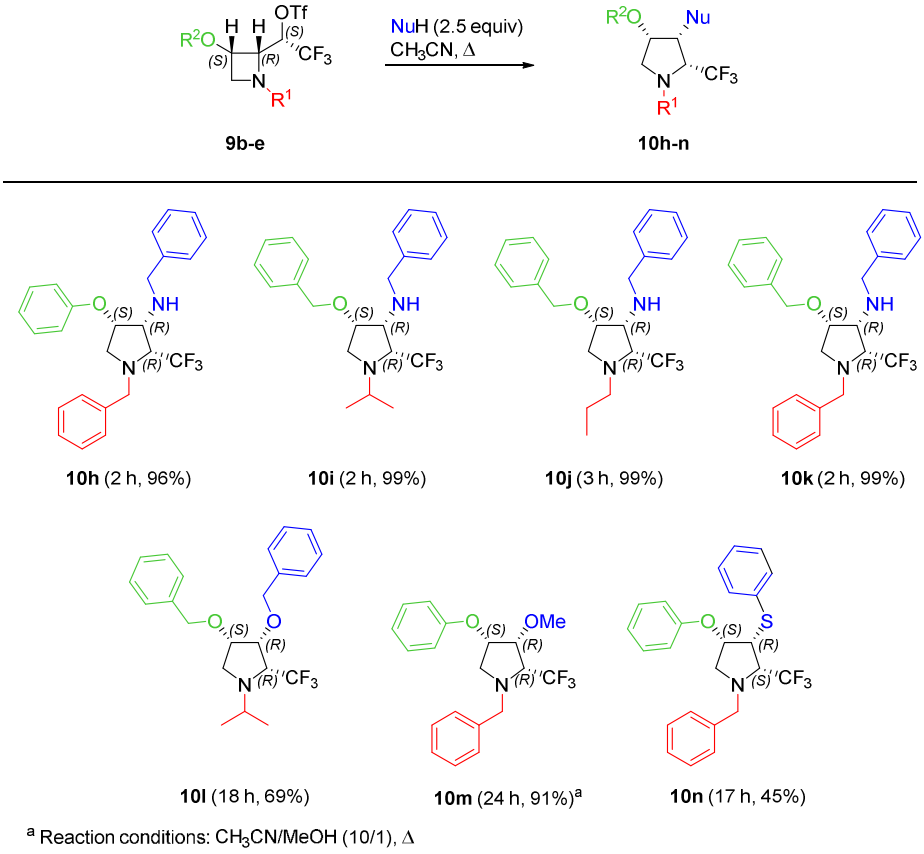


With the sulfonylated azetidines **9b-e** in hand, the premised azetidine-to-pyrrolidine ring expansion was performed using a higher boiling solvent then CH_2Cl_2. In that respect, azetidines **9b-e** were treated with benzylamine in CH_3CN, affording 3-benzylamino-2-(trifluoromethyl)pyrrolidines **10h-k** in almost quantitative yields (96-99%) and with a high diastereoselectivity (dr > 99/1, determined by NMR, $CDCl_3$) (Scheme 8). Importantly, the obtained yields in this two-step protocol were (in contrast to the one-pot approach, Scheme 5) much higher and the required reaction time for the rearrangement could be reduced significantly (from 3 days to 2-3 hours). The absolute stereochemistry of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **10** was unambiguously established by means of a single-crystal X-ray analysis of compound **10h** (see Supporting Information), pointing the diastereoselective formation of all-*cis*-pyrrolidines **10** in a double S_N2-fashion.

In order to further broaden the scope of this diastereoselective azetidine-to-pyrrolidine rearrangement, other nucleophiles instead of amines were evaluated as well. Reaction of triflate **9c** with 2.5 equiv of benzylalcohol furnished the corresponding 3-benzyloxy-2-(trifluoromethyl)pyrrolidine **10l** in 69% yield after silica gel column chromatography. Attempts to

introduce a methoxy substituent at C3 started with treatment of triflate **9b** with 2.5 equiv of sodium methoxide. After 17 hours stirring at reflux conditions in CH_3CN, a mixture of 2-(1-hydroxyethyl)azetidine **7d** and the desired 3-methoxy-2-(trifluoromethyl)pyrrolidine **10m** was obtained in a 77/23 ratio. However, by using a 10/1 mixture of CH_3CN/MeOH, triflate **9b** was fully converted to pyrrolidine **10m**, which was isolated in an excellent yield (91%). The employment of sulfur nucleophiles was also evaluated upon reaction of **9b** with thiophenol, and the corresponding 3-phenylthio-2-(trifluoromethyl)pyrrolidine **10n** was isolated in a moderate yield (45%) after column chromatography. Efforts were also made concerning the use of carbon nucleophiles to trigger this ring transformation. Unfortunately, reactions with TBACN in CH_3CN resulted in complex reaction mixtures, whereas treatment of triflates **9** with KCN in DMSO or CH_3CN resulted in full recovery of the initial azetidine substrates **7**.

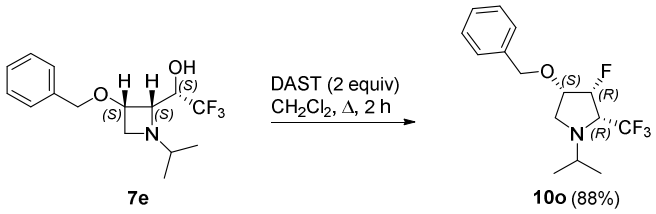
Scheme 8. Scope for the synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines 10h-n starting from triflates 9b-e.



The introduction of a fluorine substituent was also shown to be possible upon treatment of azetidine **7e** with diethylaminosulfur trifluoride (DAST, 2 equiv) in CH_2Cl_2, and the corresponding 3-fluoro-2-

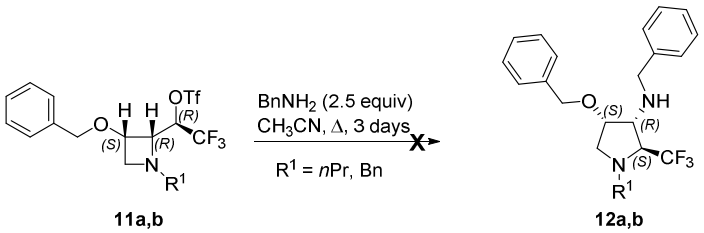
(trifluoromethyl)pyrrolidine **10o** was thus obtained in 88% yield with a high diastereoselectivity (dr > 99/1, determined by NMR, $CDCl_3$) (Scheme 9).[8a,8b,15]

Scheme 9. Synthesis of 3-fluoro-2-(trifluoromethyl)pyrrolidine 10o.



Based on the developed strategy for the synthesis of novel enantiopure 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines **10**, triflates **11** (the diastereomeric counterparts of triflates **9**, epimeric at the 1'-position) were also treated with 2.5 equiv of benzylamine in CH_3CN and stirred during 3 days at reflux conditions. Surprisingly, no ring-expansion products **12** were observed and the starting material was completely recovered (Scheme 10). Apparently, the stereochemistry of the exocyclic CF_3-substituted carbon atom has a profound influence on the ring-rearrangement proclivity of azetidines **9** versus **11**.

Scheme 10. Reaction of triflates 11 with benzylamine.



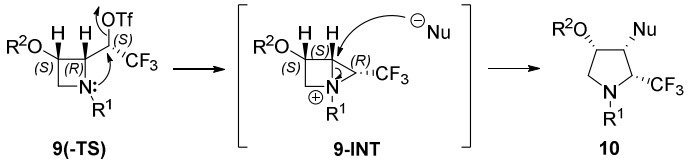
In order to rationalize this unexpected behavior of (2*R*,3*S*,1'*S*)-azetidines **9** versus (2*R*,3*S*,1'*R*)-azetidines **11** with respect to their ring-transformation ability, a computational analysis was performed to elucidate the underlying factors.

Density Functional Theory (DFT) calculations were carried out with the Gaussian 09 software package.[16] The M06-2X[17] functional, well-known for its performance at predicting accurate transition state geometries,[18] was used in conjunction with a 6-31+G(d,p) basis set for conformational analysis on all reactants, transition states and intermediates to identify most plausible conformers. Free energies are reported in kJ/mol at 1 atm and 81 °C. Normal mode analysis has been performed, as well as Intrinsic Reaction Coordinate (IRC)[19] calculations to verify the transition state geometries. The possible pathways under study were modeled using the Conductor-like Polarizable Continuum Model

(C-PCM),[20] where the solute is placed in a continuous medium characterized by a dielectric constant, to mimic the solvation effects. Energy refinements were performed at the MPW1K,[21] ωB97X-D,[22] and PBE0[23] levels of theory, combined with a triple- ζ basis set (6-311+G(3df,3pd)), proven to be particularly accurate.[24]

The ring transformation of (2*R*,3*S*,1'*S*)-azetidines **9** to pyrrolidines **10** is proposed to go through a bicyclic intermediate (**9-INT**) as shown in Scheme 11. The initial step, which leads to the bicyclic intermediate, involves a concerted displacement of the triflate leaving group via the nucleophilic attack of the nitrogen lone pair. Pre-reactive conformers (PRC's) and transition states (TS's) leading to the corresponding bicyclic intermediates were analyzed and compared for both azetidines **9** and **11**. It is important to note that only one of the *N*-invertomers for compounds **9** and **11** have the nitrogen lone pair in the right position to lead to an S_N2-type attack. To that end, a thorough conformational search of the reactants was performed to take into account the relative positions of the nitrogen and triflate groups. Incidentally, calculations have shown in both cases, the most stable invertomers are the ones that could lead to the formation of the bicyclic intermediate.

Scheme 11. Proposed mechanism for the synthesis of pyrrolidines 10 from azetidines 9 through the formation of bicyclic intermediates 9-INT.



A free-energy reaction profile has been constructed for both azetidines at the MPW1K/6-311+G(3df,3pd)//M06-2X/6-31+G(d,p) level of theory, where critical distances and angles of PRC's and TS's have also been depicted (Figure 2). When the structures of the pre-reactive conformers are closely inspected, the close proximity of the CF_3 moiety and the benzyloxy group in **9e-PRC** is shown to lead to a large geometrical distortion, which is reflected in an unusually large bond angle (126° in **9e-PRC** versus 114° in **11b-PRC**). This, in turn, causes a remarkable energy difference of around 35 kJ/mol (MPW1K/6-311+G(3df,3pd)) between the two starting compounds. As a consequence, **11b-PRC** appears to be significantly more stable than **9e-PRC**, making the latter intrinsically more reactive. This result is consistently verified with all four levels of theory employed in this study (Table 3).

Table 3. Relative Gibbs free energies (kJ/mol) of activation ($\Delta G^{\ddagger}$) and reaction (ΔG_{rxn}) with respect to 11b-PRC.

	M06-2X[a]	MPW1K[b]	ωB97X-D[c]	PBE0[d]
11b-PRC	0.0	0.0	0.0	0.0
9e-PRC	30.9	35.1	32.2	34.5
11b-TS	111.9	111.8	106.4	104.0
9e-TS	128.0	127.5	119.2	117.4
11b-INT	9.3	9.9	5.2	10.1
9e-INT	-6.2	-9.2	-18.2	-10.0

[a] Optimizations with C-PCM in acetonitrile (ε = 37.5)
[b,c,d] Energy refinements on M06-2X/6-31+G(d,p) optimized geometries using a 6-311+G(3df,3pd) basis set with C-PCM in acetonitrile (ε = 37.5).

The differences between the activation barriers ($\Delta\Delta G^{\ddagger}$) for the formation of the bicyclic intermediates are around 19 kJ/mol in a consistent manner for all levels of theory (Table 4), clearly indicating the ease of reaction for azetidines **9**. Moreover, **9e-INT** is also thermodynamically more stable than its counterpart **11b-INT**. DFT calculations, consistent with experimental work, suggest the formation of a bicyclic intermediate to be unfavorable for azetidines **11**.

Table 4. Relative Gibbs free energies (kJ/mol) of activation ($\Delta G^{\ddagger}$) and reaction (ΔG_{rxn}).

		M06-2X[a]	MPW1K[b]	ωB97X-D[c]	PBE0[d]
9e	$\Delta G^{\ddagger}$	97.1	92.4	86.9	82.9
	ΔG_{rxn}	-37.1	-44.3	-50.4	-44.5
11b	$\Delta G^{\ddagger}$	111.9	111.8	106.4	101.7
	ΔG_{rxn}	9.3	9.9	5.2	10.1

[a] Optimizations with C-PCM in acetonitrile (ε =37.5)
[b,c,d] Energy refinements on M06-2X/6-31+G(d,p) optimized geometries using a 6-311+G(3df,3pd) basis set with C-PCM in acetonitrile (ε =37.5).

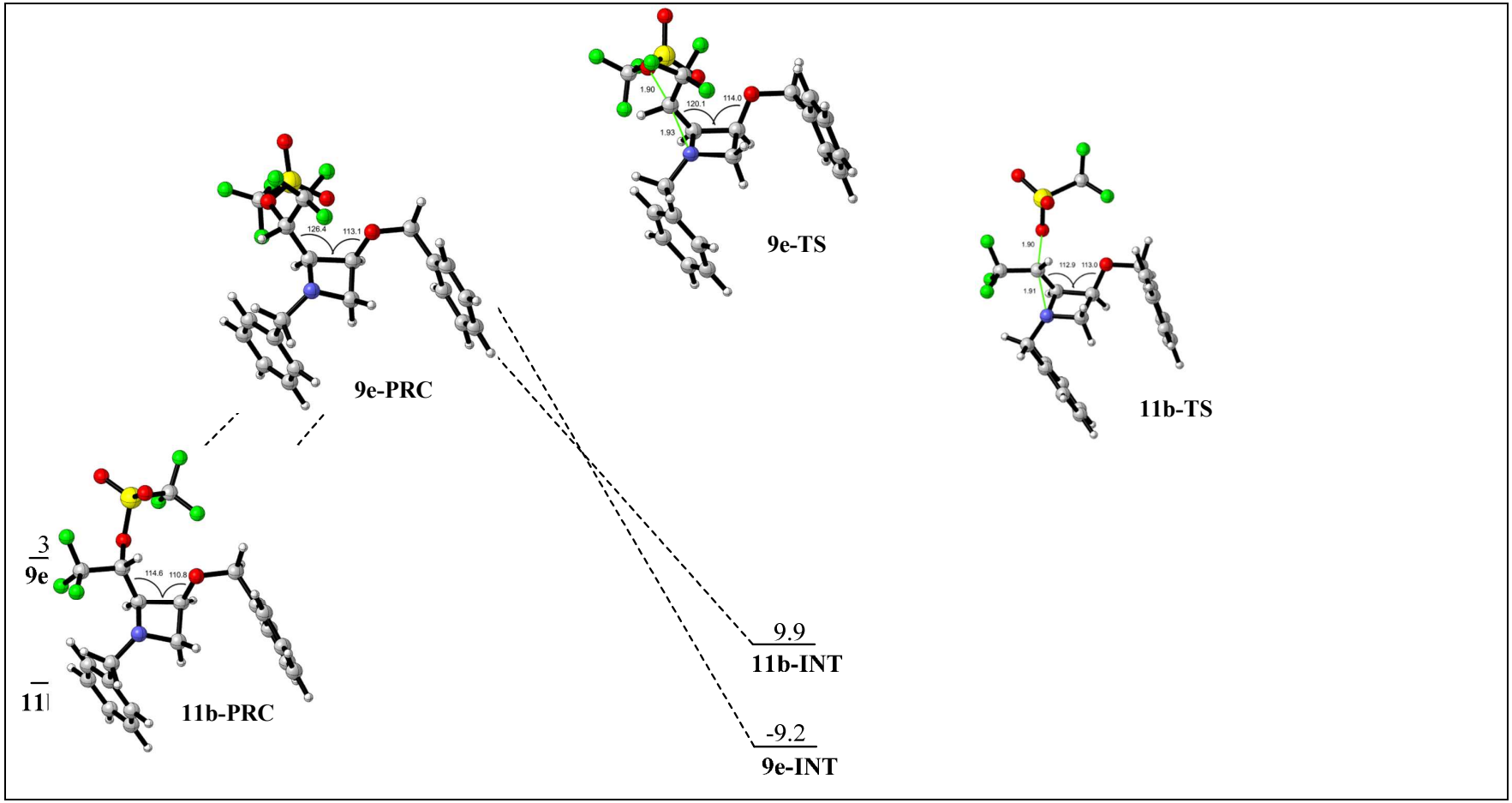
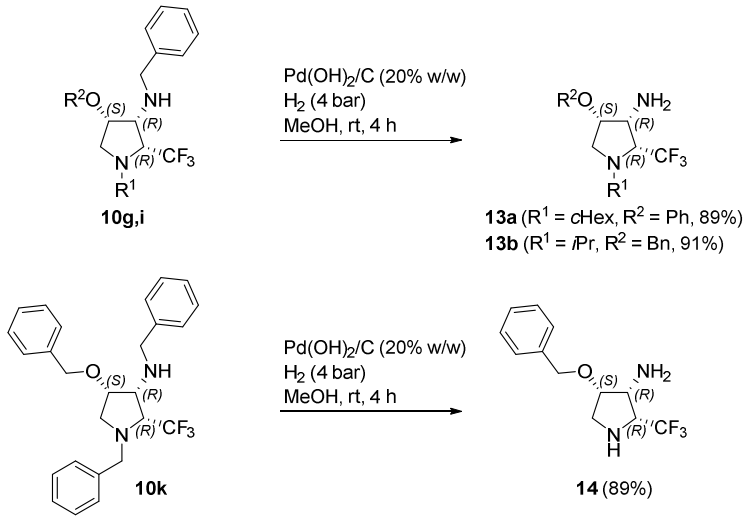


Figure 2. Free-energy profile (MPW1K/6-311+G(3df,3pd)//M06-2X/6-31+G(d,p)) for the formation of the bicyclic intermediates 9e-INT and 11b-INT (354 K and 1 atm, C-PCM in acetonitrile (ε =37.5)).

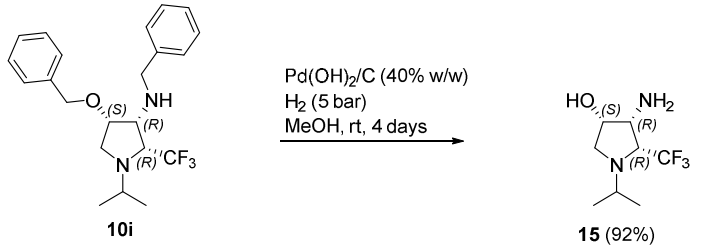
As the 3-amino-4-hydroxypyrrolidine unit has been reported to be present in compounds associated with diverse biological activities,[25] additional synthetic efforts were performed to evaluate the debenzylation aptitude of 3-benzylamino-substituted azaheterocycles **10**. To that end, a selection of 3-benzylamino-2-(trifluoromethyl)pyrrolidines **10g,i,k** was treated with $Pd(OH)_2/C$ (20% w/w) at 4 bar H_2 in MeOH, resulting in 3-amino-2-(trifluoromethyl)pyrrolidines **13** and **14** after 4 hours at room temperature in excellent yields (89-91%) (Scheme 12). In the case of pyrrolidine **10k**, a double *N*-debenzylation took place to furnish free diamine **14**.

Scheme 12. Synthesis of 3-amino-2-(trifluoromethyl)pyrrolidines 13 and 14.



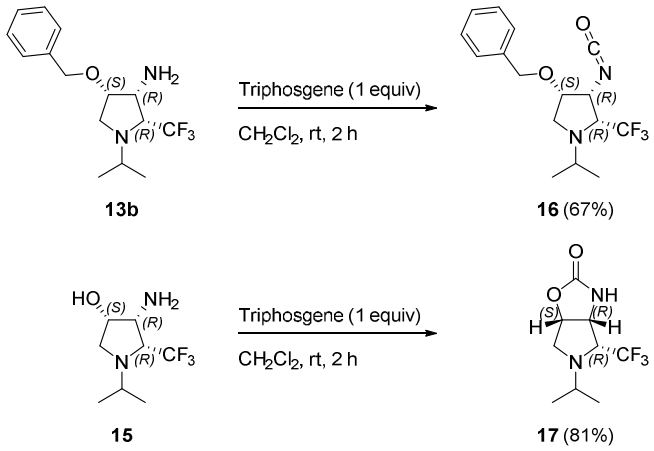
In order to encourage the *O*-debenzylation of 4-benzyloxy-substituted azaheterocycles **10** as well, in addition to *N*-debenzylation, pyrrolidine **10i** was subjected to more harsh deprotection conditions ($Pd(OH)_2/C$ (40% w/w), 5 bar H_2) and, eventually, 3-amino-4-hydroxy-2-(trifluoromethyl)pyrrolidine **15** was obtained in 92% yield after 4 days in MeOH at room temperature (Scheme 13). So, depending on the reaction conditions used for the hydrogenolysis of azaheterocycles **10** (containing a benzyl group at either the 1-, 3-amino and/or 4-hydroxy position of the pyrrolidine unit), the deprotection of these molecules can be performed in a selective way through initial *N*- and, if desired, subsequent *O*-debenzylation. Bearing in mind the large number of bioactive compounds accommodating a 3-amino-4-hydroxypyrrolidine entity, this straightforward and high-yielding debenzylation protocol undoubtedly offers perspectives for further elaboration in the framework of bioactive compound development.

Scheme 13. Synthesis of 3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine 15.



Furthermore, the free NH_2 and OH moieties in pyrrolidines **13-15** render these scaffolds very promising building blocks for incorporation in larger bioactive structures and for additional synthetic manipulations. In that respect, evaluation of the obtained 3-aminopyrrolidines was performed by treatment of 3-amino-2-(trifluoromethyl)pyrrolidine **13b** with an equimolar amount of triphosgene, affording the corresponding 3-isocyanato-2-(trifluoromethyl)pyrrolidine **16** in 67% yield (Scheme 14). In addition, 3-amino-4-hydroxypyrrolidine **15** was treated with triphosgene as well, applying the same reaction conditions as for the preparation of pyrrolidine **16** (1 equiv triphosgene, CH_2Cl_2, room temperature). After 2 hours, 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one **17** was obtained in an isolated yield of 81% after silica gel column chromatography (Scheme 14). From these selected examples, it is clear that further synthetic elaboration of the free NH_2 and OH moieties in chiral pyrrolidines **13-15** offers many new opportunities for follow-up studies.

Scheme 14. Reactions of 3-amino-2-(trifluoromethyl)pyrrolidines 13b and 15 with triphosgene.



In a final experiment, evidence for the chiral integrity of the prepared pyrrolidines was provided. In that respect, amidation of 3-amino-2-(trifluoromethyl)pyrrolidine **13b** with an equimolar amount of (1*S*)-(—)-camphanic chloride in CH_2Cl_2 at room temperature for 2 hours on an analytical scale afforded the corresponding 3-(camphanoylamino)pyrrolidine as a single diastereomer (based on ^1H NMR and GC analysis), pointing to the fact that no isomerization took place throughout the complete reaction sequence.

CONCLUSION

In summary, a straightforward and reliable four-step protocol was developed for the synthesis of chiral 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines starting from enantiopure 4-formyl-β-lactams. To that end, trifluoromethylation of these 4-formylazetidin-2-ones resulted in the diastereoselective formation of 4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-β-lactams as the major isomers. Reduction of the β-lactam carbonyl group and subsequent sulfonylation of the hydroxyl motif afforded the corresponding triflate-activated azetidines without loss of chirality. Owing to the presence of the triflate leaving group, ring expansion of these azetidine scaffolds could be realized through the intermediacy of bicyclic aziridinium ions, although the premised rearrangement appeared to be dependent on the stereochemistry of the exocyclic CF_3-substituted carbon atom. Whereas the major (1'*S*)-azetidines were easily converted to 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines with high diastereoselectivity upon reaction with a variety of nitrogen, oxygen, sulfur and fluorine nucleophiles, their diastereomeric counterparts (epimeric at 1' position) were not able to act as substrates for this type of ring rearrangement. Theoretical calculations revealed that the major (1'*S*)-azetidines are less stable than the minor (1'*R*)-azetidines, which in combination with a lower activation barrier of (1'*S*)-azetidines toward the corresponding bicyclic aziridinium ions can explain the remarkable difference in reactivity. Finally, *N*- versus *O*-selective debenzylation of some of the obtained pyrrolidine ring systems was successfully effectuated, enabling the eventual incorporation of these chiral building blocks into larger frameworks and their further synthetic elaboration, as shown by the synthesis of a 2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one scaffold.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Advance III-400 with solvents as indicated and tetramethylsilane as internal standard. ^{19}F NMR spectra were recorded at 376 MHz on a Bruker Advance III-400 with solvents as indicated. ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Advance III-400 with solvents as indicated. IR spectra were measured with a IRAffinity-1S FT-IR spectrophotometer. Electron spray (ES) mass spectra were obtained with an Agilent 1100 Series MS (ES, 4000V) mass spectrometer. High resolution electron spray (ES-TOF) mass spectra were obtained with an Agilent Technologies 6210 Series time-of-flight mass spectrometer. The Mass analyzer type used is a double focusing High Resolution Magnetic Sector (Merk: Thermo Fisher, Type: Mat95XP-Trap). Melting points were determined on a Kofler bench, type WME Heizbank of Wagner & Munz and were corrected. All other solvents and reagents were used as received from the supplier.

(*R*)-Glyceraldehyde acetonide **1** was synthesized according to literature procedures.[26]

Synthesis of 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones 2.

As a representative example, the synthesis of (3*R*,4*S*)-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidine-2-one **2a** is described. $MgSO_4$ (7.22 g, 60 mmol, 2 equiv) and isopropylamine (1.77 g, 2.58 mL, 30 mmol, 1 equiv) were added to a solution of (*R*)-glyceraldehyde acetonide **1** (3.9 g, 30 mmol, 1 equiv) in anhydrous CH_2Cl_2 (120 mL). After stirring for 2 hours at room temperature, $MgSO_4$ was removed by filtration. Evaporation of the solvent in vacuo afforded the corresponding (*E*)-*N*-[((4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]isopropylamine in high purity (> 95% based on ^{1}H NMR spectroscopy), which was used as such in the next reaction step due to its hydrolytic instability. To an ice-cooled solution of (*E*)-*N*-[((4S)-2,2-dimethyl-1,3-dioxolan-4-yl)methylidene]isopropylamine (5.13 g, 30 mmol, 1 equiv) and triethylamine (9.10 g, 12.53 mL, 90 mmol, 3 equiv) in anhydrous CH_2Cl_2 (100 mL), a solution of phenoxyacetyl chloride (6.65 g, 5.39 mL, 39 mmol, 1.3 equiv) in CH_2Cl_2 (10 mL) was added dropwise. After stirring for 15 hours at room temperature, the reaction mixture was poured into water (30 mL) and extracted with EtOAc (3 × 30 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent in vacuo afforded (3*R*,4*S*)-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one **2a**, which was isolated by means of recrystallization from EtOH in an overall yield of 73% (6.68 g, 21.9 mmol) as a white powder.

*(3R,4S)-1-Isopropyl-4-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one (**2a**).*

Yield 73% (6.68 g). White powder. Mp 86 ± 2 °C. Recrystallization from EtOH. $[\alpha]_D^{25}$ = +185.3 (*c* = 0.18, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.6 Hz, 3H), 1.34 (d, *J* = 6.6 Hz, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 3.67 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.87 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.98 (septet, *J* = 6.6 Hz, 1H), 4.25 (dd, *J* = 8.8, 6.6 Hz, 1H), 4.39 (ddd, *J* = 8.9, 6.6, 6.5 Hz, 1H), 5.13 (d, *J* = 5.2 Hz, 1H), 7.00-7.04 (m, 1H), 7.07-7.09 (m, 2H), 7.27-7.31 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 19.5 (CH_3), 21.3 (CH_3), 25.1 (CH_3), 26.8 (CH_3), 44.9 (CH), 59.9 (CH), 67.1 (CH_2), 77.1 (CH), 79.3 (CH), 109.6 (C), 115.8 (2×CH), 122.5 (CH), 129.6 (2×CH), 157.5 (C), 165.3 (C). IR (cm^{-1}): 2976, 1744, 1499, 1489, 1458, 1398, 1352, 1259, 1236, 1213, 1155, 1059, 1022, 852, 843, 758, 692, 509. MS (70 eV): *m/z* (%): 306 (M^++1, 100).

*(3R,4S)-4-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-phenoxy-1-propylazetidin-2-one (**2b**).*

Yield 81% (5.90 g). White powder. Mp 62 ± 2 °C. R_f = 0.19 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +160.9 (*c* = 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, *J* = 7.4 Hz, 3H), 1.38 (s, 3H), 1.46 (s, 3H), 1.58-1.78 (m, 2H), 3.27 (ddd, *J* = 13.7, 7.8, 5.9 Hz, 1H), 3.45 (ddd, *J* = 13.7, 7.5, 7.5 Hz, 1H), 3.68 (dd, *J* = 8.8, 6.2 Hz, 1H), 3.83 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.18 (dd, *J* = 8.8, 6.5 Hz, 1H), 4.43 (ddd, *J* = 9.0, 6.5, 6.2 Hz, 1H), 5.20 (d, *J* = 5.0 Hz, 1H), 7.00-7.04 (m, 1H), 7.07-7.09 (m, 2H), 7.28-7.32 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 20.8 (CH_2), 25.1 (CH_3), 26.8 (CH_3), 43.3 (CH_2), 60.4 (CH), 66.9 (CH_2), 77.2 (CH), 79.8 (CH), 109.7 (C), 115.7 (2×CH), 122.5 (CH), 129.6 (2×CH), 157.4 (C), 166.0 (C). IR (cm^{-1}): 2967, 2936, 1748, 1599, 1589, 1495, 1371, 1238, 1209, 1155, 1061, 1013, 854, 754, 691, 507. MS (70 eV): *m/z* (%): 306 (M^++1, 100).

*(3R,4S)-1-Cyclohexyl-4-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one (**2c**).*

Yield 87% (9.00 g). White powder. Mp 79 ± 2 °C. R_f = 0.12 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +166.9 (*c* = 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11-1.34 (m, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 1.59-1.92 (m, 7H), 3.53-3.60 (m, 1H), 3.66 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.88 (dd, *J* = 8.9, 5.2 Hz, 1H), 4.23 (dd, *J* = 8.8, 6.5 Hz, 1H), 4.38 (dt, *J* = 8.9, 6.5 Hz, 1H), 5.13 (d, *J* = 5.2 Hz, 1H), 7.00-7.03 (m, 1H), 7.07-7.09 (m, 2H), 7.27-7.31 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 25.1 (CH_3), 25.2 (CH_2), 25.36 (CH_2), 25.38 (CH_2), 26.8 (CH_3), 29.8 (CH_2), 31.1 (CH_2), 52.9 (CH), 60.0 (CH), 67.1 (CH_2), 77.2 (CH), 79.2 (CH), 109.5 (C), 115.8 (2×CH), 122.4 (CH), 129.6 (2×CH), 157.5 (C), 165.3 (C). IR (cm^{-1}): 2941, 1734, 1599, 1587, 1489, 1283, 1267, 1163, 1121, 1094, 1038, 752, 727, 691. MS (70 eV): *m/z* (%): 346 (M^++1, 100).

*(3R,4S)-1-Benzyl-4-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxyazetidin-2-one (**2d**).*

Yield 74% (7.84 g). White powder. Mp 107 ± 2 °C. R_f = 0.24 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +70.1 (*c* = 0.19, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.38 (s, 3H), 3.61 (dd, *J* = 8.9, 6.3 Hz, 1H), 3.70 (dd, *J* = 9.0, 5.1 Hz, 1H), 4.13 (dd, *J* = 8.9, 6.3 Hz, 1H), 4.29 (d, *J* = 14.6 Hz, 1H), 4.48 (dt, *J* = 9.0, 6.3 Hz, 1H), 4.87 (d, *J* = 14.6 Hz, 1H), 5.16 (d, *J* = 5.1 Hz, 1H), 7.02-7.08 (m, 3H), 7.26-7.35 (m, 7H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 25.1 (CH_3), 26.7 (CH_3), 45.4 (CH_2), 59.4 (CH), 66.9 (CH_2), 77.1 (CH), 80.0 (CH), 109.8 (C), 115.7 (CH), 122.5 (CH), 127.8 (CH), 128.7 (CH), 128.9 (CH), 129.7 (CH), 135.6 (C), 157.3 (C), 165.7 (C). IR (cm^{-1}): 2988, 1748, 1597, 1589, 1497, 1487, 1209, 1061, 1040, 856, 754, 739, 694, 669. MS (70 eV): *m/z* (%): 354 (M^++1, 100).

Spectral data of 4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetidin-2-ones **2e-g** correspond with those reported in the literature.[12,27]

Synthesis of 4-[(1*S*)-1,2-dihydroxyethyl]azetidin-2-ones 3.

As a representative example, the synthesis of (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3a** is described. To a solution of (3*R*,4*S*)-1-isopropyl-4-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-phenoxy-azetidin-2-one **2a** (1.83 g, 6 mmol, 1 equiv) in THF/H_2O (1/1, 60 mL) was added *p*TsOH·H_2O (1.14 g, 6 mmol, 1 equiv) in a single portion. After a reflux period of 4 hours, the resulting reaction mixture was allowed to cool to room temperature and was then neutralized to pH 7 with solid $NaHCO_3$. The mixture was extracted with EtOAc (3 × 30 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3a** in 99% yield (1.57 g, 5.94 mmol) as a colorless oil.

*(3R,4S)-4-[(1S)-1,2-Dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one (**3a**).*

Yield 99% (1.57 g). Colorless oil. $[\alpha]_D^{25}$ = +152.1 (*c* = 0.37, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.7 Hz), 1.41 (d, *J* = 6.7 Hz, 3H), 2.17-2.20 (m, 1H), 2.76 (d, *J* = 4.2 Hz, 1H), 3.70-3.75 (m, 1H), 3.79-3.88 (m, 1H), 3.83 (septet, *J* = 6.7 Hz, 1H), 3.96 (dd, *J* = 5.5, 5.3 Hz, 1H), 4.06-4.12 (m, 1H), 5.15 (d, *J* = 5.3 Hz, 1H), 7.01-7.05 (m, 1H), 7.08-7.11 (m, 2H), 7.28-7.32 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0 (CH_3), 21.2 (CH_3), 46.4 (CH), 58.1 (CH), 63.8 (CH_2), 71.3 (CH), 79.5 (CH), 115.9 (2×CH), 122.7 (CH), 129.7 (2×CH), 157.4 (C), 165.7 (C). IR (cm^{-1}): 3389, 2980, 2951, 1740, 1597, 1495, 1339, 1234, 1132, 1092, 1022, 910, 841, 748, 729, 689. MS (70 eV): *m/z* (%): 266 (M^++1, 100).

*(3R,4S)-4-[(1S)-1,2-Dihydroxyethyl]-3-phenoxy-1-propylazetidin-2-one (**3b**).*

Yield 95% (1.51 g). Colorless oil. $[\alpha]_D^{25}$ = +116.5 (*c* = 0.30, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.54-1.77 (m, 2H), 2.18 (br s, 1H), 2.75 (br s, 1H), 3.21 (ddd, *J* = 13.8, 8.1, 5.6 Hz, 1H), 3.52 (ddd, *J* = 13.8, 7.7, 7.7 Hz, 1H 3.69-3.73 (m, 1H), 3.79-3.83 (m, 1H), 3.97 (dd, *J* = 5.1, 5.0 Hz, 1H), 4.11-4.16 (m, 1H), 5.23 (d, *J* = 5.0 Hz, 1H), 7.02-7.04 (m, 1H), 7.09-7.11 (m, 2H), 7.28-7.32 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 20.8 (CH_2), 43.8 (CH_2), 58.2 (CH), 64.0 (CH_2), 71.3 (CH), 80.1 (CH), 115.9 (2×CH), 122.7 (CH), 129.7 (2×CH), 157.4 (C), 166.3 (C). IR (cm^{-1}): 3401, 1732, 1591, 1495, 1416, 1344, 1231, 1090, 1067, 1043, 1028, 908, 891, 752, 729, 691. MS (70 eV): *m/z* (%): 266 (M^++1, 100).

*(3R,4S)-1-Cyclohexyl-4-[(1S)-1,2-dihydroxyethyl]-3-phenoxyazetidin-2-one (**3c**).*

Yield 99% (1.81 g). Colorless oil. $[\alpha]_D^{25}$ = +102.7 (*c* = 0.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.32 (m, 3H), 1.61-1.92 (m, 6H), 2.01-2.08 (m, 2H), 2.66 (d, *J* = 4.4 Hz, 1H), 3.37-3.44 (m, 1H), 3.71-3.77 (m, 1H), 3.79-3.85 (m, 1H), 3.98 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.08-4.13 (m, 1H), 5.16 (d, *J* = 5.2 Hz, 1H), 7.01-7.05 (m, 1H), 7.09-7.10 (m, 2H), 7.27-7.32 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 25.2 (CH_2), 25.3 (CH_2), 25.4 (CH_2), 30.4 (CH_2), 31.2, (CH_2) 54.4 (CH), 58.0 (CH), 63.9 (CH_2), 71.4 (CH), 79.5 (CH), 115.9 (2×CH), 122.7 (CH), 129.7 (2×CH), 157.4 (C),

165.6 (C). IR (cm^{-1}): 3412, 2932, 2855, 1728, 1597, 1495, 1364, 1231, 1076, 1043, 907, 893, 752, 729, 689. MS (70 eV): *m/z* (%): 306 (M^++1, 100).

*(3R,4S)-1-Benzyl-4-[(1S)-1,2-dihydroxyethyl]-3-phenoxyazetidin-2-one (**3d**).*

Yield 99% (1.86 g). Colorless oil. $[\alpha]_D^{25}$ = +71.5 (*c* = 0.46, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.91 (t, *J* = 5.8 Hz, 1H), 2.46 (d, *J* = 4.3 Hz, 1H), 3.60-3.66 (m, 1H), 3.70-3.75 (m, 1H), 3.83 (dd, *J* = 5.2, 5.2 Hz, 1H), 4.09-4.14 (m, 1H), 4.39 (d, *J* = 14.9 Hz, 1H), 4.82 (d, *J* = 14.9 Hz, 1H), 5.23 (d, *J* = 5.2 Hz, 1H), 7.03-7.06 (m, 1H), 7.10-7.12 (m, 2H), 7.28-7.39 (m, 7H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 45.8 (CH_2), 58.1 (CH), 63.8 (CH_2), 71.3 (CH), 80.4 (CH), 115.9 (2×CH), 122.8 (CH), 128.0 (CH), 128.4 (CH), 129.0 (CH), 129.7 (CH), 135.6 (C), 157.3 (C), 166.4 (C). IR (cm^{-1}): 3406, 1736, 1589, 1408, 1350, 1229, 1134, 1076, 1028, 908, 839, 754, 729, 691, 646, 608. MS (70 eV): *m/z* (%): 314 (M^++1, 100).

*(3R,4S)-3-Benzyloxy-4-[(1S)-1,2-dihydroxyethyl]-1-isopropylazetidin-2-one (**3e**).*

Yield 67% (1.12 g). Colorless oil. $[\alpha]_D^{25}$ = +74.1 (*c* = 0.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.7 Hz, 3H), 1.36 (d, *J* = 6.8 Hz, 3H), 2.41 (t, *J* = 5.6 Hz, 1H), 2.93 (d, *J* = 4.1 Hz, 1H), 3.65-3.78 (m, 4H), 3.93-3.98 (m, 1H), 4.58 (d, *J* = 5.1 Hz, 1H), 4.69 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 7.31-7.36 (m, 2H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0 (CH_3), 21.2 (CH_3), 46.0 (CH), 58.1 (CH), 63.8 (CH_2), 71.3 (CH), 73.2 (CH_2), 79.8 (CH), 128.1 (2×CH), 128.2 (CH), 128.6 (2×CH), 136.7 (C), 167.3 (C). IR (cm^{-1}): 3397, 2974, 2936, 2878, 1717, 1454, 1404, 1339, 1229, 1215, 1148, 1067, 1022, 910, 779, 733, 696. MS (70 eV): *m/z* (%): 280 (M^++1, 100).

*(3R,4S)-3-Benzyloxy-4-[(1S)-1,2-dihydroxyethyl]-1-propylazetidin-2-one (**3f**).*

Yield 76% (1.27 g). Colorless oil. $[\alpha]_D^{25}$ = +69.5 (*c* = 0.36, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.48-1.70 (m, 2H), 2.50 (br s, 1H), 3.01 (br s, 1H), 3.11 (ddd, *J* = 13.8, 8.1, 5.5 Hz, 1H), 3.46 (ddd, *J* = 13.8, 7.8, 7.8 Hz, 1H), 3.64-3.77 (m, 3H), 3.97-4.01 (m, 1H), 4.66 (d, *J* = 5.0 Hz, 1H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.95 (d, *J* = 11.6 Hz, 1H), 7.29-7.38 (m, 5H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.4 (CH_3), 20.7 (CH_2), 43.5 (CH_2), 58.1 (CH), 64.0 (CH_2), 71.3 (CH), 73.3 (CH_2), 80.5 (CH), 128.1 (2×CH), 128.3 (CH), 128.6 (2×CH), 136.6 (C), 167.9 (C). IR (cm^{-1}): 3393, 2965, 2934, 2876, 1724, 1454, 1416, 1383, 1342, 1215, 1155, 1070, 1020, 907, 822, 733, 696. MS (70 eV): *m/z* (%): 280 (M^++1, 100).

*(3R,4S)-1-Benzyl-3-benzyloxy-4-[(1S)-1,2-dihydroxyethyl]azetidin-2-one (**3g**).*

Yield 98% (1.92 g). Colorless oil. $[\alpha]_D^{25}$ = +22.2 (*c* = 0.38, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.01 (br s, 1H), 2.66 (br s, 1H), 3.55-3.62 (m, 3H), 3.95-3.96 (m, 1H), 4.26 (d, *J* = 15.0 Hz, 1H), 4.68 (d, *J* = 5.1 Hz, 1H), 4.26 (d, *J* = 11.7 Hz, 1H), 4.79 (d, *J* = 15.0 Hz, 1H), 4.97 (d, *J* = 11.7 Hz, 1H), 7.25-7.39 (m, 10H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 45.5 (CH_2), 58.0 (CH), 63.9 (CH_2), 71.0 (CH), 73.4 (CH_2), 80.4 (CH), 127.9 (CH), 128.1 (2×CH), 128.30 (2×CH), 128.35 (CH), 128.6 (2×CH), 128.9 (2×CH), 135.6 (C), 136.5 (C), 167.7 (C). IR (cm^{-1}): 3397, 2926, 2876, 1728, 1497, 1454, 1406, 1341, 1217, 1155, 1074, 910, 822, 731, 696, 604. MS (70 eV): *m/z* (%): 328 (M^++1, 100).

Synthesis of 4-formylazetidin-2-ones 4.

As a representative example, the synthesis of (2*R*,3*R*)-1-isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde **4a** is described. To a solution of (3*R*,4*S*)-4-[(1*S*)-1,2-dihydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **3a** (1.59 g, 6 mmol, 1 equiv) in CH_2Cl_2/$NaHCO_3$ (sat. in H_2O) (15/1, 80 mL), $NaIO_4$ (2.57 g, 12 mmol, 2 equiv) was added portionwise during a period of 10 minutes. The resulting solution was stirred for 2 hours at room temperature. Afterward, the crude mixture was filtered and the resulting filtrate was washed with H_2O (2 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded (2*R*,3*R*)-1-isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde **4a** in 94% yield (1.31 g, 5.64 mmol) as a yellow oil, which was purified by means of column chromatography on silica gel (Petroleumether/EtOAc 4/1) to provide an analytically pure sample.

*(2R,3R)-1-Isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde (**4a**).*

Yield 94% (1.31 g). Yellow oil. R_f = 0.10 (Petroleumether/EtOAc 4/1). $[\alpha]_D^{25}$ = +86.3 (*c* = 0.28, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.7 Hz, 3H), 1.28 (d, *J* = 6.7 Hz, 3H), 4.06 (septet, *J* = 6.7 Hz, 1H), 4.37 (dd, *J* = 5.1, 3.8 Hz, 1H), 5.37 (d, *J* = 5.1 Hz, 1H), 7.00-7.06 (m, 3H), 7.26-7.32 (m, 2H), 9.74 (d, *J* = 3.8 Hz, 1H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.2 (CH_3), 21.6 (CH_3), 45.0 (CH), 62.4 (CH), 81.2 (CH), 115.6 (2×CH), 122.9 (CH), 129.7 (2×CH), 156.9 (C), 164.3 (C), 198.4 (C). IR (cm^{-1}): 2976, 1732, 1597, 1589, 1495, 1387, 1344, 1227, 1026, 845, 752, 689. MS (70 eV): *m/z* (%): 234 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{13}H_{16}NO_3$: 234.1125 [*M*+H]$^+$, found: 234.1132.

*(2R,3R)-4-Oxo-3-phenoxy-1-propylazetidine-2-carbaldehyde (**4b**).*

Yield 80% (1.12 g). Yellow oil. R_f = 0.05 (Petroleumether/EtOAc 4/1). $[\alpha]_D^{25}$ = +72.4 (*c* = 0.36, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J* = 7.4 Hz, 3H), 1.52-1.70 (m, 2H), 3.29-3.36 (m, 1H), 3.39-3.46 (m, 1H), 4.38 (dd, *J* = 5.0, 2.9 Hz, 1H), 5.46 (d, *J* = 5.0 Hz, 1H), 7.01-7.07 (m, 3H), 7.28-7.32 (m, 2H), 9.74 (d, *J* = 2.9 Hz, 1H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 21.2 (CH_2), 43.9 (CH_2), 63.8 (CH), 82.2 (CH), 115.5 (2×CH), 123.0 (CH), 129.8 (2×CH), 156.9 (C), 165.0 (C), 197.7 (C). IR (cm^{-1}): 2965, 2934, 1732, 1597, 1589, 1495, 1412, 1344, 1231, 1130, 1067, 1022, 752, 729, 689. MS (70 eV): *m/z* (%): 234 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{13}H_{16}NO_3$: 234.1125 [*M*+H]$^+$, found: 234.1124.

*(2R,3R)-1-Cyclohexyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde (**4c**).*

Yield 78% (1.16 g). Colorless oil. R_f = 0.29 (Petroleumether/EtOAc 7/3). $[\alpha]_D^{25}$ = +69.6 (*c* = 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11-2.01 (m, 10H), 3.66-3.73 (m, 1H), 4.35 (dd, *J* = 5.0, 4.1 Hz, 1H), 5.36 (d, *J* = 5.0 Hz, 1H), 6.99-7.06 (m, 3H), 7.26-7.32 (m, 2H), 9.73 (d, *J* = 4.1 Hz, 1H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 24.8 (CH_2), 24.9 (CH_2), 25.1 (CH_2), 30.6 (CH_2), 31.9 (CH_2), 52.4 (CH), 62.6 (CH), 81.3 (CH), 115.6 (2×CH), 122.9 (CH), 129.7 (2×CH), 156.9 (C), 164.4 (C), 198.6 (C). IR (cm^{-1}): 2932, 2855, 1732, 1597, 1589, 1495, 1229, 1076, 1047, 1026, 752, 691. MS (70 eV): *m/z* (%): 274 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{16}H_{20}NO_3$: 274.1438 [*M*+H]$^+$, found: 274.1436.

*(2R,3R)-3-Benzyloxy-1-isopropyl-4-oxoazetidine-2-carbaldehyde (**4e**).*

Yield 86% (1.27 g). Yellow oil. R_f = 0.09 (Petroleumether/EtOAc 7/3). $[\alpha]_D^{25}$ = +64.7 (*c* = 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (d, *J* = 6.7 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H), 4.00 (septet, *J* = 6.7 Hz, 1H), 4.11 (dd, *J* = 5.1, 4.0 Hz, 1H), 4.63 (d, *J* = 11.7 Hz, 1H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.82 (d, *J* = 5.1 Hz, 1H), 7.00-7.06 (m, 3H), 7.29-7.37 (m, 2H), 9.65 (d, *J* = 4.0 Hz, 1H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.2 (CH_3), 21.6 (CH_3), 44.6 (CH), 62.5 (CH), 73.3 (CH_2), 82.4 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 136.0 (C), 165.9 (C), 199.9 (C). IR (cm^{-1}): 2976, 2936, 2878, 1728, 1454, 1387, 1339, 1210, 1155, 1130, 1009, 912, 733, 698. MS (70 eV): *m/z* (%): 248 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{14}H_{18}NO_3$: 248.1281 [*M*+H]$^+$, found: 248.1281.

*(2R,3R)-3-Benzyloxy-4-oxo-1-propylazetidine-2-carbaldehyde (**4f**).*

Yield 97% (1.44 g). Colorless oil. $[\alpha]_D^{25}$ = +71.8 (*c* = 0.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.45-1.64 (m, 2H), 3.25 (ddd, *J* = 14.1, 8.0, 6.2 Hz, 1H), 3.35 (ddd, *J* = 14.1, 8.0, 6.8 Hz, 1H), 4.12 (dd, *J* = 5.0, 3.2 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.92 (d, *J* = 5.0 Hz, 1H), 7.31-7.38 (m, 5H), 9.62 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.4 (CH_3), 21.2 (CH_2), 43.6 (CH_2), 64.0 (CH), 73.4 (CH_2), 83.4 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 136.0 (C), 166.5 (C), 199.2 (C). IR (cm^{-1}): 2965, 2934, 2876, 1728, 1454, 1408, 1342, 1217, 1155, 1069, 1009, 735, 696. MS (70 eV): *m/z* (%): 248 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{14}H_{18}NO_3$: 248.1281 [*M*+H]$^+$, found: 248.1289.

Spectral data of 4-formylazetidin-2-ones **4d,g** correspond with those reported in the literature.[27-28]

Synthesis of 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones 5 and 6.

As a representative example, the synthesis of (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** and (3*R*,4*S*)-4-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a** is described. A solution of (2*R*,3*R*)-1-isopropyl-4-oxo-3-phenoxyazetidine-2-carbaldehyde **4a** (2.10 g, 9

mmol, 1 equiv) in dry THF (20 mL) was cooled to -78 °C. Then, CsF (4.10 g, 27 mmol, 3 equiv) and $TMSCF_3$ (1.41 g, 1.14 mL, 9.9 mmol, 1.1 equiv) were added and the resulting solution was heated up slowly to room temperature during a period of 2 hours. Next, EtOH (10 mL) was added and the solution was stirred for an additional 1 hour at room temperature. Afterward, H_2O was added and the aqueous phases were extracted with EtOAc (3 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** and (3*R*,4*S*)-4-[(1*R*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **6a** in a diastereomeric ratio of 93/7. Purification of the crude reaction mixture by means of recrystallization from EtOAc/hexane (5/1) afforded (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** as a white powder in a yield of 74% (2.02 g, 6.66 mmol). This purification method also accounts for the isolation of 4-(2,2,2-trifluoro-1-hydroxyethyl)azetidin-2-ones **5b,c,e.** 4-(2,2,2-Trifluoro-1-hydroxyethyl)azetidin-2-ones **5d,f,g** and **6g** were purified by means of column chromatography on silica gel.

*(3R,4S)-4-[(1S)-2,2,2-Trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one (**5a**).*

Yield 74% (2.02 g). White powder. Mp 161 ± 2 °C. Recrystallization from EtOAc/Hexane (5/1). $[\alpha]_D^{25}$ = +124.5 (*c* = 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (d, *J* = 6.8 Hz, 3H), 1.47 (d, *J* = 6.8 Hz, 3H), 2.73 (d, *J* = 5.2 Hz, 1H), 3.63 (septet, *J* = 6.8 Hz, 1H), 4.24 (dd, *J* = 5.1, 2.2 Hz, 1H), 4.34-4.42 (m, 1H), 5.22 (d, *J* = 5.1 Hz, 1H), 7.05-7.12 (m, 3H), 7.30-7.34 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -76.27 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.0 (CH_3), 20.6 (CH_3), 47.5 (CH), 55.5 (CH), 67.9 (q, *J* = 31.3 Hz, CH), 79.5 (CH), 116.0 (2×CH), 123.1 (CH), 124.3 (q, *J* = 281.3 Hz, C), 129.8 (2×CH), 157.1 (C), 165.3 (C). IR (cm^{-1}): 3256, 2984, 1732, 1597, 1589, 1413, 1362, 1262, 1229, 1175, 1163, 1130, 1115, 1026, 812, 754, 689, 669. MS (70 eV): *m/z* (%): 304 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{14}H_{17}F_3NO_3$: 304.1155 [*M*+H]$^+$, found: 304.1155.

*(3R,4S)-4-[(1S)-2,2,2-Trifluoro-1-hydroxyethyl]-3-phenoxy-1-propylazetidin-2-one (**5b**).*

Yield 29% (791 mg). White powder. Mp 101 ± 2 °C. Recrystallization from EtOAc/Hexane (5/1). $[\alpha]_D^{25}$ = +113.5 (*c* = 0.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.52-1.74 (m, 2H), 2.88 (d, *J* = 5.2 Hz, 1H), 3.10 (ddd, *J* = 13.8, 8.2, 5.5 Hz, 1H), 3.52-3.59 (m, 1H), 4.25 (dd, *J* = 5.0, 1.8 Hz, 1H), 4.35-4.43 (m, 1H), 5.30 (d, *J* = 5.0 Hz, 1H), 7.05-7.12 (m, 3H), 7.30-7.34 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -76.72 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.4 (CH_3), 20.5 (CH_2), 43.6 (CH_3), 55.4 (CH), 67.9 (q, *J* = 31.5 Hz, CH), 80.3 (CH), 116.0 (2×CH), 123.2 (CH), 124.3 (q, *J* = 276.7 Hz, C), 129.9 (2×CH), 157.0 (C), 165.9 (C). IR (cm^{-1}): 3377, 2978, 1753, 1495, 1418, 1285, 1236, 1173, 1155, 1150, 1125, 1113, 1028, 750, 689, 665. MS (70 eV): *m/z* (%): 304 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{14}H_{17}F_3NO_3$: 304.1155 [*M*+H]$^+$, found: 304.1163.

*(3R,4S)-1-Cyclohexyl-4-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidin-2-one (**5c**).*

Yield 16% (494 mg). White powder. Mp 136 ± 2 °C. Recrystallization from EtOAc/Hexane (15/1) $[\alpha]_D^{25}$ = +118.0 (*c* = 0.27, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17-1.29 (m, 3H), 1.61-1.95 (m, H), 2.11-2.14 (m, 1H), 2.86 (d, *J* = 5.4 Hz, 1H), 3.18-3.26 (m, 1H), 4.25 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.37 (qdd, *J* = 7.9, 5.4, 2.4, 1H), 5.21 (d, *J* = 5.1 Hz, 1H), 7.04-7.10 (m, 3H), 7.28-7.34 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.29 (d, *J* = 7.9 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 25.16 (CH_2), 25.19 (CH_2), 25.5 (CH_2), 30.2 (CH_2), 30.6 (CH_2), 55.3 (CH), 55.4 (CH), 67.8 (q, *J* = 31.3 Hz, CH), 79.4 (CH), 116.0 (2×CH), 123.1 (CH), 124.3 (q, *J* = 281.8 Hz, C), 129.8 (2×CH), 157.1 (C), 165.3 (C). IR (cm^{-1}): 3252, 2943, 1724, 1265, 1229, 1169, 1126, 1098, 808, 746, 689. MS (70 eV): *m/z* (%): 344 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{17}H_{21}F_3NO_3$: 344.1468 [*M*+H]$^+$, found: 344.1482.

*(3R,4S)-1-Benzyl-4-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidin-2-one (**5d**).*

White powder. Mp 88 ± 2 °C. R_f = 0.23 (Petroleumether/EtOAc 4/1, 4 CV 0% EtOAc, 24 CV 0-9% EtOAc, 1 CV 9-100% EtOAc, UV = 222 nm).$[\alpha]_D^{25}$ = +11.3 (*c* = 0.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.06 (d, *J* = 5.5 Hz, 1H), 4.08 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.12 (d, *J* = 15.0 Hz, 1H), 4.39 (qdd, *J* = 7.7, 5.5, 2.4, 1H), 4.97 (d, *J* = 15.0 Hz, 1H),

5.26 (d, *J* = 5.1 Hz, 1H), 7.04-7.10 (m, 3H), 7.25-7.39 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.51 (d, *J* = 7.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 45.7 (CH_2), 55.0 (CH), 67.9 (q, *J* = 31.5 Hz, CH), 80.5 (CH), 116.0 (2×CH), 123.2 (CH), 124.2 (q, *J* = 282.4 Hz, C), 128.1 (CH), 128.5 (CH), 129.0 (CH), 129.8 (CH), 135.0 (C), 157.0 (C), 166.1 (C). IR (cm^{-1}): 3422, 1755, 1489, 1418, 1229, 1179, 1169, 1125, 1078, 764, 733, 696. MS (70 eV): *m/z* (%): 352 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{18}H_{17}F_3NO_3$: 352.1155 $[M+H]^+$, found: 352.1163.

*(3R,4S)-3-Benzyloxy-4-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropylazetidin-2-one (**5e**).*

Yield 50% (1.43 g). White powder. Mp 101 ± 2 °C. Recrystallization from EtOAc/Hexane (5/1). $[\alpha]_D^{25}$ = +79.9 (*c* = 0.35, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (d, *J* = 6.8 Hz, 3H), 1.42 (d, *J* = 6.8 Hz, 3H), 3.06 (d, *J* = 4.7 Hz, 1H), 3.54 (septet, *J* = 6.8 H, 1H z), 3.99 (dd, *J* = 5.1, 2.2 Hz, 1H), 4.13-4.20 (m, 1H), 4.65 (d, *J* = 5.1 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.94 (d, *J* = 11.6 Hz, 1H), 7.31-7.40 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.10 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 20.1 (CH_3), 20.6 (CH_3), 47.3 (CH), 55.4 (CH), 67.9 (q, *J* = 31.3 Hz, CH), 73.7 (CH_2), 79.8 (CH), 124.3 (q, *J* = 282.2 Hz, C), 128.3 (CH), 128.6 (CH), 128.8 (CH), 136.2 (C), 166.9 (C). IR (cm^{-1}): 3302, 2978, 2936, 2886, 1717, 1418, 1344, 1263, 1169, 1123, 1024, 986, 818, 702, 756, 685. MS (70 eV): *m/z* (%): 318 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{19}F_3NO_3$: 318.1312 $[M+H]^+$, found: 318.1314.

*(3R,4S)-3-Benzyloxy-4-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidin-2-one (**5f**).*

White powder. Mp 101 ± 2 °C. Reversed phase column chromatography (CH_3CN/H_2O) (40 CV 33% CH_3CN, 5 CV 33-50% CH_3CN, 5 CV 50-100% CH_3CN). $[\alpha]_D^{25}$ = +62.9 (*c* = 0.18, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.45-1.65 (m, 2H), 3.01 (ddd, *J* = 14.0, 8.3, 5.4 Hz, 1H), 3.13 (d, *J* = 4.4 Hz, 1H), 3.49 (ddd, *J* = 14.0, 7.7, 7.7 Hz, 1H), 4.01 (dd, *J* = 5.0, 1.7 Hz, 1H), 4.13-4.20 (m, 1H), 4.71 (d, *J* = 11.6 Hz, 1H), 4.75 (d, *J* = 5.0 Hz, 1H), 4.95 (d, *J* = 11.6 Hz, 1H), 7.32-7.40 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.55 (d, *J* = 8.2 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.3 (CH_3), 20.4 (CH_2), 43.2 (CH_2), 55.2 (CH), 68.1 (q, *J* = 31.4 Hz, CH), 73.8 (CH_2), 80.6 (CH), 124.3 (q, *J* = 280.8 Hz, C), 128.3 (CH), 128.6 (CH), 128.8 (CH), 136.1 (C), 167.4 (C). IR (cm^{-1}): 3227, 2967, 1717, 1429, 1344, 1261, 1173, 1011, 691, 687. MS (70 eV): *m/z* (%): 318 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{19}F_3NO_3$: 318.1312 $[M+H]^+$, found: 318.1326.

*(3R,4S)-1-Benzyl-3-benzyloxy-4-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]azetidin-2-one (**5g**).*

Yield 35% (1.15 g). White powder. Mp 70 ± 2 °C. R_f = 0.04 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = -9.2 (*c* = 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.02 (d, *J* = 4.7 Hz, 1H), 3.85 (dd, *J* = 5.1, 2.0 Hz, 1H), 4.02 (d, *J* = 15.0 Hz, 1H), 4.12-4.19 (m, 1H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 5.1 Hz, 1H), 4.93 (d, *J* = 15.0 Hz, 1H), 4.96 (d, *J* = 11.6 Hz, 1H), 7.21-7.38 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.21 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 45.2 (CH_2), 54.8 (CH), 68.1 (q, *J* = 31.5 Hz, CH), 73.8 (CH_2), 81.0 (CH), 124.1 (q, *J* = 278.9 Hz, C), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.8 (CH), 128.9 (CH), 135.1 (C), 136.0 (C), 167.3 (C). IR (cm^{-1}): 3261, 3034, 2943, 1724, 1420, 1346, 1263, 1163, 1134, 1101, 1026, 825, 669. MS (70 eV): *m/z* (%): 366 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{19}H_{19}F_3NO_3$: 366.1312 $[M+H]^+$, found: 366.1328.

*(3R,4S)-3-Benzyloxy-4-[(1R)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidin-2-one (**6f**).*

Colorless oil. Reversed phase column chromatography (CH_3CN/H_2O) (40 CV 33% CH_3CN, 5 CV 33-50% CH_3CN, 5 CV 50-100% CH_3CN). $[\alpha]_D^{25}$ = +67.6 (*c* = 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.50-1.68 (m, 2H), 3.03 (ddd, *J* = 14.1, 8.1, 5.8 Hz, 1H), 3.40 (ddd, *J* = 14.1, 7.6, 7.6 Hz, 1H), 3.95 (dd, *J* = 4.7, 4.6 Hz, 1H), 4.09 (d, *J* = 8.8 Hz, 1H), 4.23-4.32 (m, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.86 (d, *J* = 4.7 Hz, 1H), 4.98 (d, *J* = 11.4 Hz, 1H), 7.32-7.40 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.27 (d, *J* = 8.0 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.4 (CH_3), 20.8 (CH_2), 42.3 (CH_2), 55.0 (CH), 70.0 (q, *J* = 31.3 Hz, CH), 73.8 (CH_2), 82.2 (CH), 124.3 (q, *J* = 283.1 Hz, C), 128.2 (CH), 128.6 (CH), 128.7 (CH), 135.7 (C), 166.6 (C). IR (cm^{-1}): 3354, 2967, 2938, 2880, 1740, 1342, 1271, 1215, 1173, 1148, 1123, 1090, 1067, 1009, 737, 698. MS (70 eV): *m/z* (%): 318 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{19}F_3NO_3$: 318.1312 $[M+H]^+$, found: 318.1325.

*(3R,4S)-1-Benzyl-3-benzyloxy-4-[(1R)-2,2,2-trifluoro-1-hydroxyethyl]azetidin-2-one (**6g**).*

Yield 23% (756 mg). Colorless oil. R_f = 0.07 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +33.2 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (dd, *J* = 4.8, 4.6 Hz, 1H), 4.04 (d, *J* = 8.9 Hz, 1H), 4.08 (d, *J* = 15.2 Hz, 1H), 4.12-4.22 (m,

1H), 4.78 (d, *J* = 15.2 Hz, 1H), 4.79 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 4.8 Hz, 1H), 4.97 (d, *J* = 11.5 Hz, 1H), 7.22-7.38 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.08 (d, *J* = 7.6 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 44.6 (CH_2), 54.5 (CH), 69.7 (q, *J* = 31.4 Hz, CH), 73.9 (CH_2), 82.5 (CH), 124.2 (q, *J* = 282.9 Hz, C), 128.2 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 129.1 (CH), 134.3 (C), 135.6 (C), 166.7 (C). IR (cm^{-1}): 3397, 3032, 2938, 1744, 1342, 1271, 1163, 1126, 1094, 1028, 739, 696. MS (70 eV): *m/z* (%): 366 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{19}H_{19}F_3NO_3$: 366.1312 $[M+H]^+$, found: 366.1313.

Synthesis of 2-(2,2,2-trifluoro-1-hydroxyethyl)azetidines 7 and 8.

As a representative example, the synthesis of (2*S*,3*S*)-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine **7a** is described. To an ice-cooled solution of $AlCl_3$ (0.6 g, 4.5 mmol, 1.5 equiv) in dry Et_2O (20 mL), a solution of $LiAlH_4$ (4.5 mL, 4.5 mmol, 1.5 equiv, 1.0 M in Et_2O) was added via a syringe. Then, the resulting solution was stirred at room temperature for 30 minutes, after which a solution of (3*R*,4*S*)-4-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidin-2-one **5a** (909 mg, 3 mmol, 1 equiv) in dry Et_2O (10 mL) was added at 0 °C, followed by stirring for 2 hours at 0 °C. Afterward, the reaction mixture was quenched with brine (10 mL) to neutralize the excess of $LiAlH_4$. Then, an excess of $MgSO_4$ (5 g) was added and the reaction mixture was filtered. Subsequently, the remaining solids on the filter were washed intensively with EtOAc (5 × 20 mL). Evaporation of the combined organic phases in vacuo afforded (2*S*,3*S*)-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine **7a** in a yield of 94% (815 mg, 2.82 mmol) as a white powder, which was purified by means of column chromatography on silica gel (Petroleumether/EtOAc 9/1) to provide an analytically pure sample. Azetidine **7e** appeared to be unstable upon purification on silica gel.

*(2S,3S)-2-[(1S)-2,2,2-Trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine (**7a**).*

Yield 94% (815 mg). White powder. Mp 87 ± 2 °C. R_f = 0.13 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +39.3 (*c* = 0.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.5 Hz, 3H), 2.89 (septet, *J* = 6.5 Hz, 1H), 3.45-3.49 (m, 1H), 3.68 (dd, *J* = 9.7, 7.3 Hz, 1H), 4.0.3-4.06 (m, 1H), 4.22-4.29 (m, 1H), 4.93 (ddd, *J* = 7.3, 7.3, 3.7 Hz, 1H), 5.63 (br s, 1H), 6.75-6.77 (m, 2H), 6.96-7.00 (m, 1H), 7.25-7.29 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -78.33 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 16.4 (CH_3), 20.0 (CH_3), 51.4 (CH), 53.0 (CH_2), 60.7, 64.0 (q, *J* = 30.9 Hz, CH), 66.7 (CH), 114.8 (2×CH), 121.7 (CH), 125.3 (q, *J* = 281.9 Hz, C), 129.7 (2×CH), 156.8 (C). IR (cm^{-1}): 3030, 1599, 1587, 1489, 1227, 1165, 1121, 1094, 908, 752, 727, 692. MS (70 eV): *m/z* (%): 290 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{14}H_{19}F_3NO_2$: 290.1362 $[M+H]^+$, found: 290.1364.

*(2S,3S)-2-[(1S)-2,2,2-Trifluoro-1-hydroxyethyl]-3-phenoxy-1-propylazetidine (**7b**).*

Yield 86% (746 mg). White powder. Mp 95 ± 2 °C. R_f = 0.14 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +96.1 (*c* = 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.36-1.46 (m, 2H), 2.49 (ddd, *J* = 11.7, 7.3, 6.2 Hz, 1H), 2.71-2.78 (m, 1H), 3.40 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.63-3.66 (m, 1H), 3.82-3.85 (m, 1H), 4.37-4.43 (m, 1H), 4.96 (ddd, *J* = 6.6, 6.5, 2.5 Hz, 1H), 6.05 (br s, 1H), 6.76-6.78 (m, 2H), 6.96-7.00 (m, 1H), 7.25-7.29 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -78.87 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 20.6 (CH_2), 58.5 (CH_2), 59.2 (CH_2), 64.7 (q, *J* = 30.8 Hz, CH), 65.2 (CH), 67.8 (CH), 114.8 (2×CH), 121.6 (CH), 125.2 (q, *J* = 282.0 Hz, C), 129.7 (2×CH), 156.7 (C). IR (cm^{-1}): 2963, 1591, 1497, 1489, 1265, 1225, 1165, 1121, 1092, 750, 691. MS (70 eV): *m/z* (%): 290 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{14}H_{19}F_3NO_2$: 290.1362 $[M+H]^+$, found: 290.1359.

*(2S,3S)-1-Cyclohexyl-2-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidine (**7c**).*

Yield 71% (701 mg). White powder. Mp 99 ± 2 °C. R_f = 0.11 (Petroleumether/EtOAc 19/1). $[\alpha]_D^{25}$ = +38.9 (*c* = 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01-1.28 (m, 5H), 1.63-1.66 (m, 1H), 1.77-1.84 (4H, m, 4H), 2.43-

2.49 (m, 1H), 3.50 (dd, *J* = 9.7, 3.9 Hz, 1H), 3.73 (dd, *J* = 9.7, 7.4 Hz, 1H), 4.13-4.15 (m, 1H), 4.19-4.25 (m, 1H), 4.94 (ddd, *J* = 7.4, 7.4, 3.9 Hz, 1H), 5.59 (br s, 1H), 6.74-6.76 (m, 2H), 6.96-7.00 (m, 1H), 7.25-7.30 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -78.17 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 24.8 (CH_2), 25.1 (CH_2), 25.7 (CH_2), 27.2 (CH_2), 30.6 (CH_2), 54.1 (CH_2), 59.9 (CH), 60.1 (CH), 63.9 (q, *J* = 30.8 Hz, CH), 67.0 (CH), 114.8 (2×CH), 121.7 (CH), 125.3 (q, *J* = 281.8 Hz, C), 129.7 (2×CH), 156.8 (C). IR (cm^{-1}): 2934, 2857, 1589, 1489, 1234, 1215, 1167, 1123, 1090, 1016, 750, 691, 669. MS (70 eV): *m/z* (%): 330 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{17}H_{23}F_3NO_2$: 330.1675 [*M*+H]$^+$, found: 330.1673.

*(2S,3S)-1-Benzyl-2-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidine (**7d**).*

Yield 43% (435 mg). White powder. Mp 110 ± 2 °C. Reversed phase column chromatography (CH_3CN/H_2O) (2 CV 40% CH_3CN, 20 CV 40-60% CH_3CN, 5 CV 60% CH_3CN). $[\alpha]_D^{25}$ = +67.6 (*c* = 0.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.46-3.53 (m, 2H), 3.62 (d, *J* = 13.1 Hz, 1H), 4.01 (d, *J* = 13.1 Hz, 1H), 4.06-4.08 (m, 1H), 4.26 (~q, *J* = 8.0 Hz, 1H), 4.95 (ddd, *J* = 6.5, 6.5, 3.4 Hz, 1H), 5.34 (br s, 1H), 6.71-6.73 (m, 2H), 6.94-6.98 (m, 1H), 7.23-7.7.36 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -78.68 (d, *J* = 8.0 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 57.9 (CH_2), 59.8 (CH_2), 64.2 (CH), 64.9 (q, *J* = 30.9 Hz, CH), 67.4 (CH), 114.7 (2×CH), 121.6 (CH), 125.1 (q, *J* = 281.3 Hz, C), 127.8 (CH), 128.6 (CH), 128.7 (CH), 129.7 (CH), 136.3 (C), 156.7 (C). IR (cm^{-1}): 3030, 2698, 1599, 1489, 1362, 1227, 1165, 1121, 1094, 1040, 752, 727, 691. MS (70 eV): *m/z* (%): 338 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{18}H_{19}F_3NO_2$: 338.1362 [*M*+H]$^+$, found: 338.1359.

*(2S,3S)-3-Benzyloxy-2-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidine (**7f**).*

Yield 41% (373 mg). Yellow oil. Reversed phase column chromatography (CH_3CN/H_2O) (3 CV 30-35% CH_3CN, 30 CV 35-70% CH_3CN, 5 CV 70% CH_3CN). $[\alpha]_D^{25}$ = +50.1 (*c* = 0.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.31-1.43 (m, 2H), 2.38 (ddd, *J* = 11.6, 7.7, 5.9 Hz, 1H), 2.64-2.71 (m, 1H), 3.11 (dd, *J* = 9.3, 6.5 Hz, 1H), 3.52-3.55 (m, 1H), 3.60-3.63 (m, 1H), 4.26 (ddd, *J* = 6.6, 6.5, 2.5 Hz, 1H), 4.30 (qd, J_{HF} = 8.0, *J* = 3.4 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 6.05 (br s, 1H), 7.26-7.35 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -78.67 (d, *J* = 8.0 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 20.6 (CH_2), 58.5 (CH_2), 59.2 (CH_2), 64.7 (q, *J* = 30.7 Hz, CH), 65.8 (CH), 69.2 (CH), 71.1 (CH_2), 125.3 (q, *J* = 281.8 Hz, C), 127.6 (2×CH), 127.8 (CH), 128.5 (2×CH), 137.4 (C). IR (cm^{-1}): 3076, 2961, 2878, 1456, 1281, 1265, 1165, 1121, 1040, 908, 729, 692. MS (70 eV): *m/z* (%): 304 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{21}F_3NO_2$: 304.1519 [*M*+H]$^+$, found: 304.1528.

*(2S,3S)-1-Benzyl-3-benzyloxy-2-[(1S)-2,2,2-trifluoro-1-hydroxyethyl]azetidine (**7g**).*

Yield 80% (842 mg). Colorless oil. R_f = 0.16 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +48.8 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.22 (dd, *J* = 9.5, 6.7 Hz, 1H), 3.46-3.53 (m, 1H), 3.52 (d, *J* = 13.1 Hz, 1H), 3.86-3.88 (m, 1H), 3.94 (d, *J* = 13.1 Hz, 1H), 4.26 (qd, J_{HF} = 8.2, *J* = 1.3 Hz, 1H), 4.30 (ddd, *J* = 6.9, 6.7, 2.7 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.54 (d, *J* = 12.1 Hz, 1H), 5.31 (br s, 1H), 7.20-7.38 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -78.58 (d, *J* = 8.2 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 58.1 (CH_2), 60.0 (CH_2), 64.8 (CH), 65.0 (q, *J* = 30.8 Hz, CH), 69.0 (CH), 71.2 (CH_2), 125.4 (q, *J* = 276.7 Hz, C), 127.52 (2×CH), 127.54 (CH), 127.9 (CH), 128.51 (2×CH), 128.54 (2×CH), 128.8 (2×CH), 137.0 (C), 137.3 (C). IR (cm^{-1}): 3030, 2930, 2862, 1454, 1265, 1217, 1163, 1115, 1028, 849, 752, 731, 694, 627, 604. MS (70 eV): *m/z* (%): 352 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{19}H_{21}F_3NO_2$: 352.1519 [*M*+H]$^+$, found: 352.1520.

*(2S,3S)-3-Benzyloxy-2-[(1R)-2,2,2-trifluoro-1-hydroxyethyl]-1-propylazetidine (**8b**).*

Yield 15% (136 mg). Purity = 80%. Yellow oil. Reversed phase column chromatography (CH_3CN/H_2O) (3 CV 30-35% CH_3CN, 30 CV 35-70% CH_3CN, 5 CV 70% CH_3CN). $[\alpha]_D^{25}$ = +70.0 (*c* = 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.4 Hz, 3H), 1.36-1.52 (m, 2H), 2.29 (ddd, *J* = 11.3, 8.4, 6.5 Hz, 1H), 2.60 (ddd, *J* = 11.3, 8.8, 7.0 Hz, 1H), 2.93 (dd, *J* = 9.0, 5.6 Hz, 1H), 3.39-3.41 (m, 1H), 3.60-3.62 (m, 1H), 4.15 (qd, J_{HF} = 8.0, *J* = 4.1 Hz, 1H), 4.40-4.44 (m, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.56-4.68 (m, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 7.27-7.39 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.91 (d, *J* = 8.0 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.8 (CH_3), 21.0 (CH_2), 58.2 (CH_2), 60.0 (CH_2), 65.9 (CH), 71.4 (q, *J* = 30.1 Hz, CH), 71.5 (CH_2), 73.5 (CH), 124.9 (q, *J* = 283.2 Hz, C), 127.9 (2×CH), 128.2 (CH), 128.6 (2×CH), 136.6 (C). IR (cm^{-1}): 3435, 2961, 2936, 2876, 1456, 1269, 1153, 1117, 1101,

1045, 1028, 853, 737, 692. MS (70 eV): *m/z* (%): 304 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{21}F_3NO_2$: 304.1519 [*M*+H]$^+$, found: 304.1527.

*(2S,3S)-1-Benzyl-3-benzyloxy-2-[(1R)-2,2,2-trifluoro-1-hydroxyethyl]azetidine (**8c**).*

Yield 79% (832 mg). Colorless oil. R_f = 0.16 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +78.8 (*c* = 0.21, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.05 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.54-3.57 (m, 2H), 3.63 (d, *J* = 12.7 Hz, 1H), 3.74 (d, *J* = 12.7 Hz, 1H), 3.85 (dqd, *J* = 8.2, J_{HF} = 8.1, *J* = 3.8 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.43-4.45 (m, 1H), 4.60 (d, *J* = 12.1 Hz, 1H), 4.58 (d, *J* = 8.2 Hz, 1H), 7.24-7.36 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -76.91 (d, *J* = 8.1 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 57.7 (CH_2), 61.5 (CH_2), 65.2 (CH), 71.3 (q, *J* = 29.9 Hz, CH), 71.5 (CH_2), 73.5 (CH), 124.8 (q, *J* = 283.2 Hz, C), 127.5 (CH), 127.9 (2×CH), 128.2 (CH), 128.5 (2×CH), 128.6 (2×CH), 128.9 (2×CH), 136.5 (C), 137.0 (C). IR (cm^{-1}): 3447, 3030, 2934, 2866, 1454, 1269, 1171, 1117, 1105, 1057, 1028, 854, 713, 692, 604. MS (70 eV): *m/z* (%): 352 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{19}H_{21}F_3NO_2$: 352.1519 [*M*+H]$^+$, found: 352.1532.

Synthesis of trifluoromethanesulfonates 9 and 11.

As a representative example, the synthesis of 1-[(2*R*,3*S*)-1-benzyl-3-phenoxyazetidin-2-yl]-(1*S*)-2,2,2-trifluoroethyl trifluoromethanesulfonate **9b** is described. To an ice-cooled solution of (2*S*,3*S*)-1-benzyl-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-3-phenoxyazetidine **7d** (1.01 g, 3 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL), *N*,*N*,*N*',*N*'-tetramethylnaphthalene-1,8-diamine (1.28 g, 6 mmol, 2 equiv) and triflic anhydride (0.93 g, 0.55 mL, 3.3 mmol, 1.1 equiv) were added via a syringe. Then, the resulting solution was stirred at 0 °C for 40 minutes. Afterward, the solvent was evaporated and the resulting crude solid reaction mixture was washed with Et_2O (3 × 10 mL) and filtered. The filtrate was evaporated and the crude reaction mixture was purified by means of column chromatography on silica gel to afford 1-[(2*R*,3*S*)-1-benzyl-3-phenoxyazetidin-2-yl]-(1*S*)-2,2,2-trifluoroethyl trifluoromethanesulfonate **9b** in 95% yield (1.34 g, 2.85 mmol) as a colorless oil. Triflate **9c** appeared to be unstable upon purification on silica gel.

*(1S)-2,2,2-Trifluoro-1-[(2R,3S)-1-isopropyl-3-phenoxyazetidin-2-yl]ethyl trifluoromethanesulfonate (**9a**).*

Yield 61% (770 mg). Colorless oil. R_f = 0.29 (Petroleumether/EtOAc 96/4). $[\alpha]_D^{25}$ = +27.9 (*c* = 0.54, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (d, *J* = 6.4 Hz, 6H), 2.83 (septet, *J* = 6.4 Hz, 1H), 3.48-3.55 (m, 2H), 3.96-4.00 (m, 1H), 4.91 (ddd, *J* = 7.2, 6.4, 3.7 Hz, 1H), 5.83 (dq, *J* = 8.7 Hz, J_{HF} = 5.9 Hz, 1H), 6.76-6.78 (m, 2H), 6.98-7.02 (m, 1H), 7.26-7.30 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -78.37 (s, 3F), -63.75 (br s, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 16.6 (CH_3), 20.1 (CH_3), 53.8 (CH_2), 53.9 (CH), 59.0 (CH), 65.9 (CH), 77.9 (q, *J* = 32.7 Hz, CH), 115.1 (2×CH), 118.5 (q, *J* = 319.5 Hz, C), 121.9 (CH), 122.1 (q, *J* = 281.0 Hz, C), 129.7 (2×CH), 156.2 (C). IR (cm^{-1}): 2990, 1591, 1495, 1389, 1223, 1152, 1028, 756, 691, 637. MS (70 eV): *m/z* (%): 331 (M^++1, 100), 422 (M^++1, 35).

*1-[(2R,3S)-1-Benzyl-3-phenoxyazetidin-2-yl]-(1S)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**9b**).*

Yield 95% (1.34 g). Colorless oil. R_f = 0.25 (Petroleumether/EtOAc 19/1). $[\alpha]_D^{25}$ = +88.0 (*c* = 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.41-3.43 (m, 1H), 3.46 (d, *J* = 12.6 Hz, 1H), 3.94 (dd, *J* = 9.4, 6.6 Hz, 1H), 4.20 (d, *J* = 12.6 Hz, 1H), 4.86 (ddd, *J* = 6.6, 5.8, 1.9 Hz, 1H), 5.94 (dq, *J* = 9.4 Hz, J_{HF} = 5.6 Hz, 1H), 6.71-6.74 (m, 2H), 6.95-6.99 (m, 1H), 7.23-7.34 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -75.66 till -75.61 (m, 3F), -74.26 till -74.23 (m, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 57.1 (CH_2), 62.0 (CH_2), 62.6 (CH), 67.3 (CH), 79.1 (q, *J* = 33.5 Hz, CH), 115.0 (2×CH), 118.4 (q, *J* = 319.5 Hz, C), 121.7 (q, *J* = 281.4 Hz, C), 121.7 (CH), 127.5 (CH), 128.4 (2×CH), 128.8 (2×CH), 129.7 (2×CH), 136.3 (C), 156.1 (C). IR (cm^{-1}): 3032, 1497, 1422, 1366, 1285, 1267, 1213, 1190, 1136, 1101, 991, 858, 752, 725, 691, 611. MS (70 eV): *m/z* (%): 431 (M^++1, 100), 470 (M^++1, 95). HRMS (ESI): *m/z* calcd for $C_{19}H_{18}F_6NO_4S$: 470.0855 [*M*+H]$^+$, found: 470.0872.

*1-[(2R,3S)-3-Benzyloxy-1-propylazetidin-2-yl]-(1S)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**9d**).*

Yield 93% (1.21 g). Colorless oil. R_f = 0.35 (Petroleumether/EtOAc 5/1). $[\alpha]_D^{25}$ = +32.6 (*c* = 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.27-1.47 (m, 2H), 2.23 (ddd, *J* = 10.9, 9.0, 4.9 Hz, 1H), 2.74 (ddd, *J* = 10.9, 9.8, 6.8 Hz, 1H), 2.92 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.54 (dd, *J* = 9.6, 6.5 H, 1H z), 3.57-3.59 (m, 1H), 4.21 (ddd, *J* = 6.5, 6.0, 1.7 Hz, 1H), 4.40 (d, *J* = 12.1 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 5.69 (dq, *J* = 9.6 Hz, J_{HF} = 5.9 Hz, 1H), 7.28-7.37 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -75.69 till -75.64 (m, 3F), -74.53 till -74.50 (m, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 20.5 (CH_2), 57.8 (CH_2), 60.9 (CH_2), 63.7 (CH), 68.4 (CH), 71.0 (CH_2), 79.2 (q, *J* = 33.1 Hz, CH), 118.4 (q, *J* = 319.5 Hz, C), 121.9 (q, *J* = 276.4 Hz, C), 127.7 (2×CH), 127.9 (CH), 128.5 (2×CH), 137.1 (C). IR (cm^{-1}): 2968, 2878, 1423, 1279, 1215, 1134, 1028, 988, 934, 860, 752, 696, 638, 611. MS (70 eV): *m/z* (%): 303 (M^++1, 35), 436 (M^++1, 55).

*1-[(2R,3S)-1-Benzyl-3-benzyloxyazetidin-2-yl]-(1S)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**9e**).*

Yield 90% (1.30 g). Colorless oil. R_f = 0.21 (Petroleumether/EtOAc 14/1). $[\alpha]_D^{25}$ = +72.8 (*c* = 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.94 (dd, *J* = 9.3, 6.0 Hz, 1H), 3.35-3.38 (m, 2H), 3.73 (dd, *J* = 9.8, 6.5 Hz, 1H), 4.14 (d, *J* = 12.6 Hz, 1H), 4.21 (ddd, *J* = 6.5, 6.0, 1.7 Hz, 1H), 4.37 (d, *J* = 12.1 Hz, 1H), 4.57 (d, *J* = 12.1 Hz, 1H), 5.81 (dq, *J* = 9.8 Hz, J_{HF} = 5.5 Hz, 1H), 7.23-7.35 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -75.63 till -75.58 (m, 3F), -74.40 till -74.36 (m, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 56.8 (CH_2), 62.2 (CH_2), 63.1 (CH), 68.2 (CH), 70.9 (CH_2), 79.2 (q, *J* = 33.3 Hz, CH), 118.4 (q, *J* = 319.6 Hz, C), 121.8 (q, *J* = 281.3 Hz, C), 127.4 (CH), 127.7 (2×CH), 128.0 (CH), 128.3 (2×CH), 128.5 (2×CH), 128.9 (2×CH), 136.6 (C), 137.0 (C). IR (cm^{-1}): 3032, 2934, 2868, 1420, 1366, 1267, 1211, 1192, 1136, 1061, 1028, 986, 856, 727, 696, 611. MS (70 eV): *m/z* (%): 484 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{20}H_{20}F_6NO_4S$: 484.1012 $[M+H]^+$, found: 484.1030.

*1-[(2R,3S)-3-Benzyloxy-1-propylazetidin-2-yl]-(1R)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**11a**).*

Yield 74% (966 mg). Colorless oil. R_f = 0.33 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = -48.6 (*c* = 0.11, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.4 Hz, 3H), 1.57-1.67 (m, 2H), 3.28-3.42 (m, ~4H), 3.45-3.49 (m, 1H), 3.60-3.64 (m, ~1H), 3.78-3.82 (m, 1H), 4.52 (d, *J* = 11.3 Hz, 1H), 4.71 (d, *J* = 11.3 Hz, 1H), 7.29-7.40 (5H, m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -75.26 (s, 3F), -73.79 (d, *J* = 4.4 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 10.7 (CH_3), 21.0 (CH_2), 49.5 (CH_2), 51.3 (q, *J* = 41.3 Hz, CH), 52.0 (CH_2), 54.4 (CH), 73.8 (CH_2), 74.4 (CH), 120.0 (q, *J* = 324.7 Hz, C), 122.3 (q, *J* = 276.2 Hz, C), 128.1 (2×CH), 128.4 (CH), 128.7 (2×CH), 136.7 (C). IR (cm^{-1}): 2972, 2884, 1391, 1288, 1125, 1161, 1130, 1047, 908, 741, 698. MS (70 eV): *m/z* (%): 436 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{16}H_{23}F_6N_2O_4S$: 453.1277 $[M+NH_4]^+$, found: 453.1297.

*1-[(2R,3S)-1-Benzyl-3-benzyloxyazetidin-2-yl]-(1R)-2,2,2-trifluoroethyl trifluoromethanesulfonate (**11b**).*

Yield 71% (1.03 g). Colorless oil. R_f = 0.23 (Petroleumether/EtOAc 14/1). $[\alpha]_D^{25}$ = -35.9 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.14-3.15 (m, 1H), 3.32-3.38 (m, 2H), 3.49-3.59 (m, 2H), 4.38 (d, *J* = 11.3 Hz, 1H), 4.56 (br s, 2H), 4.60 (d, *J* = 11.3 Hz, 1H), 7.22-7.41 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): δ -75.13 (s, 3F), -73.82 (d, *J* = 4.4 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 48.8 (CH_2), 51.4 (q, *J* = 41.4 Hz, CH), 53.7 (CH_2), 54.3 (CH), 73.5 (CH_2), 73.9 (CH), 120.0 (q, *J* = 322.9 Hz, C), 122.2 (q, *J* = 275.4 Hz, C), 128.2 (CH), 128.4 (CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 133.7 (C), 136.7 (C). IR (cm^{-1}): 3034, 2934, 2878, 1387, 1285, 1225, 1148, 1117, 1016, 927, 905, 789, 735, 696, 685, 608. MS (70 eV): *m/z* (%): 442 (M^++1, 100), 484 (M^++1, 18). HRMS (ESI): *m/z* calcd for $C_{20}H_{20}F_6NO_4S$: 484.1012 $[M+H]^+$, found: 484.1013.

Synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines 10a-g.

As a representative example, the synthesis of (2*R*,3*R*,4*S*)-3-benzylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10a** is described. To an ice-cooled solution of (2*S*,3*S*)-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropyl-3-phenoxyazetidine **7a** (0.29 g, 1 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) was added *N*,*N*,*N*',*N*'-tetramethylnaphthalene-1,8-diamine (0.43 g, 3 mmol, 2 equiv) and triflic anhydride (0.31 g, 0.18 mL, 1.1 mmol, 1.1 equiv). Then, the resulting solution was stirred at 0 °C for 40 minutes. Subsequently, benzylamine

(0.27 g, 0.27 mL, 2.5 mmol, 2.5 equiv) was added and the reaction mixture was stirred for another 3 days at reflux temperature. Afterward, H_2O was added and the aqueous phases were extracted with CH_2Cl_2 (3 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded a crude reaction mixture, which was purified by means of column chromatography on silica gel to afford (2*R*,3*R*,4*S*)-3-benzylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10a** in 67% yield (0.25 g, 0.67 mmol) as a colorless oil.

*(2R,3R,4S)-3-Benzylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10a**).*

Yield 67% (250 mg). Colorless oil. R_f = 0.15 (Petroleumether/EtOAc 4/1). $[\alpha]_D^{25}$ = +71.2 (*c* = 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 2.20 (br s, 1H), 2.93 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.12-3.22 (m, 2H), 3.48-3.60 (m, 2H), 3.84 (s, 2H), 4.70-4.73 (m, 1H), 6.87-6.90 (m, 2H), 6.94-6.98 (m, 1H), 7.22-7.34 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.66 (d, *J* = 8.5 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 14.9 (CH_3), 21.1 (CH_3), 48.4 (CH_2), 50.9 (CH), 52.3 (CH_2), 61.5 (CH), 62.1 (q, *J* = 27.9 Hz, CH), 74.7 (CH), 115.8 (2×CH), 121.1 (CH), 126.3 (q, *J* = 283.8 Hz, C), 127.0 (CH), 128.0 (2×CH), 128.4 (2×CH), 129.5 (2×CH), 140.1 (C), 157.8 (C). IR (cm^{-1}): 2968, 1597, 1587, 1495, 1454, 1391, 1366, 1267, 1240, 1179, 1121, 1026, 918, 883, 750, 691, 669, 635, 590, 573, 509. MS (70 eV): *m/z* (%): 379 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{21}H_{26}F_3N_2O$: 379.1992 $[M+H]^+$, found: 379.1985.

*(2R,3R,4S)-3-Allylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10b**).*

Yield 61% (200 mg). Yellow oil. R_f = 0.25 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +67.7 (*c* = 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.93 (br s, 1H), 2.98 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.12-3.22 (m, 2H), 3.28-3.30 (m, 2H), 3.49-3.59 (m, 2H), 4.77-4.79 (m, 1H), 5.06-5.10 (m, 1H), 5.15-5.21 (m, 1H), 5.86 (dddd, *J* = 17.1, 10.2, 5.9, 5.9 Hz, 1H), 6.89-6.91 (m, 2H), 6.94-6.98 (m, 1H), 7.26-7.30 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.78 (d, *J* = 8.6 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 14.9 (CH_3), 21.0 (CH_3), 48.5 (CH_2), 50.9 (CH), 51.1 (CH_2), 61.4 (CH), 62.1 (q, *J* = 28.0 Hz, CH), 74.7 (CH), 115.8 (2×CH), 116.3 (CH_2), 121.2 (CH), 126.2 (q, *J* = 283.8 Hz, C), 129.5 (2×CH), 136.7 (CH), 157.7 (C). IR (cm^{-1}): 2970, 1599, 1495, 1366, 1271, 1240, 1179, 1119, 1076, 1028, 995, 918, 883, 872, 752, 691, 629, 509. MS (70 eV): *m/z* (%): 329 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{17}H_{24}F_3N_2O$: 329.1835 $[M+H]^+$, found: 329.1842.

*(2R,3R,4S)-3-Butylamino-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10c**).*

Yield 78% (268 mg). Colorless oil. R_f = 0.26 (Petroleumether/EtOAc 4/1). $[\alpha]_D^{25}$ = +62.6 (*c* = 0.18, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.3 Hz, 3H), 0.96 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 1.25-1.35 (m, 2H), 1.40-1.48 (m, 2H), 1.71 (br s, 1H), 2.57-2.66 (m, 2H), 2.98 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.12-3.22 (m, 2H), 3.46-3.50 (m, 1H), 3.56 (~pentet, *J* = 8.7 Hz, 1H), 4.79-4.82 (m, 1H), 6.89-6.97 (m, 2H), 7.25-7.29 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.78 (d, *J* = 8.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.9 (CH_3), 14.9 (CH_3), 20.3 (CH_2), 21.0 (CH_3), 32.5 (CH_2), 48.5 (CH_2), 48.6 (CH_2), 50.9 (CH), 62.1 (q, *J* = 28.0 Hz, CH), 62.7 (CH), 74.6 (CH), 115.8 (2×CH), 121.1 (CH), 126.2 (q, *J* = 283.9 Hz, C), 129.4 (2×CH), 157.8 (C). IR (cm^{-1}): 2961, 2930, 1599, 1587, 1494, 1366, 1271, 1240, 1180, 1140, 1115, 1076, 1059, 1028, 881, 750, 691, 631, 507. MS (70 eV): *m/z* (%): 345 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{18}H_{28}F_3N_2O$: 345.2148 $[M+H]^+$, found: 345.2152.

*(2R,3R,4S)-3-(N-Benzyl-N-methylamino)-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10d**).*

Yield 65% (255 mg). Colorless oil. R_f = 0.20 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +20.3 (*c* = 0.16, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 2.29 (br s, 1H), 3.07-3.12 (m, 2H), 3.19-3.23 (m, 2H), 3.61 (d, *J* = 13.0 Hz, 1H), 3.66 (~pentet, *J* = 8.0 Hz, 1H), 3.79 (d, *J* = 13.0 Hz, 1H), 4.84-4.86 (m, 1H), 6.89-6.96 (m, 3H), 7.22-7.36 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.87 (d, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 14.4 (CH_3), 21.2 (CH_3), 40.6 (CH_3), 48.7 (CH_2), 50.9 (CH), 61.3 (CH_2), 62.7 (q, *J* = 28.3 Hz, CH), 68.7 (CH), 75.8 (CH), 115.7 (2×CH), 121.0 (CH), 126.0 (q, *J* = 283.6 Hz, C), 126.9 (CH), 128.1 (2×CH), 128.9 (2×CH), 129.5 (2×CH), 138.9 (C), 157.5 (C). IR (cm^{-1}): 2968, 1599, 1587, 1495, 1454, 1391, 1366, 1277, 1240, 1202, 1179, 1119,

1076, 1059, 1028, 934, 908, 885, 908, 750, 733, 691, 669, 642, 507. MS (70 eV): *m/z* (%): 393 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{22}H_{28}F_3N_2O$: 393.2148 [*M*+H]$^+$, found: 393.2153.

*(2R,3R,4S)-3-[(2-Hydroxyethyl)amino]-1-isopropyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10e**).*

Yield 79% (262 mg). Brown oil. R_f = 0.05 (Petroleumether/EtOAc 19/1). $[\alpha]_D^{25}$ = +68.2 (*c* = 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.4 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 2.24 (br s, 2H), 2.76 (ddd, *J* = 12.3, 6.2, 4.8 Hz, 1H), 2.88 (ddd, *J* = 12.3, 5.5, 4.4 Hz, 1H), 3.00 (dd, *J* = 11.0, 4.7 Hz, 1H), 3.13-3.23 (m, 2H), 3.49-3.61 (m, 4H), 4.77-4.79 (m, 1H), 6.89-6.91 (m, 2H), 6.95-6.99 (m, 1H), 7.26-7.30 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.62 (d, *J* = 8.5 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 14.6 (CH_3), 21.1 (CH_3), 48.2 (CH_2), 50.2 (CH_2), 50.7 (CH), 60.9 (CH_2), 62.1 (CH), 62.2 (q, *J* = 27.9 Hz, CH), 74.9 (CH), 115.7 (2×CH), 121.3 (CH), 126.1 (q, *J* = 283.4 Hz, C), 129.6 (2×CH), 157.6 (C). IR (cm^{-1}): 3350, 2968, 2932, 1597, 1587, 1495, 1391, 1366, 1269, 1240, 1179, 1121, 1028, 922, 881, 866, 804, 752, 692, 669, 633, 507. MS (70 eV): *m/z* (%): 215 (M^++1, 100), 333 (M^++1, 65). HRMS (ESI): *m/z* calcd for $C_{16}H_{24}F_3N_2O_2$: 333.1784 [*M*+H]$^+$, found: 333.1776.

*(2R,3R,4S)-3-Benzylamino-4-phenoxy-1-propyl-2-(trifluoromethyl)pyrrolidine (**10f**).*

Yield 75% (284 mg). Colorless oil. R_f = 0.32 (Petroleumether/EtOAc 4/1). $[\alpha]_D^{25}$ = +66.9 (*c* = 0.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J* = 7.4 Hz, 3H), 1.38-1.49 (m, 2H), 2.32 (br s, 1H), 2.52 (ddd, *J* = 12.1, 7.9, 5.6 Hz, 1H), 2.64 (dd, *J* = 10.9, 4.1 Hz, 1H), 2.80 (ddd, *J* = 12.1, 8.5, 7.9 Hz, 1H), 3.35 (~d, *J* = 10.9 Hz, 1H), 3.39 (~pentet, *J* = 9.1 Hz, 1H), 3.64 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.83 (d, *J* = 13.5 Hz, 1H), 3.87 (d, *J* = 13.5 Hz, 1H), 4.72-4.74 (m, 1H), 6.89-6.91 (m, 2H), 6.95-6.99 (m, 1H), 7.23-7.34 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.72 (br s, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.4 (CH_3), 20.7 (CH_2), 52.3 (CH_2), 55.4 (CH_2), 57.9 (CH_2), 60.8 (CH), 65.2 (q, *J* = 27.8 Hz, CH), 74.7 (CH), 116.0 (2×CH), 121.3 (CH), 126.1 (q, *J* = 283.3 Hz, C), 127.1 (CH), 128.0 (2×CH), 128.4 (2×CH), 129.5 (2×CH), 139.9 (C), 157.7 (C). IR (cm^{-1}): 2968, 2814, 1597, 1585, 1487, 1452, 1273, 1229, 1175, 1153, 1136, 1115, 1090, 1080, 1061, 1049, 1026, 883, 756, 738, 694, 644. MS (70 eV): *m/z* (%): 379 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{21}H_{26}F_3N_2O$: 379.1992 [*M*+H]$^+$, found: 379.1991.

*(2R,3R,4S)-3-Benzylamino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10g**).*

Yield 89% (372 mg). Yellow oil. R_f = 0.27 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +64.1 (*c* = 0.25, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98-1.28 (m, 5H), 1.59-1.81 (m, 1H), 2.20 (br s, 1H), 2.64-2.71 (m, 1H), 3.01 (dd, *J* = 11.0, 4.7 Hz, 1H), 3.18 (~d, *J* = 11.0 Hz, 1H), 3.48-3.51 (m, 1H), 3.65 (~pentet, *J* = 8.8 Hz, 1H), 3.84 (s, 2H), 4.69-4.72 (m, 1H), 6.86-6.88 (m, 2H), 6.94-6.97 (m, 1H), 7.21-7.34 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.52 (d, *J* = 8.8 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 25.5 (CH_2), 25.6 (CH_2), 26.08 (CH_2), 26.11 (CH_2), 31.7 (CH_2), 49.8 (CH_2), 52.3 (CH_2), 59.8 (CH), 61.46 (CH), 61.51 (q, *J* = 27.9 Hz, CH), 74.7 (CH), 115.8 (2×CH), 121.1 (CH), 126.3 (q, *J* = 284.2 Hz, C), 127.1 (CH), 128.0 (2×CH), 128.4 (2×CH), 129.5 (2×CH), 140.1 (C), 157.8 (C). IR (cm^{-1}): 2928, 2855, 1597, 1587, 1495, 1452, 1238, 1121, 1043, 1026, 995, 910, 891, 750, 733, 691, 648, 627, 507. MS (70 eV): *m/z* (%): 419 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{24}H_{30}F_3N_2O$: 419.2305 [*M*+H]$^+$, found: 419.2306.

Synthesis of 3,4-disubstituted 2-(trifluoromethyl)pyrrolidines 10h-n.

As a representative example, the synthesis of (2*R*,3*R*,4*S*)-1-benzyl-3-benzylamino-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10h** is described. To a solution of 1-[(2*R*,3*S*)-1-benzyl-3-phenoxyazetidin-2-yl]-(1*S*)-2,2,2-trifluoroethyl trifluoromethanesulfonate **9b** (0.47 g, 1 mmol, 1 equiv) in dry CH_3CN (20 mL) was added benzylamine (0.27 g, 0.27 mL, 2.5 mmol, 2.5 equiv). Then, the resulting solution was stirred at reflux temperature for 2 hours and, afterward, the reaction mixture was cooled to room temperature. Evaporation of the solvent and the excess of benzylamine in vacuo afforded (2*R*,3*R*,4*S*)-1-benzyl-3-benzylamino-4-phenoxy-2-(trifluoromethyl)pyrrolidine **10h** in 96% yield (0.41 g, 0.96 mmol) as a colorless oil, which was purified by means of column chromatography on silica gel to provide an analytically pure sample.

*(2R,3R,4S)-1-Benzyl-3-benzylamino-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10h**).*

Yield 96% (410 mg). White crystals. Mp 124 ± 2 °C. R_f = 0.16 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +79.4 (*c* = 0.22, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (br s, 1H), 2.66 (dd, *J* = 11.0, 4.1 Hz, 1H), 3.35 (~d, *J* = 11.0 Hz, 1H), 3.55-3.64 (m, 2H), 3.68 (d, *J* = 13.7 Hz, 1H), 3.81 (d, *J* = 13.6 Hz, 1H), 3.86 (d, *J* = 13.6 Hz, 1H), 4.15 (d, *J* = 13.7 Hz, 1H), 4.66-4.68 (m, 1H), 6.84-6.86 (m, 2H), 6.94-6.96 (m, 1H), 7.22-7.34 (m, 12H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.62 (d, *J* = 8.2 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 52.3 (CH_2), 55.3 (CH_2), 59.3 (CH_2), 61.1 (CH), 64.2 (q, *J* = 27.7 Hz, CH), 74.6 (CH), 116.0 (2×CH), 121.3 (CH), 126.2 (q, *J* = 283.4 Hz, C), 127.1 (CH), 127.2 (CH), 128.0 (2×CH), 128.39 (2×CH), 128.41 (2×CH), 128.5 (2×CH), 129.5 (2×CH), 137.6 (C), 140.0 (C), 157.7 (C). IR (cm^{-1}): 1597, 1584, 1485, 1450, 1368, 1294, 1273, 1265, 1248, 1136, 1115, 1061, 1047, 1026, 889, 758, 738, 696, 646, 627, 507. MS (70 eV): *m/z* (%): 427 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{25}H_{26}F_3N_2O$: 427.1992 $[M+H]^+$, found: 427.1990.

*(2R,3R,4S)-3-Benzylamino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine (**10i**).*

Yield 99% (388 mg). Colorless oil. R_f = 0.28 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +54.4 (*c* = 0.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 2.13 (br s, 1H), 2.69 (dd, *J* = 10.7, 4.5 Hz, 1H), 3.13-3.22 (m, 2H), 3.44 (~pentet, *J* = 8.7 Hz, 1H), 3.46 (dd, *J* = 8.7, 5.1 Hz, 1H), 3.73 (d, *J* = 13.8 Hz, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.92-3.94 (m, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 7.23-7.36 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.71 (d, *J* = 8.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 14.4 (CH_3), 21.2 (CH_3), 47.6 (CH_2), 50.7 (CH), 52.3 (CH_2), 61.4 (CH), 62.1 (q, *J* = 27.7 Hz, CH), 71.5 (CH_2), 75.9 (CH), 126.3 (q, *J* = 283.4 Hz, C), 126.9 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 138.5 (C), 140.4 (C). IR (cm^{-1}): 2968, 2916, 2872, 1454, 1269, 1121, 1069, 1028, 733, 696, 635. MS (70 eV): *m/z* (%): 393 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{22}H_{28}F_3N_2O$: 393.2148 $[M+H]^+$, found: 393.2145.

*(2R,3R,4S)-3-Benzylamino-4-benzyloxy-1-propyl-2-(trifluoromethyl)pyrrolidine (**10j**).*

Yield 99% (388 mg). Colorless oil. R_f = 0.23 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +27.2 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.4 Hz, 3H), 1.40-1.54 (m, 2H), 2.21 (br s, 1H), 2.41 (dd, *J* = 10.8, 4.0 Hz, 1H), 2.47 (ddd, *J* = 11.9, 8.6, 5.2 Hz, 1H), 2.81 (ddd, *J* = 11.9, 9.1, 7.5 Hz, 1H), 3.28 (~pentet, *J* = 9.1 Hz, 1H), 3.36 (~d, *J* = 10.8 Hz, 1H), 3.46 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.74 (d, *J* = 13.6 Hz, 1H), 3.79 (d, *J* = 13.6 Hz, 1H), 3.95-3.97 (m, 1H), 4.44 (d, *J* = 12.3 Hz, 1H), 4.71 (d, *J* = 12.3 Hz, 1H), 7.23-7.35 (m, 10H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.65 (d, *J* = 9.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 11.5 (CH_3), 20.7 (CH_2), 52.2 (CH_2), 55.0 (CH_2), 58.2 (CH_2), 60.6 (CH), 65.3 (q, *J* = 27.8 Hz, CH), 71.5 (CH_2), 75.6 (CH), 126.1 (q, *J* = 283.0 Hz, C), 127.1 (CH), 127.56 (CH), 127.59 (CH), 128.0 (CH), 128.37 (CH), 128.40 (CH), 138.3 (C), 139.8 (C). IR (cm^{-1}): 2963, 2932, 2874, 2810, 1454, 1271, 1139, 1121, 1088, 1065, 1028, 733, 696, 638. MS (70 eV): *m/z* (%): 393 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{22}H_{28}F_3N_2O$: 393.2148 $[M+H]^+$, found: 393.2145.

*(2R,3R,4S)-1-Benzyl-3-benzylamino-4-benzyloxy-2-(trifluoromethyl)pyrrolidine (**10k**).*

Yield 99% (436 mg). Colorless oil. R_f = 0.06 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +65.6 (*c* = 0.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.22 (br s, 1H), 2.39 (dd, *J* = 10.9, 3.8 Hz, 1H), 3.15 (~d, *J* = 10.9 Hz, 1H), 3.40-3.50 (m, 2H), 3.59 (d, *J* = 13.5 Hz, 1H), 3.70 (d, *J* = 13.6 Hz, 1H), 3.78 (d, *J* = 13.6 Hz, 1H), 3.88-3.90 (m, 1H), 4.19 (d, *J* = 13.7 Hz, 1H), 4.35 (d, *J* = 12.3 Hz, 1H), 4.61 (d, *J* = 12.3 Hz, 1H), 7.22-7.34 (m, 15H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.63 (d, *J* = 8.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 52.2 (CH_2), 54.8 (CH_2), 59.7 (CH_2), 61.1 (CH), 64.4 (q, *J* = 27.5 Hz, CH), 71.3 (CH_2), 75.5 (CH), 126.2 (q, *J* = 282.8 Hz, C), 127.0 (CH), 127.2 (CH), 127.4 (CH), 127.5 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 138.0 (C), 138.4 (C), 140.4 (C). IR (cm^{-1}): 3028, 2868, 2805, 1495, 1454, 1273, 1140, 1119, 1063, 1028, 735, 696, 629. MS (70 eV): *m/z* (%): 441 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{26}H_{28}F_3N_2O$: 441.2148 $[M+H]^+$, found: 441.2152.

*(2R,3R,4S)-3,4-Dibenzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine (**10l**).*

Yield 69% (271 mg). Colorless oil. R_f = 0.41 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = -8.3 (*c* = 0.16, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.4 Hz, 3H), 1.09 (d, *J* = 6.8 Hz, 3H), 2.83 (dd, *J* = 10.6, 5.8 Hz, 1H), 3.07-3.17 (m, 2H), 3.44-3.52 (m, 1H), 3.87-3.91 (m, 1H), 4.09 (dd, *J* = 7.0, 4.4 Hz, 1H), 4.63 (d, *J* = 12.4 Hz, 1H), 4.674 (d, *J* = 12.0 Hz, 1H), 4.675 (d, *J* = 12.4 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 7.25-7.37 (m, 10H). ^{19}F NMR (376 MHz, ref =

$CDCl_3$): -68.82 (d, *J* = 7.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.9 (CH_3), 21.7 (CH_3), 47.1 (CH_2), 50.6 (CH), 62.0 (q, *J* = 28.8 Hz, CH), 72.0 (CH_2), 73.3 (CH_2), 77.0 (CH), 78.6 (CH), 125.7 (q, *J* = 282.2 Hz, C), 127.56 (CH), 127.60 (CH), 127.63 (CH), 128.3 (CH), 128.33 (CH), 138.0 (C), 138.4 (C). IR (cm^{-1}): 2968, 2934, 2876, 1680, 1454, 1364, 1134, 1028, 735, 696. MS (70 eV): *m/z* (%): 393 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{22}H_{27}F_3NO_2$: 394.1988 [*M*+H]$^+$, found: 394.2001.

*(2R,3R,4S)-1-Benzyl-3-methoxy-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**10m**).*

Yield 91% (319 mg). Colorless oil. R_f = 0.25 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +32.8 (*c* = 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.84 (dd, *J* = 11.0, 5.6 Hz, 1H), 3.25 (dd, *J* = 11.0, 4.3 Hz, 1H), 3.45 (s, 3H), 3.63 (qd, J_{HF} = 7.7, *J* = 7.3 Hz, 1H), 3.70 (d, *J* = 13.8 Hz, 1H), 4.14 (d, *J* = 13.8 Hz, 1H), 4.15 (dd, *J* = 7.3, 4.6 Hz, 1H), 4.70-4.74 (m, 1H), 6.89-6.96 (m, 3H), 7.23-7.32 (m, 7H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.86 (d, *J* = 7.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 54.4 (CH_2), 59.3 (CH_2), 59.9 (CH_3), 64.4 (q, *J* = 29.0 Hz, CH), 74.9 (CH), 80.5 (CH), 116.0 (2×CH), 121.4 (CH), 125.6 (q, *J* = 282.1 Hz, C), 127.3 (CH), 128.5 (2×CH), 128.6 (2×CH), 129.5 (2×CH), 137.5 (C), 157.8 (C). IR (cm^{-1}): 2936, 1597, 1493, 1373, 1283, 1238, 1134, 1074, 1051, 1016, 752, 737, 691, 662. MS (70 eV): *m/z* (%): 352 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{19}H_{21}F_3NO_2$: 352.1519 [*M*+H]$^+$, found: 352.1536.

*(2S,3R,4S)-1-Benzyl-4-phenoxy-3-phenylthio-2-(trifluoromethyl)pyrrolidine (**10n**).*

Yield 45% (193 mg). White crystals. Mp 120 ± 2 °C. R_f = 0.21 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +132.0 (*c* = 0.15, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.79 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.26 (~d, *J* = 10.8 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 3.76-3.84 (m, 1H), 3.98 (dd, *J* = 9.3, 5.0 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 4.84-4.86 (m, 1H), 6.86-6.89 (m, 2H), 6.94-6.96 (m, 1H), 7.22-7.31 (m, 10H), 7.40-7.43 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -69.00 (d, *J* = 8.1 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 51.9 (CH), 56.3 (CH_2), 59.6 (CH_2), 64.2 (q, *J* = 28.6 Hz, CH), 78.4 (CH), 116.2 (2×CH), 121.5 (CH), 125.6 (q, *J* = 283.6 Hz, C), 127.1 (CH), 127.4 (CH), 128.5 (4×CH), 129.1 (2×CH), 129.5 (2×CH), 131.1 (2×CH), 135.8 (C), 137.5 (C), 157.7 (C). IR (cm^{-1}): 2941, 1599, 1584, 1489, 1481, 1452, 1439, 1391, 1373, 1306, 1292, 1281, 1229, 1148, 1117, 1074, 1045, 1024, 988, 750, 737, 698, 687. MS (70 eV): *m/z* (%): 430 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{24}H_{23}F_3NOS$: 430.1447 [*M*+H]$^+$, found: 430.1459.

Synthesis of (2*R*,3*R*,4*S*)-4-benzyloxy-3-fluoro-1-isopropyl-2-(trifluoromethyl)pyrrolidine 10o.

To an ice-cooled solution of (2*S*,3*S*)-3-benzyloxy-2-[(1*S*)-2,2,2-trifluoro-1-hydroxyethyl]-1-isopropylazetidine **7e** (0.30 g, 1 mmol, 1 equiv) in dry CH_2Cl_2 (20 mL) was added diethylaminosulfur trifluoride (DAST, 0.32 g, 0.26 mL, 2 mmol, 1 equiv). Then, the resulting solution was heated to reflux and stirred for 2 hours. Afterward, the solution was cooled to room temperature and quenched with sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), dried with $MgSO_4$, filtrated and evaporated in vacuo to afford (2*R*,3*R*,4*S*)-4-benzyloxy-3-fluoro-1-isopropyl-2-(trifluoromethyl)pyrrolidine **10o** in 88% yield (0.27 g, 0.88 mmol). Purification by means of column chromatographic on silica gel provided an analytically pure sample.

Yield 88% (270 mg). Colorless oil. R_f = 0.29 (Petroleumether/EtOAc 9/1). $[\alpha]_D^{25}$ = +9.9 (*c* = 0.23, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 2.99-3.08 (m, 1H), 3.07 (d, *J* = 8.3 Hz, 2H), 3.51 (qdd, *J* = 11.6, 8.7, 4.4 Hz, 1H), 3.80 (dtd, *J* = 21.3, 8.3, 3.9 Hz, 1H), 4.43 (d, *J* = 12.4 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 5.13 (ddd, *J* = 53.9, 4.4, 3.9 Hz, 1H), 7.29-7.37 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -213.57 till -213.42 (m, 1F), -69.26 till -69.20 (m, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 14.2 (CH_3), 22.2 (CH_3), 47.1 (CH_2), 50.8 (CH), 63.5 (qd, *J* = 29.6, 16.8 Hz, CH), 72.2 (CH_2), 76.7 (CH), 89.5 (d, *J* = 196.1 Hz, CH), 124.9 (qd, *J* = 282.2, 2.9 Hz, C), 127.9 (CH), 128.1 (CH), 128.5 (CH), 137.4 (C). IR (cm^{-1}): 2970, 2878, 1456, 1366, 1283, 1165, 1138, 1119, 1094, 1030, 833, 737, 698, 658. MS (70 eV): *m/z* (%): 306 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{20}F_4NO$: 306.1476 [*M*+H]$^+$, found: 306.1473.

Synthesis of 3-amino-2-(trifluoromethyl)pyrrolidines 13 and 14.

As a representative example, the synthesis of (2*R*,3*R*,4*S*)-3-amino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **13a** is described. To a solution of (2*R*,3*R*,4*S*)-3-benzylamino-1-cyclohexyl-4-

phenoxy-2-(trifluoromethyl)pyrrolidine **10g** (84 mg, 0.2 mmol) in methanol (5 mL) was added $Pd(OH)_2$ on activated carbon (20% w/w), and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 4 hours at room temperature while applying 4 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite and evaporation of the solvent in vacuo afforded (2*R*,3*R*,4*S*)-3-amino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine **13a** in a yield of 89% (58 mg, 0.178 mmol) as a colorless oil.

*(2R,3R,4S)-3-Amino-1-cyclohexyl-4-phenoxy-2-(trifluoromethyl)pyrrolidine (**13a**).*

Yield 89% (58 mg). Colorless oil. $[\alpha]_D^{25}$ = +44.9 (*c* = 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01-1.27 (m, 5H), 1.62-1.84 (m, 1H), 2.65-2.70 (m, 1H), 3.09 (dd, *J* = 10.9, 5.2 Hz, 1H), 3.18 (dd, *J* = 10.9, 2.8 Hz, 1H), 3.50-3.59 (m, 1H), 3.78 (dd, *J* = 7.8, 5.3 Hz, 1H), 4.64 (ddd, *J* = 5.3, 5.2, 2.8 Hz, 1H), 6.90-6.98 (m, 3H), 7.25-7.29 (m, 2H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.10 (d, *J* = 8.5 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 24.8 (CH_2), 25.5 (CH_2), 26.1 (CH_2), 26.2 (CH_2), 32.1 (CH_2), 49.2 (CH_2), 55.4 (CH), 59.4 (CH), 62.9 (q, *J* = 27.0 Hz, CH), 77.2 (CH), 115.8 (2×CH), 121.3 (CH), 126.1 (q, *J* = 283.2 Hz, C), 129.5 (2×CH), 157.8 (C). IR (cm^{-1}): 3418, 2930, 2855, 1599, 1587, 1495, 1275, 1240, 1153, 1115, 1043, 754, 692. MS (70 eV): *m/z* (%): 329 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{17}H_{24}F_3N_2O$: 329.1835 [*M*+H]$^+$, found: 329.1843.

*(2R,3R,4S)-3-Amino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine (**13b**).*

Yield 91% (137 mg). Colorless oil. $[\alpha]_D^{25}$ = +28.3 (*c* = 0.17, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (d, *J* = 6.6 Hz, 3H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.54 (br s, 2H), 2.84 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.05 (dd, *J* = 10.6, 3.7 Hz, 1H), 3.15 (septet, *J* = 6.6 Hz, 1H), 3.31-3.40 (m, 1H), 3.46 (dd, *J* = 7.4, 5.2 Hz, 1H), 3.87-3.91 (m, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 4.65 (d, *J* = 12.2 Hz, 1H), 7.27-7.37 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.84 (d, *J* = 8.3 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.5 (CH_3), 21.6 (CH_3), 47.1 (CH_2), 50.1 (CH), 55.0 (CH), 63.4 (q, *J* = 27.7 Hz, CH), 71.8 (CH_2), 78.4 (CH), 126.1 (q, *J* = 282.6 Hz, C), 127.4 (2×CH), 127.6 (CH), 128.4 (2×CH), 138.6 (C). IR (cm^{-1}): 2968, 2916, 2872, 1454, 1269, 1121, 1069, 1028, 733, 696, 635. MS (70 eV): *m/z* (%): 303 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{15}H_{22}F_3N_2O$: 303.1679 [*M*+H]$^+$, found: 303.1688.

*(2R,3R,4S)-3-Amino-4-benzyloxy-2-(trifluoromethyl)pyrrolidine (**14**).*

Yield 89% (116 mg). Colorless oil. $[\alpha]_D^{25}$ = +9.5 (*c* = 0.22, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.90 (br s, 3H), 3.11-3.18 (m, 2H), 3.58-3.66 (m, 1H), 3.70 (dd, *J* = 6.0, 5.4 Hz, 1H), 3.88-3.90 (~dt, *J* = 6.0, 5.7 Hz, 1H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 7.29-7.38 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -69.88 (d, *J* = 8.3 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 48.4 (CH_2), 53.3 (CH), 61.0 (q, *J* = 27.9 Hz, CH), 72.1 (CH_2), 79.0 (CH), 125.6 (q, *J* = 279.9 Hz, C), 127.6 (CH), 127.9 (CH), 128.5 (CH), 137.8 (C). IR (cm^{-1}): 3350, 2926, 2876, 1454, 1281, 1202, 1113, 1028, 735, 696, 610. MS (70 eV): *m/z* (%): 261 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{12}H_{16}F_3N_2O$: 261.1209 [*M*+H]$^+$, found: 261.1209.

Synthesis of (2*R*,3*R*,4*S*)-3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine 15.

To a solution of (2*R*,3*R*,4*S*)-3-benzylamino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **10i** (78 mg, 0.2 mmol) in methanol (5 mL) was added $Pd(OH)_2$ on activated carbon (40% w/w), and the resulting mixture was placed in a Parr apparatus. The inside of the Parr apparatus was then degassed and filled with hydrogen gas, after which the mixture was stirred for 4 days at room temperature while applying 5 bar of hydrogen gas. Filtration of the heterogeneous mixture through Celite and evaporation of the solvent in vacuo afforded (2*R*,3*R*,4*S*)-3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **15** in a yield of 92% (39 mg, 0.184 mmol) as a white solid.

White solid. Mp 70 ± 2 °C. Yield 92%. $[\alpha]_D^{25}$ = +40.5 (*c* = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 2.27 (br s, 3H), 2.81 (dd, *J* = 10.5, 3.6 Hz, 1H), 2.92 (dd, *J* = 10.5, 5.7 Hz, 1H), 3.12-3.22 (m, 1H), 3.39 (dq, *J* = 8.0 Hz, J_{HF} = 7.9 Hz, 1H), 3.53-3.56 (m, 1H), 4.04-4.07 (m, 1H). ^{19}F NMR (282 MHz, ref = $CDCl_3$): -67.78 (d, *J* = 7.9 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.1 (CH_3), 21.8 (CH_3), 49.5 (CH), 50.0 (CH_2), 55.3 (CH), 62.9 (br s, CH), 70.5 (CH), 126.1 (q, *J* = 281.8 Hz, C). IR (cm^{-1}): 3169, 2970, 2938, 1387, 1271, 1177, 1146, 1101, 1080, 1051, 1020, 945, 908, 889. MS (70 eV): *m/z* (%): 213 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_8H_{16}F_3N_2O$: 213.1209 $[M+H]^+$, found: 213.1217.

Synthesis of (2*R*,3*R*,4*S*)-4-benzyloxy-3-isocyanato-1-isopropyl-2-(trifluoromethyl)pyrrolidine 16.

To a solution of (2*R*,3*R*,4*S*)-3-amino-4-benzyloxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **13b** (151 mg, 0.5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added triphosgene (149 mg, 0.5 mmol, 1 equiv). The resulting solution was stirred for 2 hours at room temperature. Afterward, the solution was quenched with sat. $NaHCO_3$ (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and evaporated in vacuo to afford a crude reaction mixture, which was purified by means of silica gel column chromatography to afford (2*R*,3*R*,4*S*)-4-benzyloxy-3-isocyanato-1-isopropyl-2-(trifluoromethyl)pyrrolidine **16** as a colorless oil in a yield of 67% (110 mg, 0.335 mmol).

Yield 67% (110 mg). Colorless oil. R_f = 0.36 (Petroleumether/EtOAc 6/1). $[\alpha]_D^{25}$ = +5.9 (*c* = 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, *J* = 6.4 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 3.03 (d, *J* = 7.1 Hz, 2H), 3.05-3.15 (m, 1H), 3.31-3.40 (qd, J_{HF} = 6.7, *J* = 6.4 Hz, 1H), 3.95 (td, *J* = 7.1, 5.1 Hz, 1H), 4.05-4.07 (m, 1H), 4.56 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 7.30-7.38 (m, 5H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -68.80 (d, *J* = 6.7 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 13.4 (CH_3), 22.0 (CH_3), 46.9 (CH_2), 49.7 (CH), 55.9 (CH), 63.0 (q, *J* = 29.0 Hz, CH), 72.1 (CH_2), 77.0 (CH), 125.0 (q, *J* = 283.3 Hz, C), 126.4 (C), 127.8 (2×CH), 128.1 (CH), 128.6 (2×CH), 136.9 (C). IR (cm^{-1}): 2974, 2257, 1670, 1599, 1566, 1470, 1348, 1277, 1134, 814, 735, 606. MS (70 eV): *m/z* (%): 329 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_{16}H_{20}F_3N_2O_2$: 329.1471 $[M+H]^+$, found: 329.1474.

Synthesis of (1*S*,5*R*,6*R*)-7-isopropyl-6-trifluoromethyl-2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one 17.

To a solution of (2*R*,3*R*,4*S*)-3-amino-4-hydroxy-1-isopropyl-2-(trifluoromethyl)pyrrolidine **15** (106 mg, 0.5 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added triphosgene (149 mg, 0.5 mmol, 1 equiv). The resulting solution was stirred for 2 hours at room temperature. Afterward, the solution was quenched with sat. $NaHCO_3$ (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried with $MgSO_4$, filtered and evaporated in vacuo to afford a crude reaction mixture, which was purified by means of silica gel column chromatography to afford (1*S*,5*R*,6*R*)-7-isopropyl-6-trifluoromethyl-2-oxa-4,7-diazabicyclo[3.3.0]octan-3-one **17** as a colorless oil in a yield of 81% (96 mg, 0.405 mmol).

Yield 81% (96 mg). Colorless oil. R_f = 0.12 (Petroleumether/EtOAc 1/1). $[\alpha]_D^{25}$ = +31.5 (*c* = 0.33, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 6.4 Hz, 3H), 1.17 (d, *J* = 6.8 Hz, 3H), 2.70 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.16-3.29 (m, 2H), 3.30 (~d, *J* = 11.5 Hz, 1H), 4.39-4.43 (m, 1H), 5.00 (~dd, *J* = 7.8, 5.0 Hz, 1H), 5.50 (br s, 1H). ^{19}F NMR (376 MHz, ref = $CDCl_3$): -65.51 (d, *J* = 6.5 Hz, 3F). ^{13}C NMR (100 MHz, ref = $CDCl_3$): δ 12.0 (CH_3), 21.8 (CH_3), 47.1 (CH), 50.4 (CH_2), 56.3 (CH), 64.5 (q, *J* = 27.8 Hz, CH), 76.7 (CH), 124.7 (q, *J* = 281.1 Hz, C), 158.7 (C). IR (cm^{-1}): 3269, 1751, 2976, 1396, 1277, 1233, 1192, 1161, 1125, 1099, 1055, 1026, 961. MS (70 eV): *m/z* (%): 239 (M^++1, 100). HRMS (ESI): *m/z* calcd for $C_9H_{14}F_3N_2O_2$: 239.1002 $[M+H]^+$, found: 239.1000.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of the NMR spectra (^{1}H, ^{19}F, ^{13}C) of all the intermediates **2-9,11** and pyrrolidines **10**, **13-17** synthesized in this work.

Crystal data of compounds **5a**, **5e**, **7a**, **7b** and **10h**.

Computational details

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