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Synthesis of Trifluoromethylated Azetidines, Aminopropanes, 1,3-Oxazinanes, and 1,3-Oxazinan-2-ones Starting from 4-Trifluoromethyl-β-lactam Building Blocks

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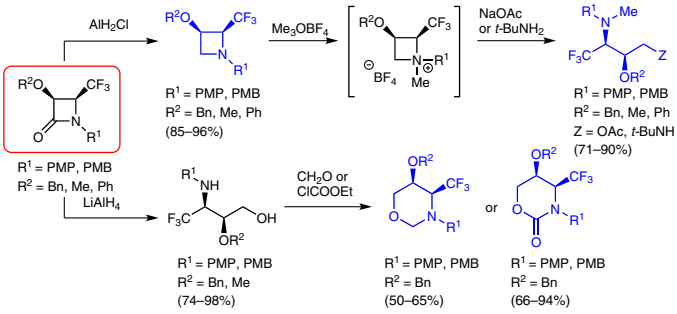

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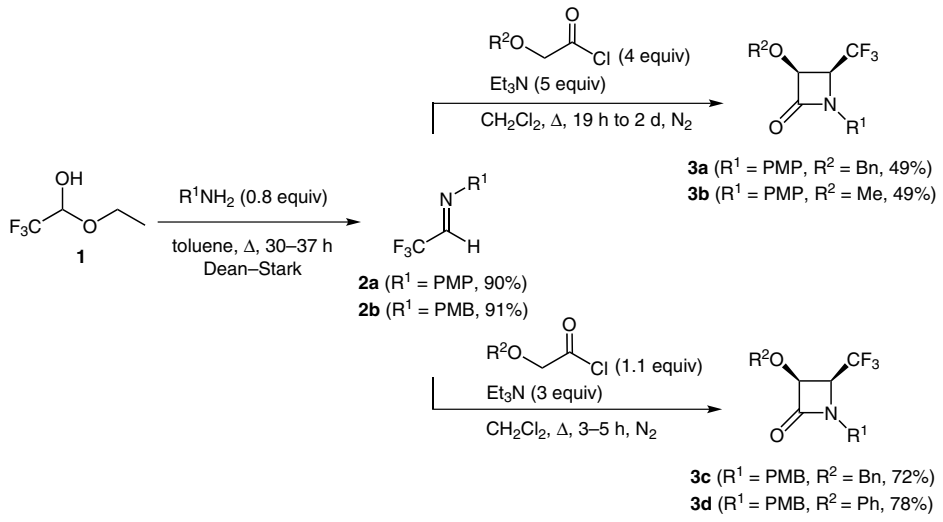
Abstract This paper reports on the preparation of 4-(trifluoromethyl)azetidin-2-ones and their synthetic potential as eligible new building blocks for the construction of CF_3-containing azetidines, diaminopropanes, aminopropanol derivatives, 1,3-oxazinanes, and 1,3-oxazinan-2-ones. This β-lactam building block approach provides a convenient new entry into trifluoromethylated scaffolds as useful synthetic intermediates *en route* to a variety of CF_3-functionalized target structures.

Key words β-lactams, azetidines, aminopropanes, oxazinanes, fluorine, CF_3

Due to their inherent chemical and biological properties, β-lactams or azetidin-2-ones represent an important class of four-membered azaheterocycles. In addition to their celebrated antibacterial activities, β-lactams are for example known to inhibit HIV-1 protease[1a] and to exhibit antitumor or antimalarial effects,[1b,c] enabling their use in different therapeutic areas. Besides their pharmacological relevance, β-lactams are also considered as important building blocks in organic chemistry for the synthesis of a wide variety of acyclic and heterocyclic compounds, which in their turn can serve as synthons for the development of novel, biologically relevant target structures.[1d,e]

Because of the specific chemical and physical properties of fluorine, the introduction of a CF_3 moiety in pharmacologically active compounds is known to convey beneficial biological effects to the resulting molecules, hence the increasing interest from organic and medicinal chemists in polyfunctional CF_3-substituted scaffolds.[2] Nonetheless, the preparation of libraries of sensitive and strained CF_3-decorated structures has been thwarted by difficulties associated with the (late-stage) introduction of a CF_3 group. As an alternative strategy, the application of CF_3-containing building blocks can be pursued, thus avoiding the use of trifluoromethylating agents during the synthesis. In that respect, the direct installation of a trifluoromethyl group on azetidin-2-ones comprises an interesting field of research and is increasingly applied to modify the biological and pharmacological properties of these compounds and their transformation products.[3,4]

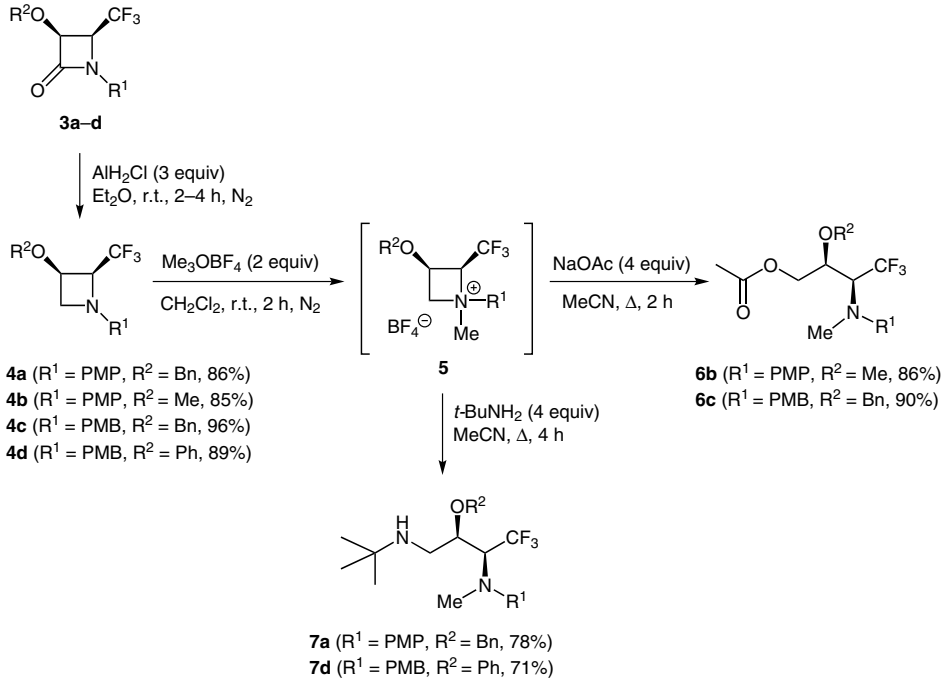
In the present paper, the synthesis of novel 3-alkoxy/aryloxy-4-(trifluoromethyl)azetidin-2-ones is aspired, and their synthetic elaboration into a variety of biologically relevant nitrogen compounds is evaluated to assess their versatility and applicability. A powerful method in organic synthesis involves the use of β-lactams for the preparation of functionalized azetidines by treatment with monochloroalane (AlH_2Cl), providing selective carbonyl removal without affecting the four-membered-ring system. Although this approach has been widely applied on nontrifluoromethylated β-lactams,[5] the selective reduction of 4-(trifluoromethyl)azetidin-2-ones to azetidines has not been reported in the literature to date. Therefore, the monochloroalane reduction of 4-(trifluoromethyl)azetidin-2-ones as an entry into 2-(trifluoromethyl)azetidines will be evaluated in this study. Subsequently, activation of these novel (trifluoromethyl)azetidines and regiospecific ring opening of the resulting azetidinium ions with different nucleophiles will be pursued *en route* to a diversity of functionalized trifluoromethyl-substituted aminopropanes as potential leads for the synthesis of biologically relevant compounds. In addition, the synthetic potential of 4-trifluoromethyl-β-lactams will be further investigated by converting them into amino alcohols upon a $LiAlH_4$-mediated reductive ring opening, analogous to the known reactivity of their nonfluo-



Scheme 1 Staudinger synthesis of 4-(trifluoromethyl)azetidin-2-ones **3**

rinated counterparts.[6] Furthermore, cyclization of the thus obtained CF_3-substituted γ-amino alcohols with formation of synthetically and biologically relevant 1,3-oxazinane and 1,3-oxazinan-2-one heterocycles is proposed.

In a first step of this study, the reaction of commercially available 1-ethoxy-2,2,2-trifluoroethanol (**1**) with 4-methoxyaniline or 4-methoxybenzylamine in toluene under Dean–Stark conditions gave rise to the desired trifluoromethyl aldimines **2** in excellent yields.[7] Subsequently, these imines were treated with an (alkyl/aryl)oxyacetyl chloride in the presence of triethylamine, affording the corresponding *cis*-3-alkoxy/aryloxy-4-(trifluoromethyl)azetidin-2-ones **3** (Scheme 1).[7–10] Only for 3-methoxy-1-(4-methoxyphenyl)-β-lactam **3b**, a minor amount of the corresponding *trans* isomer was observed as well (*cis*/*trans* = 10:3). The *cis* selectivity was determined based on the ^{1}H NMR spectra of β-lactams **3**, as the observed coupling constants between the two vicinal protons at C3 and C4 (J = 5–6 Hz, $CDCl_3$) cor-



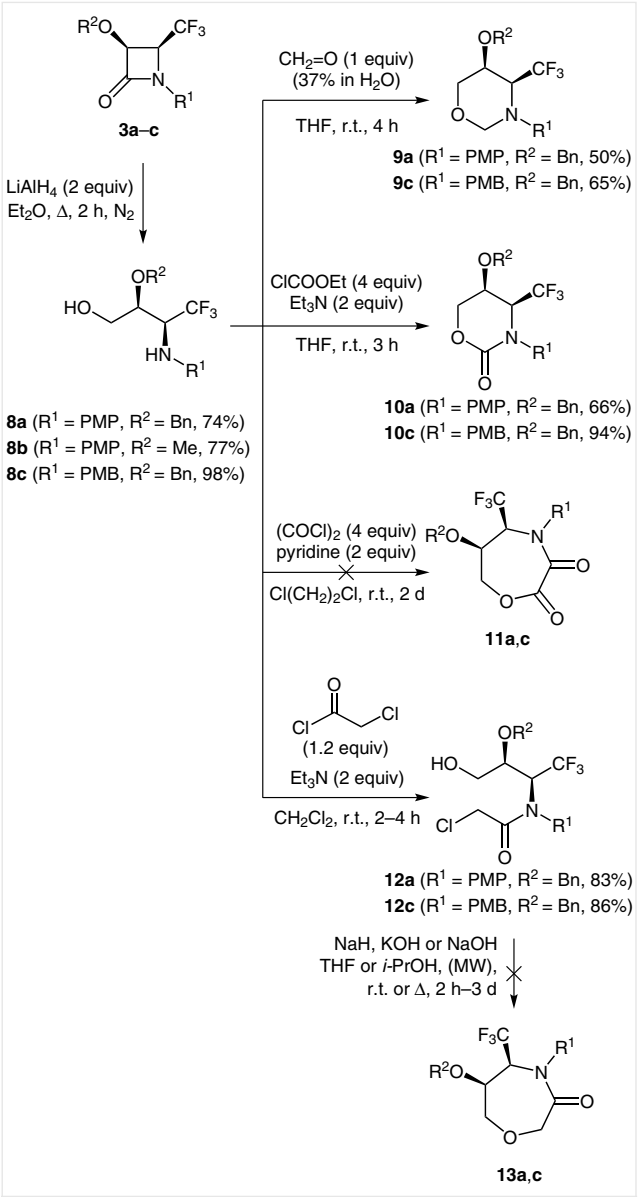
Scheme 2 Monochloroalane reduction of 4-(trifluoromethyl)azetidin-2-ones **3** towards azetidines **4** and their subsequent ring opening

responded well with those reported in the literature for *cis*-β-lactams.[7b,c,8,9] In this way, novel *cis*-trifluoromethyl-β-lactams **3a**–**d** were prepared *via* a diastereoselective cyclocondensation reaction between an imine **2**, prepared from 1-ethoxy-2,2,2-trifluoroethanol (**1**), and an *in situ* generated ketene.

In the next part, the reduction of the synthesized 4-(trifluoromethyl)azetidin-2-ones **3** by means of monochloroalane was evaluated to provide an entry into 2-(trifluoromethyl)azetidines **4**, and treatment of β-lactams **3** with monochloroalane, *in situ* prepared from $LiAlH_4$ and $AlCl_3$, furnished the desired azetidines **4** in excellent yields (Scheme 2).[5,11] It should be noted that little information on 2-(trifluoromethyl)azetidines is available in the literature.[12] The application of these novel *cis*-3-alkoxy/aryloxy-2-(trifluoromethyl)azetidines **4** as building blocks for the synthesis of a diversity of functionalized trifluoromethyl-substituted aminopropanes was evaluated next.[6,7a] In that respect, alkylation of 2-(trifluoromethyl)azetidines **4** towards the corresponding azetidinium ions **5** utilizing trimethyloxonium tetrafluoroborate ($Me_3O{\cdot}BF_4$) and subsequent ring opening by treatment with sodium acetate or *tert*-butylamine, afforded the desired *syn*-2-alkoxy/aryloxy-3-amino-4,4,4-trifluorobutyl acetates **6b**,**c**[13] and *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutane-1,3-diamines **7a**,**d**,[14] respectively, in good to excellent yields (Scheme 2). It should be noted that, in line with our previous findings on similar substrates, ring opening of 2-(trifluoromethyl)azetidinium salts **5** proceeded regiospecifically at C4, in contrast with the reactivity of azetidinium salts bearing other types of electron-withdrawing groups (e.g., acyl or cyano) at C2.[2c]

In light of the known biological properties of compounds bearing a functionalized aminopropane skeleton,[6,15,16] acetates **6b**,**c** and diamines **7a**,**d** might constitute valuable new chemical entities for further elaboration. For example, the class of diaminopropanols is known for its protease-inhibiting, antiarrhythmic, and anesthetic activity.[15] Moreover, due to the specific properties of fluorine, trifluoromethyl-containing functionalized aminopropanol derivatives could play an important role in the development of analogues of these bioactive compounds.[7a,17]

On the other hand, *cis*-azetidin-2-ones **3** were subjected to a reductive ring opening by means of lithium aluminium hydride, in analogy with the known chemical behavior of their nonfluorinated counterparts.[6] As illustrated in Scheme 3, treatment of β-lactams **3a**–**c** with lithium aluminium hydride afforded the corresponding *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutanols **8a**–**c** in good yields.[5b,18] This *syn* relationship in amino alcohols **8** is a direct consequence of the selective Staudinger synthesis of stereodefined *cis*-β-lactams **3**, followed by transfer of the stereochemical information through the following $LiAlH_4$-mediated reduction step.



Scheme 3 Reductive ring opening of 4-(trifluoromethyl)azetidin-2-ones **3** and formation of oxazinanes **9**, oxazinan-2-ones **10**, α-chloroamides **12** and attempted formation of 1,4-oxazepanes **11**and**13**

These γ-amino alcohols **8** bear significant biological potential because of their structural similarity to several classes of bioactive compounds. For example, the 1-alkylamino-3-aryloxypropan-2-ol family, including propranolol and timolol, provides β-adrenergic blocking agents (β-blockers) for the treatment of various vascular disorders.[16] Moreover, 2-alkoxy-3-amino-3-arylpropan-1-ols have recently been shown to exhibit a promising antimalarial activity.[6b] The introduction of a trifluoromethyl substituent in these scaffolds could induce interesting beneficial changes in their biological properties.[19] Therefore, CF_3-substituted γ-amino alcohols **8**, which have not been described in the

literature so far, are expected to serve as valuable templates for further development in the field of medicinal chemistry and chemical biology.

With the intention to introduce conformational constraint into the target compounds, *syn*-2-alkoxy/aryloxy-4,4,4-trifluorobutanols **8a**,**c** were subsequently converted into new trifluoromethylated oxazinanes **9** and oxazinan-2-ones **10**. Several literature reports describe the synthesis of nonfluorinated oxazinanes starting from amino alcohols, either as biologically relevant targets or as synthons for further elaboration.[16b,c] 3-Aminopropan-1-ols **8a**,**c** were thus treated with formaldehyde (37% in water), resulting in new *cis*-5-benzyloxy-4-trifluoromethyl-1,3-oxazinanes **9a**,**c**.[20] 3-Aminopropan-1-ols **8a**,**c** were also shown to be efficient precursors for the synthesis of a new class of CF_3-substituted oxazinan-2-ones **10**, of which nonfluorinated counterparts have been explored as inhibitors in the treatment of obesity and insulin resistance,[21] and fluorinated analogues have been applied in breast tumor imaging.[7] For this purpose, 3-aminopropan-1-ols **8a**,**c** were treated with ethyl chloroformate and triethylamine, affording *cis*-5-benzyloxy-4-trifluoromethyl-1,3-oxazinan-2-ones **10a**,**c**[22] in good yields (Scheme 3). The 1,3-oxazinan-2-one motif has been encountered as a core structure in many natural products and pharmaceutical drugs, and these heterocycles have for example been explored as inhibitors of 11-β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) or as antibacterial agents.[21a,c] Besides, compounds accommodating the 1,3-oxazinane system have also successfully been screened for their *in vitro* antiplasmodial activity and cytotoxicity.[16b]

In addition, the preparation of seven-membered oxazepane analogues **11a**,**c** as potential targets[21a,b] was attempted by direct treatment of *syn*-2-benzyloxy-4,4,4-trifluorobutanols **8a**,**c** with oxalyl chloride in the presence of pyridine in 1,2-dichloroethane, in analogy with the synthesis of 1,3-oxazinan-2-ones **10**.[23] However, this cyclization reaction did not proceed as anticipated, resulting in complex mixtures. Other methods for constructing 1,4-oxazepanes were also tested, including the initial conversion of the amino group in butanols **8a**,**c** into the corresponding amides **12a**,**c** via *N*-acylation using chloroacetyl chloride and triethylamine (Scheme 3), followed by treatment with different bases (KOH, NaOH, or NaH) under different reaction conditions (solvent–time–temperature combinations) to effect cyclization towards 1,4-oxazepan-3-ones **13**. However, none of the conditions tested seemed appropriate to produce the desired seven-membered heterocycles.

In conclusion, 4-trifluoromethyl-β-lactams were efficiently prepared and deployed as novel building blocks in the synthesis of CF_3-containing molecules with potential biological relevance. To that end, a suitable synthetic method was established for the conversion of these 4-(trifluoromethyl)azetidin-2-ones into novel 3-alkoxy/aryloxy-2-(trifluoromethyl)azetidines by means of a selective monochloroalane reduction protocol. Furthermore, the synthetic potential of 2-CF_3-azetidines was demonstrated by their conversion into a variety of α-CF_3-substituted diaminopropanes and aminopropanol derivatives via transient azetidinium intermediates, which could serve as valuable precursors for the preparation of different target compounds. In addition, the conversion of 4-trifluoromethyl-β-lactams by means of reductive ring opening using lithium aluminium hydride furnished functionalized CF_3-containing γ-amino alcohols in a concise and efficient manner. Cyclization of the latter γ-amino alcohols employing formaldehyde or ethyl chloroformate afforded a convenient entry into the corresponding new *cis*-4-trifluoromethyl-1,3-oxazinanes and *cis*-4-trifluoromethyl-1,3-oxazinan-2-ones, respectively.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561316.

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(11) ***cis*-3-Benzyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidine (4a)**
To an ice-cooled solution of $AlCl_3$ (2.22 g, 16.62 mmol, 3 equiv) in dry Et_2O (30 mL), $LiAlH_4$ (0.63 g, 16.62 mmol, 3 equiv) was carefully added dropwise under N_2. The reaction mixture was allowed to reach room temperature and was then heated for 30 min at reflux temperature. Afterwards, the reaction mixture was cooled to 0 °C and *cis*-azetidin-2-one **3a** (1.94 g, 5.54 mmol, 1 equiv) was added. After stirring for 3 h at room temperature, the reaction was quenched with H_2O (15 mL) and filtered through a short pad of Celite®. Extraction with CH_2Cl_2 (3 × 10 mL), drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded *cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidine (**4a**) in 86% yield in high purity (>95% based on NMR); orange crystals; yield 86%; mp 59 °C. Elem. Anal. calcd. for $C_{18}H_{18}F_3NO_2$: C 64.09, H 5.38, N 4.15; found: C 63.96, H 5.14, N 4.12. IR (ATR): ν_{max} = 1510, 1242, 1124, 813, 735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.75 (3 H, s), 3.93 (1 H, dd, *J* = 8.3, 7.7 Hz), 4.17 (1 H, dd, *J* = 8.3, 4.4 Hz), 4.43–4.61 (2 H, m), 4.52 and 4.68 (2 × 1 H, 2 d, *J* = 11.6 Hz), 6.50–6.56 and 6.79–6.86 (4 H, 2 m), 7.29–7.38 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 59.7, 67.4 (q, *J* = 31.2 Hz), 67.8, 72.3, 113.1, 114.7, 124.8 (q, *J* = 281.5 Hz), 127.6, 128.0, 128.5, 137.2, 142.5, 153.0. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –70.03 (3 F, d, *J* = 6.6 Hz). MS (70 eV): *m/z* (%) = 338 (100) [M^+ + H]. ESI-HRMS: *m/z* calcd for $C_{18}H_{19}F_3NO_2^+$: 338.1362 [M + H]$^+$; found: 338.1365.

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(13) ***syn*-2-Methoxy-3-[*N*-(4-methoxyphenyl)-*N*-methylamino]-4,4,4-trifluorobutyl Acetate (6b)**
In a flame-dried flask under nitrogen atmosphere, $Me_3O{\cdot}BF_4$ (0.17 g, 1.14 mmol, 2 equiv) was added to an ice-cooled solution of *cis*-3-methoxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidine (**4b**, 0.15 g, 0.57 mmol, 1 equiv) in dry CH_2Cl_2 (4 mL). After stirring for 2 h at room temperature, the solvent was evaporated, and the resulting residue was redissolved in MeCN (5 mL), after which NaOAc (0.19 g, 2.28 mmol, 4 equiv) was added. After stirring at reflux temperature for 2 h, the reaction mixture was poured into a sat. solution of $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (3 × 5 mL), and washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded *syn*-4,4,4-trifluoro-2-methoxy-3-[*N*-(4-methoxyphenyl)-*N*-methylamino]butyl acetate (**6b**), which was purified by means of preparative TLC (hexane–EtOAc); pale yellow oil, yield 86%; R_f = 0.07 (PE–EtOAc, 95:5). IR (ATR): ν_{max} = 1745 (CO), 1512, 1242, 1097, 1053, 1038, 818 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.01 (3 H, s), 3.02 (3 H, s), 3.48 (3 H, s), 3.76 (3 H, s), 3.91 (1 H, qd, *J* = 5.5, 1.1 Hz), 4.14 (1 H, dd, *J* = 12.1, 6.6 Hz), 4.21–4.27 (2 H, m), 6.82 (4 H, br s). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.6, 34.7, 55.6, 59.4, 61.9 (q, *J* = 26.9 Hz), 77.8, 114.6, 116.0, 125.9 (q, *J* = 288.5 Hz), 145.0, 152.9, 170.4. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –68.36 (3 F, d, *J* = 7.9 Hz). MS (70 eV): *m/z* (%) = 336 (80) [M^+ + H], 321 (100) [M^+ – CH_3]. ESI-HRMS: *m/z* calcd for $C_{15}H_{21}F_3NO_4^+$: 336.1417 [M + H]$^+$; found: 336.1433.

(14) ***syn*-2-Benzyloxy-4,4,4-trifluoro-N^3-(4-methoxyphenyl)-N^3-methyl-N^1-*tert*-butylbutane-1,3-diamine (7a)**
In a flame-dried flask under nitrogen atmosphere, $Me_3O{\cdot}BF_4$ (0.13 g, 0.88 mmol, 2 equiv) was added to an ice-cooled solution of *cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidine (**4a**, 015 g, 0.44 mmol, 1 equiv) in dry CH_2Cl_2 (3 mL). After stirring for 2 h at room temperature, the solvent was evaporated, and the residue was redissolved in MeCN (3 mL), followed by the addition of *tert*-butylamine (0.13 g, 1.76 mmol, 4 equiv). After heating for 4 h at reflux temperature, the reaction mixture was poured into a sat. solution of $NaHCO_3$ (4 mL), extracted with CH_2Cl_2 (3 × 3 mL), and washed with brine (3 × 3 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent yielded *syn*-2-benzyloxy-4,4,4-trifluoro-N^3-(4-methoxyphenyl)-N^3-methyl-N^1-*tert*-butylbutane-1,3-diamine (**7a**), which was purified by means of preparative TLC (hexane–EtOAc, 95:5); pale yellow oil, yield 78%; R_f = 0.04 (PE–EtOAc, 95:5). IR (ATR): ν_{max} = 3308 (NH), 1512, 1243, 1144, 1113, 1029, 814, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.95 (9 H, s), 2.68 (1 H, dd, *J* = 12.1, 7.2 Hz), 2.77 (1 H, dd, *J* = 12.1, 5.5 Hz), 3.04 (3 H, s), 3.77 (3 H, s), 3.98–4.01 (1 H, m), 4.51 (1 H, dq, *J* = 8.4, 5.0 Hz), 4.59 and 4.67 (2 × 1 H, 2 d, *J* = 11.6 Hz), 6.83 and 6.89 (2 × 2 H, 2 d, *J* = 8.8 Hz), 7.29–7.36 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.9, 34.8, 42.4, 50.5, 55.8, 62.1 (q, *J* = 26.6 Hz), 73.6, 79.1, 114.7, 115.7, 126.4 (q, *J* = 288.4 Hz), 127.9, 128.5, 138.2, 145.2, 152.6. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –67.85 (3 F, d, *J* = 9.2 Hz). MS (70 eV): *m/z* (%) = 425 (100) [M^+ + H]. ESI-HRMS: *m/z* calcd for $C_{23}H_{32}F_3N_2O_2^+$: 425.2410 [M + H]$^+$; found: 425.2421.

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(18) ***syn*-2-Benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol (8a)**

To an ice-cooled solution of *cis*-3-benzyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**3a**; 0.39 g, 1.1 mmol, 1 equiv) in Et_2O (7 mL) was added $LiAlH_4$ (2.2 mL, 2.2 mmol, 2 equiv, 1 M in Et_2O) in small portions whilst stirring under N_2. After heating for 2 h at reflux temperature, the reaction mixture was cooled to 0 °C, quenched with H_2O (5 mL) and filtered through a short pad of Celite®. Extraction with Et_2O (3 × 5 mL), drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded *syn*-2-benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol (**8a**), which was purified by recrystallization (heptane–EtOAc = 8:2); white crystals, yield 74%; mp 104 °C (from heptane–EtOAc 8:2). IR (ATR): ν_{max} = 3418 (NH), 3372 (OH), 1516, 1246, 1151, 1122, 1065, 1031, 818 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.16 (1 H, br s), 3.50–3.56 and 3.60–3.66 (2 × 1 H, 2 m), 3.70 (3 H, s), 3.95 (1 H, dd, *J* = 6.6, 6.1 Hz), 4.00–4.04 (1 H, m), 4.15 (1 H, d, *J* = 9.9 Hz), 4.59 (1 H, d, *J* = 11.0 Hz), 4.66 (1 H, d, *J* = 11.0 Hz), 6.63 and 6.74 (2 × 2 H, 2 d, *J* = 8.8 Hz), 7.31–7.37 (5 H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.7, 56.4 (q, *J* = 28.8 Hz), 61.1, 73.6, 76.3, 114.9, 115.1, 126.0 (q, *J* = 285.0 Hz), 128.20, 128.25, 128.6, 137.4, 140.6, 152.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –73.13 (3 F, d, *J* = 6.6 Hz). MS (70 eV): *m/z* (%) = 356 (100) $[M^+ + H]$. ESI-HRMS: *m/z* calcd for $C_{18}H_{21}F_3NO_3^+$: 356.1468 $[M + H]^+$; found: 356.1476.

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(20) ***cis*-5-Benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane (9a)**

To a solution of *syn*-2-benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol (**8a**; 0.50 g, 1.41 mmol, 1 equiv) in THF (20 mL) was added formaldehyde (0.11 g, 1.41 mmol, 1 equiv, 37% solution in H_2O). The resulting mixture was stirred for 4 h at room temperature, after which the solvent was removed *in vacuo*. Water (100 mL) was added to the mixture. Extraction with EtOAc (3 × 70 mL), drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded *cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane (**9a**), which was purified by means of recrystallization (hexane–EtOAc, 8:1); white crystals, yield 50%; mp 58.5 °C (from hexane–EtOAc, 8:1). IR (ATR): ν_{max} = 1510, 1360, 1252, 1240, 1171, 1154, 1094, 1029, 983, 909, 810, 737, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (3 H, s), 3.85–3.92 (1 H, m), 3.96–4.03 (2 H, m), 4.08–4.17 (1 H, m), 4.48 and 4.65 (2 × 1 H, 2 d, *J* = 11.6 Hz), 4.80 and 4.85 (2 × 1 H, 2 d, *J* = 11.7 Hz), 6.82 and 7.09 (2 × 2 H, 2 d, *J* = 9.0 Hz), 7.28–7.35 (5 H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.6, 62.1 (q, *J* = 27.6 Hz), 65.8, 68.1, 71.9, 77.6, 114.5, 121.7, 125.8 (q, *J* = 285.0 Hz), 127.6, 128.0, 128.5, 137.3, 144.0, 155.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –64.87 (3 F, d, *J* = 9.2 Hz). MS: *m/z* (%) = 368 (100) $[M^+ + H]$. ESI-HRMS: *m/z* calcd for $C_{19}H_{21}F_3NO_3^+$: 368.1468 $[M + H]^+$; found: 368.1480.

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(22) ***cis*-5-Benzyloxy-4-trifluoromethyl-3-(4-methoxyphenyl)-1,3-oxazinan-2-one (10a)**

To a solution of *syn*-2-benzyloxy-4,4,4-trifluoro-3-(4-methoxyphenylamino)butan-1-ol (**8a**, 0.1 g, 0.28 mmol, 1 equiv) in dry THF (20 mL) was added Et_3N (0.06 g, 0.56 mmol, 2 equiv) at 0 °C. Ethyl chloroformate (0.12 g, 1.13 mmol, 4 equiv) was added dropwise to the solution. The mixture was stirred at room temperature for 4 h, the solvent was removed *in vacuo*, and the residue was redissolved in EtOAc (20 mL) and washed with H_2O (2 × 20 mL). The aqueous phase was extracted with EtOAc (2 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent *in vacuo* afforded *cis*-5-benzyloxy-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one (**10a**), which was further purified by means of recrystallization from EtOH to white crystals, yield 66%; mp 141 °C (EtOH). IR (ATR): ν_{max} = 1700 (CO), 1514, 1415, 1261, 1238, 1136, 1167, 1036, 827, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (3 H, s), 4.32–4.43 (3 H, m), 4.47–4.52 (1 H, m), 4.67 and 4.75 (2 × 1 H, 2 d, *J* = 11.6 Hz), 6.90 and 7.14 (2 × 2 H, 2 d, *J* = 8.9 Hz), 7.35–7.43 (5 H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 55.5, 60.9 (q, *J* = 28.0 Hz), 65.8, 68.0, 72.5, 114.6, 124.0 (q, *J* = 285.8 Hz), 128.0, 128.5, 128.7, 128.8, 134.3, 136.1, 151.3, 159.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –66.96 (3 F, d, *J* = 7.7 Hz). MS: *m/z* (%) = 382 (100) $[M^+ + H]$. ESI-HRMS: *m/z* calcd for $C_{19}H_{19}F_3NO_4^+$: 382.1261 $[M + H]^+$; found: 382.1261.

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