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# Use of 3-Hydroxy-4-(trifluoromethyl)azetidin-2-ones as Building Blocks for the Preparation of Trifluoromethyl-Containing Aminopropanes, 1,3-Oxazinan-2-ones, Aziridines, and 1,4-Dioxan-2-ones

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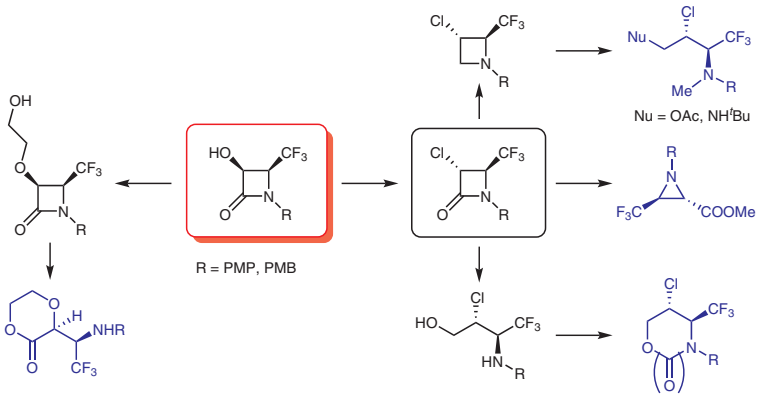


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**Abstract** 3-Hydroxy-4-(trifluoromethyl)azetidin-2-ones were synthesized from the corresponding 3-benzyloxy-β-lactams and successfully transformed into new 3-chloro-4-(trifluoromethyl)azetidin-2-one building blocks. The latter chlorides were shown to be eligible precursors for the construction of $CF_3$-containing aminopropanes, 1,3-oxazinanes, 1,3-oxazinan-2-ones, and aziridines. In addition, 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones proved to be interesting substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones via intramolecular cyclization of 3-(2-hydroxyethoxy)-β-lactam intermediates.

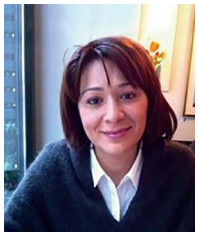
## Introduction

Given the fact that nearly 30% of the leading blockbuster drugs contain at least one fluorine atom in their structure, fluorinated molecules are considered to be key building blocks in medicinal chemistry and hence attractive targets in organic synthesis.[1] The increasing interest in fluorinated compounds is due to the beneficial effect of fluorine on different properties of bioactive agents, and thus, organic chemistry has witnessed the development of numerous synthetic methods to incorporate one or more fluorine atoms into organic structures in recent years.[2] An important part of these endeavors has been devoted to the introduction of a trifluoromethyl group into (constrained) nitrogen ring systems,[3] such as β-lactams. Besides their interesting pharmacological properties, azetidin-2-ones or β-lactams also represent important compounds in organic synthesis due to their high ring strain, which allows for further elaboration toward a variety of nitrogen-containing acyclic and heterocyclic target compounds. In light of the favorable effects of fluorine introduction, β-lactams bearing a trifluoromethyl group comprise interesting entities for the construction of novel targets with promising bioactivities. For example, $CF_3$-substituted β-lactams have been applied for the modification of the taxol side chain to generate second-generation fluoro-taxoids, which exhibit substantially better in vitro potency against several human cancer cell lines than the parent taxoids.[4] In general, $CF_3$-containing molecules can be synthesized by either a late-stage trifluoromethylation approach or by a building block strategy.[5] The preparation of sensitive and strained $CF_3$-decorated structures, however, is often hampered by difficulties associated with the late-stage introduction of the $CF_3$ group. As an alternative, the application of $CF_3$-containing building blocks can be practiced, thus avoiding the use of trifluoromethylating agents during the synthesis. The most important synthetic routes toward 4-(trifluoromethyl)azetidin-2-ones using the building block strategy are based on [2+2] ketene-imine cyclocondensations (Staudinger synthesis), enolate-imine cyclocondensations, intramolecular N-acylations, intramolecular C-alkylations, ring expansions of aziridines, the Kinugasa reaction, and the Reformatsky reaction.[6] However, the reactivity study of 4-(trifluoromethyl)azetidin-2-ones toward both ring opening and ring transformation for

## Biographical Sketches

**Hang Dao Thi** was born in 1987 in Hai Duong (Vietnam). She obtained a Master's degree in Natural Products Synthesis Medicinal Chemistry, Chemical Sciences at Rennes I University (France) in 2011, with a thesis on the isolation of the low polar chemical composition of the hexane fraction from *S. philipinense* (Stereocaulaceae) using different methods. Currently, she is a Ph.D. student working at the Department of Sustainable Organic Chemistry and Technology at Ghent University (Belgium) under the guidance of Prof. Matthias D'hooghe. Her research interests are in the synthesis and synthetic application of $CF_3$-substituted β-lactams for the construction of biologically $CF_3$-substituted mono- and spirocyclic azaheterocycles.

**Giang Le Nhat Thuy** was born in 1984 in Dong Nai (Vietnam). She received a Ph.D. in 2014 (Doctor in Organometallic Chemistry) from Irkutsk National Research Technical University, Russia, under the supervision of Prof. Dr. Baryshok V. P. Since 2015, she became researcher at Laboratory of Medicinal Chemistry at the Institute of Chemistry, Vietnam Academy of Science and Technology in Hanoi (Vietnam). She performed a short postdoctoral stay with Prof. Dr. Matthias D'hooghe at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University (Belgium) in the field of synthesis of β-lactams in 2016. Her main research interests are focused on the synthesis and deployment of $CF_3$-substituted β-lactams for the construction of biologically $CF_3$-substituted mono- and spirocyclic azaheterocycles and the synthesis of different classes of bioactive heterocyclic compounds.



**Saron Catak** joined the Department of Chemistry at Bogazici University as full-time faculty in 2013 and is currently an Associate Professor working in the field of computational chemistry. She is also a Guest Professor at the Center for Molecular Modeling (CMM), Ghent University since 2015. She obtained a joint Ph.D. in Computational Chemistry from the University of Lorraine (Nancy, France) and Bogazici University in 2008. She was a postdoctoral researcher in Prof. Ken N. Houk's group at the University of California, Los Angeles, before joining the Center for Molecular Modeling (CMM) at Ghent University as a research associate. Prior to joining the Department of Chemistry at Bogazici University, she worked at Syngenta Crop Protection (Basel, Switzerland) as team leader in 'computer-aided drug design'. In 2014, she co-founded the 'Computational Chemistry and Biochemistry' research group at Bogazici University. Her main research topics consist of first principles modeling of catalytic processes, biological reactions in proteins, heterogeneous reactions on surfaces, and multiscale-modeling of nanomaterials for environmental purposes.

**Veronique Van Speybroeck** is full professor at the Ghent University within the Faculty of Engineering and Architecture. She obtained her Ph.D. in 2001 at Ghent University on a subject dealing with theoretical simulations of chemical reactions with static and dynamical approaches. Together with Prof. M. Waroquier she founded the Center for Molecular Modeling (CMM) at that time. She is now leading the center, which is currently composed of about 40 researchers. She built up a large expertise in first principle kinetics in nanoporous materials in the frame of an ERC starting grant, awarded in 2009. Her current research focuses on first principle molecular dynamics simulations of complex chemical transformation in nanoporous materials, for which she received an ERC Consolidator grant in 2015. She is an elected member of the Royal (Flemish) Academy for Science and the Arts of Belgium.

**Tuyen Van Nguyen** was born in Thanh Hoa province, Vietnam, in 1961. He received his Ph.D. under the supervision of Professor Dr. P. F. Vlad in 1991, Kishinev, Moldavia. From May 1993 to October 1995, he worked as a postdoctoral fellow at the Department of Pharmacognosy, College of Pharmacy, University of Illinois at Chicago, USA under the supervision of Prof. Dr. H. S. H. Fong. From 1998 to 2003, he performed postdoctoral research at the Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Belgium, under the guidance of Prof. N. De Kimpe. Since 1993, he has been head of the Laboratory of Medicinal Chemistry at the Institute of Chemistry, Vietnamese Academy of Science and Technology in Hanoi (Vietnam) and since 2007 he has been Deputy Director of the Institute of Chemistry, then since 2010 he has been Director of the Institute of Chemistry. He is full professor at the Institute of Chemistry – Vietnam Academy of Science and Technology established in 2013. He has published over 120 peer-reviewed articles. His research is focused on azaheterocyclic chemistry and the synthesis of biologically active compounds used in medicine.

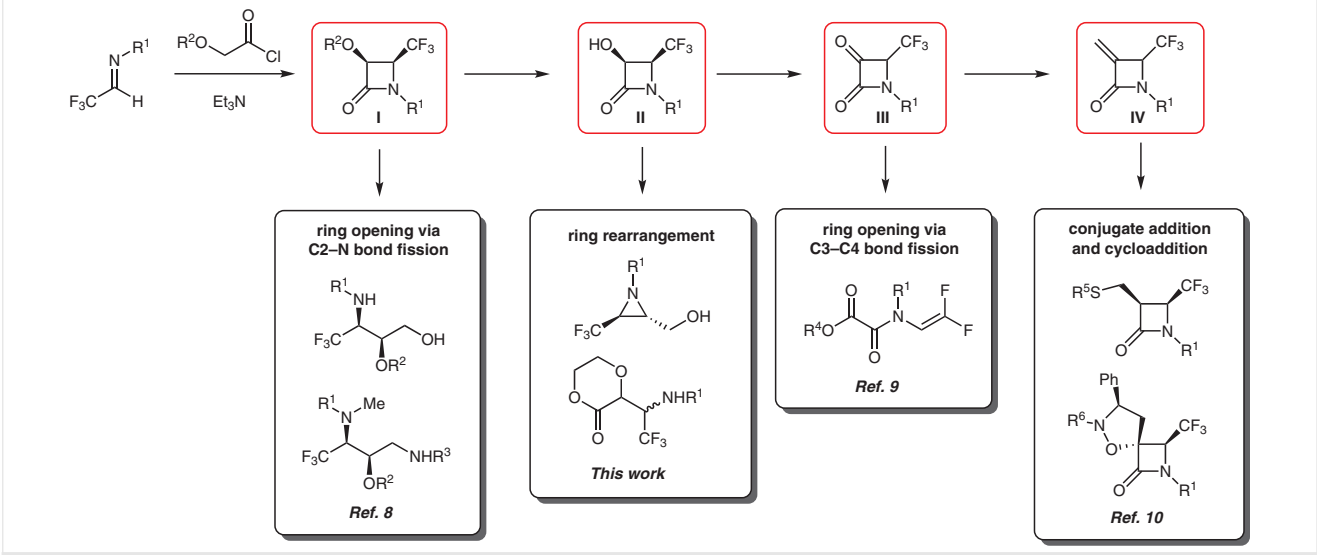
**Matthias D'hooghe** was born in Kortrijk, Belgium, in 1978. He received a Master's degree in 2001 (Master of Science in Bioscience Engineering: Chemistry) and a Ph.D. in 2006 (Doctor in Applied Biological Sciences: Chemistry), both from Ghent University, Belgium, with Prof. N. De Kimpe as promoter. In 2007, he became postdoctoral assistant at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, and in 2009 he performed a short postdoctoral stay with Prof. D. Vogt at Eindhoven University of Technology (The Netherlands) in the field of homogeneous catalysis. In October 2010, he was promoted to Professor (Research Professor) at the Department of Sustainable Organic Chemistry and Technology (Ghent University), and he was granted tenure in 2015. His main research interests include the chemistry of small-ring azaheterocycles, with a special focus on aziridines, azetidines and β-lactams, and the synthesis of different classes of bioactive heterocyclic compounds. Prof. D'hooghe has been elected as a laureate of the DSM Science & Technology Awards 2007, finalist of the European Young Chemist Award 2012 and recipient of the Thieme Chemistry Journal Award 2013. He is the author of 140 publications in international peer-reviewed journals.

the preparation of trifluoromethylated amines and heterocyclic compounds has received very little attention up to now, in sharp contrast to their non-fluorinated analogues.[4,7]

Because of the versatile synthetic potential of β-lactams on the one hand and the beneficial impact of the trifluoromethyl group on biological properties on the other hand, we recently embarked on the synthesis and synthetic application of 4-trifluoromethyl-β-lactams as new building blocks in organic chemistry. Within that framework, [2+2] cyclocondensation between 2,2,2-trifluoroethan-1-imines, prepared from the commercially available 1-ethoxy-2,2,2-trifluoroethanol under Dean–Stark conditions, and the ketenes derived from alkoxy/aryloxyacetyl chlorides provided a convenient access to 3-alkoxy/aryloxy-4-trifluoromethyl-β-lactams **I** as a first new class of building blocks (Scheme 1). The aptitude of these systems **I** with respect to ring-opening reactions was explored to enable an entry to functionalized aminopropane systems bearing a terminal $CF_3$ group. This study resulted in two successful routes, based on either direct reductive β-lactam ring opening or initial carbonyl removal to azetidine intermediates, followed by ring opening. In both cases, C2–N bond fission afforded the proposed aminopropanols or diaminopropanes in high yields and purity.[8] For 3-benzyloxy-β-lactams **I** ($R^2$ = Bn), hydrogenolysis of the benzyl ether fragment allowed the formation of 3-hydroxy-4-trifluoromethyl-β-lactams **II** as a second class of potential (but mainly unexplored) new building blocks. So far, only alcohol oxidation was evaluated, which gave rise to 3-oxo-β-lactams **III** as a third class of new building blocks. Attempts to form and trap the corresponding 2,3-dioxoazetidin-4-yl anions unexpectedly resulted in ring opening through C3–C4 bond fission, culminating in 2-[(2,2-difluorovinyl)amino]-2-oxoacetate products. This peculiar mechanism was investigated in depth, both experimentally and computationally.[9] Furthermore, an addition/elimination sequence applied to 3-oxo-β-lactams **III** afforded 3-methylene-β-lactams **IV** as a fourth class of new building blocks, which were shown to be eligible substrates for Michael additions, electrophilic additions, and cycloadditions en route to a variety of stereodefined mono- and spirocyclic 4-trifluoromethyl-β-lactams.[10] In order to further demonstrate the broad diversity of these 4-trifluoromethyl-β-lactam building blocks, we recently explored the synthetic applicability of 3-hydroxy-4-trifluoromethyl-β-lactams **II**. In particular, manipulation of the alcohol group enabled the construction of trifluoromethyl-containing ring-rearranged products, including aziridines through a ring-contraction protocol via 3-chloro-β-lactam intermediates and dioxan-2-ones via initial O-allylation, about which will be communicated in this paper.

## Results and Discussion

In addition to the preparation of 3-hydroxy-4-trifluoromethyl-β-lactams **3a**,**b** as described in our previous study,[8,10] a set of four new 3-hydroxy-4-trifluoromethyl-β-lactams **3c–f** was successfully synthesized, with slight modifications in the procedure. In the first step, 1-ethoxy-2,2,2-trifluoroethanol (**1**) was condensed with (a) isopropylamine in dichloromethane in the presence of $MgSO_4$ as drying agent and with (b) different arylamines (*p*-phenetidine, *p*-toluidine, 4-iodoaniline) in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid under Dean–Stark conditions. The resulting mixtures of imines and their hemiaminal precursors were immediately used for the Staudinger synthesis, yielding *cis*-3-benzyloxy-β-lactams **2c–f** in acceptable yields (Table 1). Besides the expected

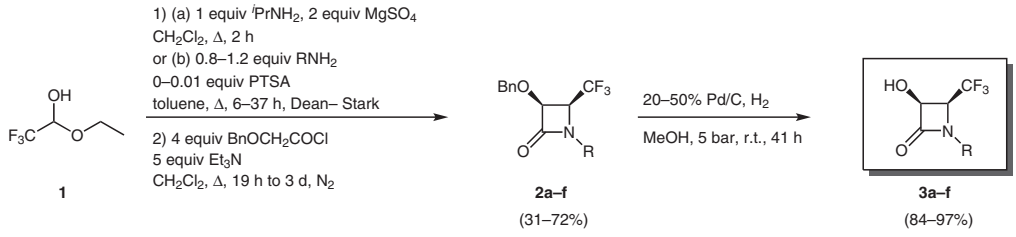



**Scheme 1** Overview of and interconnection between different 4-trifluoromethyl-β-lactam building blocks and their synthetic applications

*cis*-β-lactams **2c–f**, minor to rather significant amounts of *trans*-isomers of **2c–f** were also detected (2–46%). The formation of these *trans*-β-lactams was confirmed based on $^1$H NMR analysis, showing a coupling constant of 1–2 Hz ($CDCl_3$) between the two vicinal protons at the C3 and C4 position, as opposed to *cis*-β-lactams (5–6 Hz, $CDCl_3$).[8,11] The previously reported synthesis of β-lactams **2a**,**b** was achieved through a [2+2] ketene-imine cyclocondensation between a trifluoromethylaldimine and benzyloxyacetyl chloride in the presence of $Et_3N$. Under these conditions, the *cis*-β-lactams **2a**,**b** were obtained in a relatively high stereoselectivity (*cis*/*trans* 95–98:5–2). However, the relative amount of *trans*-β-lactams in the **2c–f** cases was higher compared to those of **2a**,**b** (*cis*/*trans* 54–78:46–22, Table 1). This stereoselectivity issue might be due to the outcome of the cyclocondensation reaction between either a hemiaminal or a mixture of hemiaminal and imine, with benzyloxyacetyl chloride in the presence of $Et_3N$ in the synthetic procedure toward β-lactams **2c–f**. It should indeed be noted that the treatment of 1-ethoxy-2,2,2-trifluoroethan-1-ol (**1**) with isopropylamine (a) led to 2,2,2-trifluoro-1-(isopropylamino)ethan-1-ol, whereas the use of arylamines (b) afforded a mixture of hemiaminals and imines. The *cis*-β-lactams **2c–f** were easily isolated through chromatography and subjected to hydrogenolysis (Pd/C) to produce the corresponding *cis*-alcohols **3c–f** in excellent yields (Table 1). In the case of *cis*-3-benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one (**2d**), the hydrogenolysis furnished *cis*-3-benzyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one instead of the expected *cis*-3-hydroxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one, probably due to hydrogenolytic scission of the $C_{arene}$–I bond over the Pd/C catalyst.[12] Because the high adsorption of the in situ produced iodide anion led to a decrease in the catalytic activity of Pd/C, the resulting *cis*-3-benzyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one was filtered through Celite prior to debenzylation.[12] The latter was finally transformed into the corresponding *cis*-3-hydroxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one (**3d**), in an overall yield of 84%.

In the next part, the eligibility of these 3-hydroxy-4-trifluoromethyl-β-lactams **3** as building blocks for the synthesis of functionalized trifluoromethyl-substituted compounds was assessed. In that respect, representative *cis*-3-hydroxy-4-(trifluoromethyl)azetidin-2-ones **3a**,**b** were transformed into *trans*-3-chloro-β-lactams **4a**,**b** in excellent yields (91–97%, Scheme 2) upon treatment with 2 equivalents of $Ph_3P$ and a small amount of $NaHCO_3$ as catalyst in $CCl_4$ under reflux for 10 hours.[13] The *trans*-configuration of β-lactams **4a**,**b** was confirmed based on the $^1$H NMR spectrum ($J_{H3,H4}$ = 1–2 Hz, $CDCl_3$), implying a clean $S_N2$ process. In order to simplify the synthetic procedure, the preparation of β-lactams **4** was attempted directly through the Staudinger synthesis using the same imines combined with chloroacetyl chloride and a variety of bases (2,6-lutidine, $Et_3N$, pyridine, proton sponge), in analogy with the synthesis of their non-fluorinated β-lactam counterparts.[14] However, this direct approach appeared to be unsuccessful for the preparation of trifluoromethylated β-lactams **4**. Therefore, a short detour was necessary, utilizing alcohols **3a**,**b** as valuable synthons to obtain the desired β-lactams **4a**,**b**. Besides this method, two complementary approaches have been reported to furnish 3-chloro-4-trifluoromethyl-

**Table 1** Isolated Yields of Compounds **2**, **3**, and *cis*/*trans* Ratios of Compounds **2**

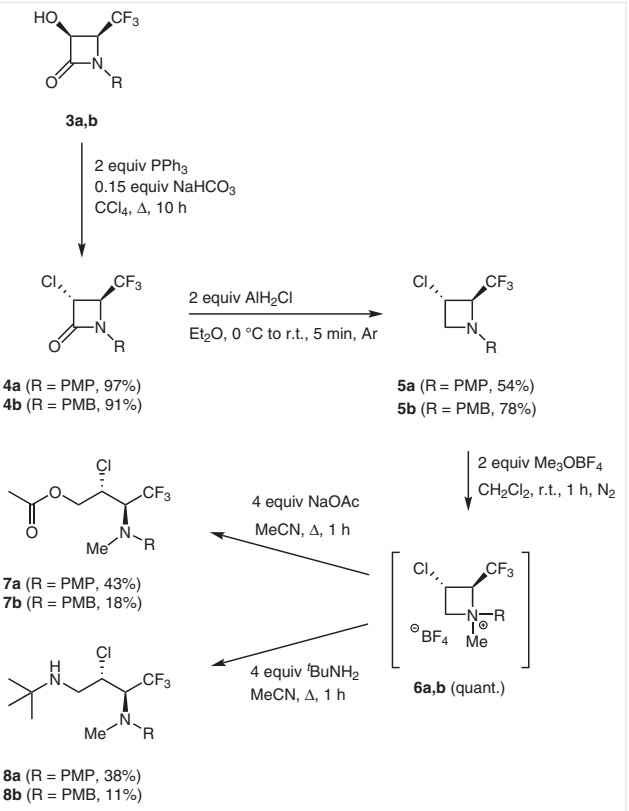



| Entry | R | 2 | *cis*/*trans*[a] 2 | 3 |
|---|---|---|---|---|
| 1 | 4-MeOC$_6$H$_4$ | **2a** (49%) | 98:2 | **3a** (87%) |
| 2 | 4-MeOC$_6$H$_4$CH$_2$ | **2b** (72%) | 95:5 | **3b** (93%) |
| 3 | 4-EtOC$_6$H$_4$ | **2c** (47%) | 78:22 | **3c** (94%) |
| 4 | 4-IC$_6$H$_4$/Ph | **2d** (35%)[b] | 54:46 | **3d** (84%)[c] |
| 5 | 4-MeC$_6$H$_4$ | **2e** (31%) | 67:33 | **3e** (87%) |
| 6 | *i*-Pr | **2f** (59%) | 75:25 | **3f** (97%) |

[a] Determined by $^{19}$F NMR spectroscopy ($CDCl_3$) of the crude reaction mixture **2**.
[b] R = 4-IC$_6$H$_4$.
[c] R = Ph.

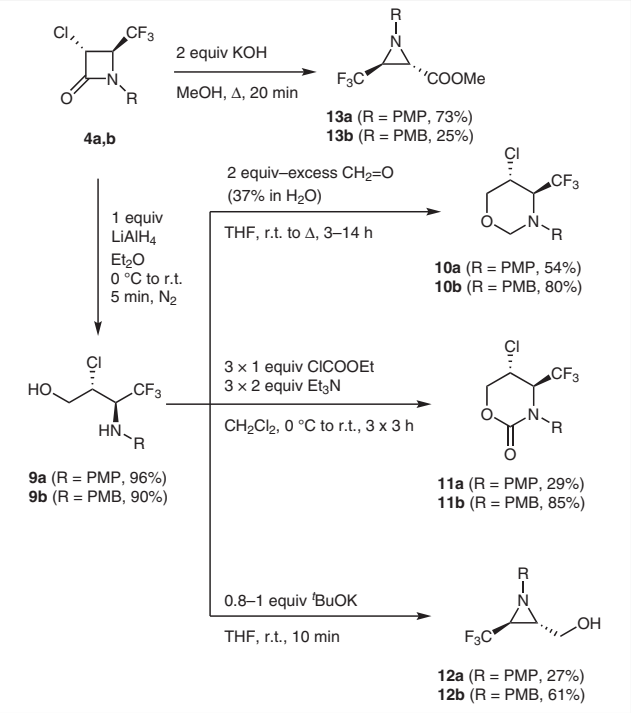
β-lactam analogues, either by intramolecular cyclization of the corresponding β-amino esters[11] or by ring expansion of the corresponding aziridines.[15] The reactivity of 3-chloro-4-trifluoromethyl-β-lactams is virtually unexplored in the literature to date, in contrast to 3-chloro-β-lactams having no trifluoromethyl group at the C4 position. In that respect, the selective reduction of *trans*-3-chloro-4-trifluoromethyl-β-lactams **4a**,**b** by means of monochloroalane was evaluated to provide an entry into *trans*-3-chloro-2-(trifluoromethyl)azetidines **5a**,**b**.[8] Treatment of β-lactams **4a**,**b** with two equivalents of monochloroalane, in diethyl ether at room temperature for five minutes, produced the desired azetidines **5a**,**b** in good yields (54–78%, Scheme 2).[8] In contrast to the reduction of 3-non-chlorinated 4-trifluoromethyl-β-lactams, the use of monochloroalane for the reduction of 3-chloro-2-(trifluoromethyl)azetidin-2-ones **4** required precise and optimized reaction conditions (time, temperature, and molar equivalents of the reductant) to limit the formation of side products due to ring opening. Having these azetidines **5** in hand, their eligibility for the synthesis of a diversity of functionalized trifluoromethyl-substituted aminopropanes was evaluated. N-Alkylation of 3-chloro-2-(trifluoromethyl)azetidines **5** was performed prior to ring opening, upon treatment with trimethyloxonium tetrafluoroborate, furnishing the corresponding azetidinium salts **6a**,**b** in a quantitative way (Scheme 2). Subsequently, these salts were subjected to ring opening by using an oxygen and nitrogen nucleophile, providing a convenient entry toward a variety of α-(trifluoromethyl)amines. In particular, azetidinium salts **6** were treated with four equivalents of sodium acetate or *tert*-butylamine, affording *anti*-2-chloro-3-amino-4,4,4-trifluorobutyl acetates **7a**,**b** and *anti*-2-chloro-4,4,4-trifluorobutane-1,3-diamines **8a**,**b**, respectively (Scheme 2), accompanied by a certain amount of azetidines **5** (20–47%). These results can be rationalized by considering the competition between a ring-opening reaction at the C4 position and an N-demethylation reaction of azetidinium salts **6a**,**b** by the nucleophiles utilized.[8,16] Sodium acetate and *tert*-butylamine were selected as nucleophiles in analogy with previous investigations on the ring opening of *cis*-3-alkoxy-2-(trifluoromethyl)azetidines.[8] In line with our previous findings on the chemistry of 2-(trifluoromethyl)azetidinium ions,[3b,8] ring opening of *trans*-3-chloro-2-(trifluoromethyl)azetidinium salts **6** proceeded regiospecifically at the non-substituted C4 position, in contrast with the reactivity of azetidinium salts bearing other types of electron-withdrawing groups (acyl, cyano). It is also noteworthy that the treatment of non-chlorinated 2-(trifluoromethyl)azetidinium salts with nucleophiles exclusively led to a regiospecific ring opening at the C4 position, without an accompanying N-demethylation pathway.[3b,16]

In analogy with 3-non-chlorinated 4-(trifluoromethyl)azetidin-2-ones, 3-chloro-β-lactams **4a**,**b** might be valuable precursors for the stereoselective synthesis of fluorinated β-amino alcohols.[8] In that respect, *trans*-3-chloro-4-(trifluoromethyl)azetidin-2-ones **4a**,**b** were subjected to a $LiAlH_4$-mediated reductive ring opening, using 1 equivalent of $LiAlH_4$ in $Et_2O$ at room temperature for five minutes, furnishing the corresponding *anti*-3-amino-2-chloro-4,4,4-trifluorobutanols **9a**,**b** in excellent yields (90–96%, Scheme 3). It should be noted that use of a stoichiometric amount of $LiAlH_4$ and a precise timing are required to avoid the generation of undesired side products. The use of 2 equivalents of $LiAlH_4$ in different solvents ($Et_2O$, THF) at room temperature or under reflux only led to decomposition of the starting material **4**, as opposed to the results obtained upon treatment of non-trifluoromethyl-substituted 2-chloro-β-lactams with $LiAlH_4$.[17] Trifluoromethyl-substituted 1,3-amino alcohols have been recognized as potential substrates for the preparation of a wide range of interesting trifluoromethyl-containing azaheterocyclic compounds.[8,18] For that purpose, the cyclization of *anti*-3-amino-2-chloro-4,4,4-trifluorobutanols **9a**,**b** was pursued to generate novel trifluoromethylated oxazinanes and oxazinan-2-ones. As such, the treatment of 3-aminopropan-1-ols **9a**,**b** with formaldehyde (37% in water) in THF resulted in the corresponding new *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinanes **10a**,**b** in 54–80% yield (Scheme 3). 1,3-Oxazinane scaffolds have been encountered as a core structure in many natural products and pharmaceuticals, because they




**Scheme 2** Reactions of **3a**,**b**

possess a wide spectrum of biological activities such as anti-HIV, antibacterial, antitumor, antituberculosis, and fungicidal properties.[19] Hence, a number of methods has been developed to enable their synthesis. However, reports on the synthesis of 1,3-oxazinanes with new functional groups remain rather scarce in the literature.[3b,8,18b] In that respect, the utilization of β-amino alcohols bearing a trifluoromethyl group might provide interesting trifluorinated 1,3-oxazinanes with promising biological properties.



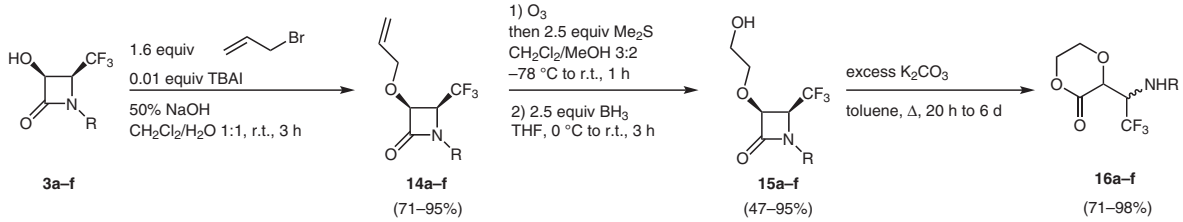

**Scheme 3** Reactions of **4a**,**b**

In addition, the cyclization of 3-aminopropan-1-ols **9a**,**b** was performed utilizing three times one equivalent of ethyl chloroformate and two equivalents of triethylamine in $CH_2Cl_2$ at room temperature for three hours, furnishing the corresponding *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinan-2-ones **11a**,**b** in 29–85% yield (Scheme 3).[8,20] 1,3-Oxazinan-2-ones are of interest due to their valuable biological activities as well. For example, they have been employed in the treatment of Alzheimer's disease, in herbicides with excellent crop-weed selectivity, in the treatment of diseases related to kinase activity, and in the regulation of cholesterol.[20,21] Therefore, new *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinan-2-ones **11a**,**b** might possess interesting properties for further applications.

In addition, the reactivity of *trans*-3-chloro-4-trifluoromethyl-β-lactams **4a**,**b** was explored to effect ring contraction toward the synthesis of 2-substituted 3-(trifluoromethyl)aziridines. According to a previous study from our group, reductive ring contraction of *trans*-4-aryl-3-chloroazetidin-2-ones toward aziridines was directly achieved utilizing $LiAlH_4$ in THF or $Et_2O$.[14b,17a] However, the analogous reduction of *trans*-3-chloro-4-trifluoromethyl-β-lactams **4** with 1–2 equivalents of $LiAlH_4$ in $Et_2O$ at room temperature or under reflux for two hours did not furnish the desired aziridines **12**. This could be due to the strong inductive effect of the trifluoromethyl group, rendering the nitrogen atom less basic, thus prohibiting the cyclization. To provide access to the aziridines **12a**,**b**, a base-induced ring closure of amino alcohols **9a**,**b** upon treatment with 0.8–1 equivalent of *t*-BuOK in THF was explored successfully (Scheme 3).[22] On the other hand, treatment of *trans*-3-chloro-4-(trifluoromethyl)azetidine-2-ones **4a**,**b** with 2 equivalents of KOH in methanol under reflux for 20 minutes afforded the corresponding aziridine-2-carboxylates **13a**,**b** in 25–73% yield. Although 2-substituted 3-(trifluoromethyl)aziridines constitute eligible substrates for the synthesis of valuable fluorinated compounds, synthetic pathways toward these structures remain scarce, and most of these methods use diazo compounds or require harsh reaction conditions. For instance, Akiyama et al. have reported the preparation of *cis*-2-chloro-3-(trifluoromethyl)aziridine **12a** from the corresponding trifluoromethyl-substituted aziridine carboxylate, which was also derived from a diazoacetate.[23] In recent research of our group, a novel stereoselective approach toward the synthesis of *trans*-2-substituted 3-(trifluoromethyl)aziridines starting from the commercially available trifluoromethyl ketones has been developed.[24] The use of *trans*-3-chloro-4-trifluoromethyl-β-lactams as versatile substrates for the synthesis of trifluoromethylated aziridines offers a new approach to this interesting aziridine subclass.

In the final part of this study, alcohols **3a**–**f** were evaluated as building blocks toward the synthesis of novel trifluoromethyl-containing 1,4-dioxan-2-ones. In that respect, *cis*-alcohols **3a**–**f** were subjected to initial O-allylation, yielding the corresponding *cis*-3-allyloxy-4-(trifluoromethyl)azetidin-2-ones **14a**–**f** in high yields (71–95%, Table 2) upon treatment with 1.6 equivalents of allyl bromide in the presence of TBAI as a catalyst, under basic conditions (Table 2).[25] The direct preparation of β-lactams **14** was attempted using the Staudinger synthesis between the corresponding imine and allyloxyacetyl chloride, in accordance with the preparation of their non-fluorinated β-lactam counterparts.[26] However, this approach only resulted in a complex mixture instead of the desired products **14**. In the following step, *cis*-3-allyloxy-4-(trifluoromethyl)azetidin-2-ones **14a**–**f** were subjected to an ozonolysis reaction followed by a reductive workup with 2.5 equivalents of $Me_2S$, providing the corresponding aldehyde intermediates. These aldehydes were immediately reduced with 2.5 equivalents of $BH_3$ (1 M in $Et_2O$) in THF at room temperature for three hours, furnishing the corresponding *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15a**–**f** in yields of 47–95% (Table 2).[26] It should be noted that

**Table 2** Isolated Yields of Compounds **14**, **15**, **16** and *syn*/*anti* Ratios of Compounds **16**




**3a–f** → **14a–f** (71–95%) → **15a–f** (47–95%) → **16a–f** (71–98%)

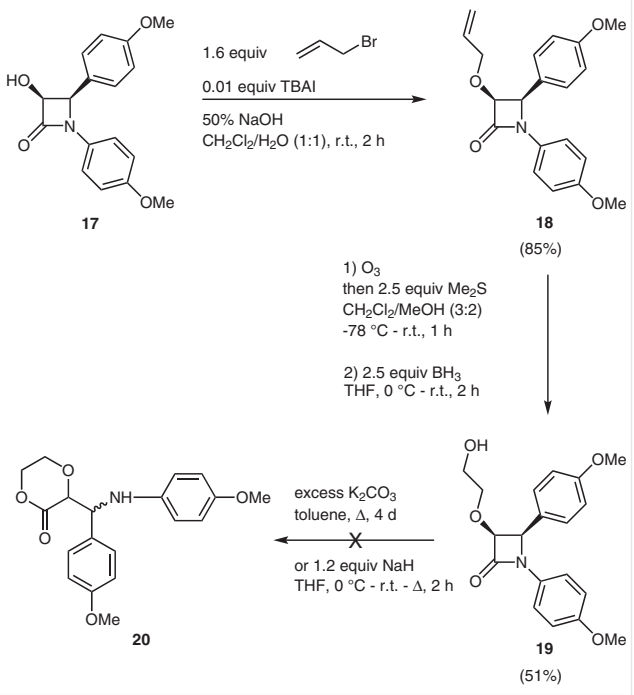
| Entry | R | 14 | 15 | 16 | *d.r.* 16 |
|---|---|---|---|---|---|
| 1 | 4-$MeOC_6H_4$ | **14a** (94%) | **15a** (72%) | **16a** (81%) | 78:22 |
| 2 | 4-$MeOC_6H_4CH_2$ | **14b** (95%) | **15b** (77%) | **16b** (0%) | – |
| 3 | 4-$EtOC_6H_4$ | **14c** (84%) | **15c** (72%) | **16c** (86%) | 72:28 |
| 4 | Ph | **14d** (77%) | **15d** (95%) | **16d** (71%) | 69:31 |
| 5 | 4-$MeC_6H_4$ | **14e** (71%) | **15e** (63%) | **16e** (98%) | 75:25 |
| 6 | *i*-Pr | **14f** (79%) | **15f** (47%) | **16f** (0%) | – |

the use of $BH_3$ (1 M in $Et_2O$) was observed to be superior to the use of $NaBH_4$ or $LiBH_4$ in this reductive reaction, because attempts with the latter agents were always accompanied by a reductive β-lactam ring opening.

Due to the combination of the constrained β-lactam ring system and a nucleophilic alcohol group at a remote position, 3-(2-hydroxyethoxy)- and 3-(2-hydroxyethyl)-β-lactams have been documented to undergo ring rearrangement to generate five- and six-membered azaheterocycles.[26,27] Hence, the potency of *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15a–f** with respect to ring transformation toward 1,4-dioxan-2-ones **16** was evaluated in the next step. In order to transform β-lactams **15a–f** into ring-rearranged products **16**, a set of different reaction conditions was assessed. In particular, treatment of β-lactams **15** with a variety of bases (NaH, pyridine, $Et_3N$, LiOH) in different solvents (THF, toluene, DMF, $CH_2Cl_2$) under different temperatures (0 °C, r.t., reflux) led to either complex mixtures or recovery of the substrates. Fortunately, treatment of *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15** with an excess of $K_2CO_3$ in toluene under reflux proved to be optimal to enable the desired intramolecular ring-opening reaction, furnishing an inseparable diastereomeric mixture of 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16** in excellent yields (71–98%, Table 2).[26,27] Only in the case of β-lactams **15b**,**f**, no ring transformation products **16b**,**f** were observed. These results show that the presence of electron-withdrawing substituents at the N1 position might accelerate the intramolecular ring opening of β-lactams to give trifluoromethylated 1,4-dioxan-2-ones **16**. Indeed, the stabilizing effect of an aromatic ring at nitrogen in **15a**,**c–e** promotes the formation of the corresponding nitrogen anion after ring opening, whereas the presence of an electron-donating alkyl group in **15b**,**f** impedes this process.

In the course of our study on trifluoromethyl-substituted β-lactams, we realized that a trifluoromethyl group does significantly affect the behavior of these molecules. Therefore, in order to gain insight into the influence of the trifluoromethyl group with respect to intramolecular cyclization, *cis*-3-(2-hydroxyethoxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one (**19**) was synthesized (Scheme 4), which bears a 4-methoxyphenyl group at the C4 position (instead of the trifluoromethyl group). This compound **19** was prepared from the corresponding *cis*-3-allyloxy-1,4-bis(4-methoxyphenyl)azetidin-2-one **18**, derived from alcohol **17**,[28] using the above-described procedure (Scheme 4). The preparation of β-lactam **18** has also been reported by Zarei upon treatment of allyloxyacetic acid with Schiff base and phosphonitrilic chloride in the presence of triethylamine.[29] Surprisingly, the treatment of *cis*-3-(2-hydroxyethoxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one (**19**) with an excess of $K_2CO_3$ in toluene under reflux for four days solely led to recovery of the starting material **19**. As $K_2CO_3$ might not be strong enough as a base to realize nucleophilic ring opening in this case, a more potent base (NaH) was used. However, the intramolecular cyclization toward 1,4-dioxan-2-one **20** was never observed, and this approach resulted in either the recovery of starting material **19** or a complex mixture (Scheme 4). This observation indicates that the specific combination of the aromatic group at N1 and the trifluoromethyl group at C4, as in *cis*-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones **15**, is important for the base-induced transformation into trifluoromethyl-substituted 1,4-dioxan-2-ones **16**. It should be stressed that the synthetic chemistry concerning 1,4-dioxan-2-one scaffolds, starting from monocyclic β-lactams, has been sporadically documented in the literature (as side products).[26] These 1,4-dioxan-2-one derivatives have been mainly synthesized from 1,2-diols,[30] glycolic acid[31] and

glycerol derivatives.[32] In addition, 1,4-dioxan-2-one derivatives play an important role as intermediates in the synthetic field of polymers, corrosion inhibitors, and biomaterials.[33] In that respect, the convenient approach toward trifluoromethyl-substituted 1,4-dioxan-2-ones **16** using trifluoromethyl-substituted β-lactam alcohols **15** as building blocks provided new insights and opportunities from both a fundamental and applied point of view.

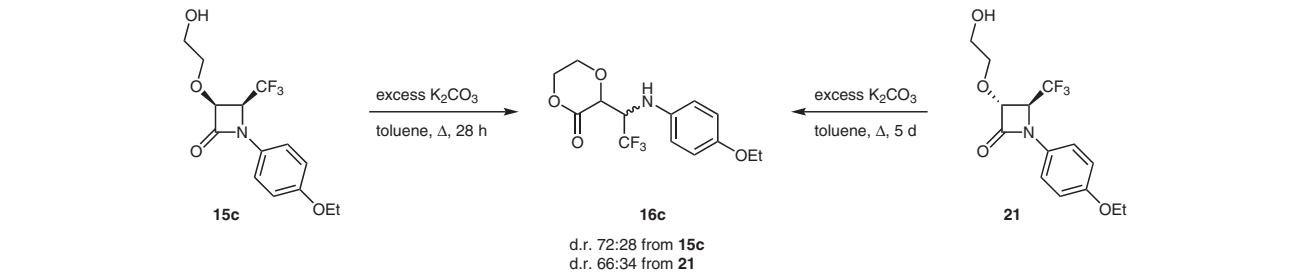



**Scheme 4** Attempted peparation of 1,4-dioxan-2-one **20**

Because the resulting diastereoisomers **16** could not be separated by means of column chromatography on silica gel, preparative HPLC (Supelco Ascentis C18; $H_2O$/MeCN), and recrystallization ($CH_2Cl_2$/$Et_2O$ 1:1 or $Et_2O$), other attempts were made to determine the relative stereochemistry of 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16**. For that reason, three additional experiments were performed to examine the behavior of *cis*-β-lactams **15** toward intramolecular cyclization under basic conditions. In the first experiment, the intramolecular cyclization of *trans*-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one (**21**) [the *trans* counterpart of *cis*-β-lactam **15c**, derived from the corresponding *trans*-1-(4-ethoxyphenyl)-3-allyloxy-4-(trifluoromethyl)azetidin-2-one in an overall yield of 11%] as a model compound toward 3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one (**16c**) was tested. Remarkably, the use of identical reactions conditions (excess of $K_2CO_3$ in toluene under reflux for five days) applied to *trans*-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one (**21**) also led to a mixture of two isomers **16c** in a ratio of 66:34, similar to the 72:28 mixture obtained from **15c** (Scheme 5).

In the second experiment, the pure diastereoisomer *cis*-3-allyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**14c**) was treated with an excess of $K_2CO_3$ in toluene under reflux for five days, resulting in a *cis*/*trans* mixture of 3-allyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one in a ratio of 40:60 (*cis*/*trans*). In the last experiment, the diastereomeric mixture of 3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one **16c** (d.r. 72:28) was treated with an excess of $K_2CO_3$ in toluene under reflux for one day, which did not affect the diastereomeric ratio.

Based on these experimental results, we propose that a dynamic equilibrium between intramolecular ring opening and epimerization of *cis*-alcohols **15** occurred in the presence of $K_2CO_3$, which led to the corresponding (3*S*,1′*R*;3*R*,1′*S*)-3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16** (as major products) and *trans*-alcohols **15**. Then, *trans*-alcohols **15** were in turn subjected to intramolecular ring opening, leading to the corresponding (3*R*,1′*R*;3*S*,1′*S*)-3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones **16** (as minor isomers). In addition to the experiments, DFT calculations were performed to assess the stability of the diastereomeric pairs. Relative Gibbs free energies indicate that (3*S*,1′*R*;3*R*,1′*S*)-**16** is more stable than (3*R*,1′*R*;3*S*,1′*S*)-**16** if the mixture of the two diastereoisomers is considered (see Supporting Information). Hence, 3-(2,2,2-trifluoro-1-aminoethyl-1,4-dioxan-2-ones (3*S*,1′*R*)- and (3*R*,1′*S*)-**16** are proposed to be the major products in the inseparable mixture of diastereoisomers (Figure 1).




**Scheme 5** Preparation of 1,4-dioxan-2-one **16c**

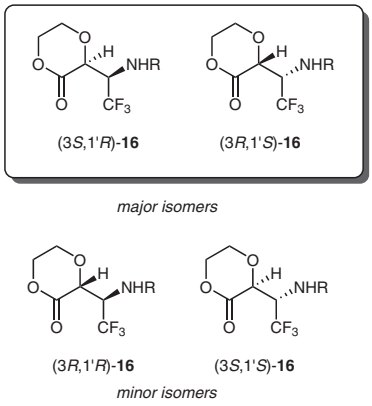



**Figure 1** Overview of possible isomers for structures **16**

## Conclusion

In conclusion, a set of *cis*-3-hydroxy-4-(trifluoromethyl)-azetidin-2-ones were effectively synthesized and successfully used as versatile new building blocks for the construction of a variety of trifluoromethyl-containing amines and heterocyclic molecules. To that end, *cis*-3-hydroxy-4-trifluoromethyl-β-lactams were transformed into *trans*-3-chloro-4-trifluoromethyl-β-lactams, which served as eligible substrates for the preparation of α-trifluoromethyl-substituted aminopropane derivatives through a regiospecific ring opening of intermediate azetidinium salts. Besides, new *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinanes and *trans*-5-chloro-4-trifluoromethyl-1,3-oxazinan-2-ones were produced through cyclization of trifluoromethylated γ-amino alcohols, with formaldehyde or ethyl chloroformate, respectively. Moreover, 2-substituted 3-trifluoromethylated aziridines were synthesized, either by base-induced ring closure of γ-amino alcohols or upon direct treatment of 3-chloro-γ-lactams with KOH. In addition, 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones proved to be suitable substrates for the synthesis of novel 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones in high yields through ring rearrangement.

All reagents were purchased as commercially available sources without further purification. $Et_2O$, THF, and toluene were distilled from Na benzophenone ketyl or Na, while $CH_2Cl_2$ was distilled from $CaH_2$ prior to use. Solvents were removed under reduced pressure using a rotary evaporator. Silica gel (0.035–0.070 mm, pore diameter ca. 6 nm) was used for column chromatography. Solvent systems were determined via initial TLC analysis on glass-backed silica plates (Merck Kieselgel 60 with F254 indicator, precoated 0.25 mm). These plates were developed using standard visualization techniques or agents, UV fluorescence (254 and 366 nm) and/or coloring with a $KMnO_4$ solution. High-resolution $^1H$ NMR (400 MHz), $^{13}C$ NMR (100.6 MHz), and $^{19}F$ NMR (376 MHz) spectra were recorded with a Bruker Avance III Nanobay NMR spectrometer using deuterated solvents and TMS and $CFCl_3$ as internal standards. Low-resolution mass spectra were recorded via direct injection on an Agilent 1100 Series (ES, 4000 V) LC/MSD type SL mass spectrometer with Electron Spray Ionization Geometry (ESI 70 eV) and using a Mass Selective Detector (quadrupole). High-resolution electron spray (ES) mass spectra were obtained with an Agilent Technologies 6210 Series Time-of-Flight. IR spectra were recorded on a PerkinElmer Spectrum BX FT-IR spectrometer (in neat form) with an ATR (Attenuated Total Reflectance) accessory. Melting points of crystalline compounds were measured using a Büchi B-540 apparatus or a Kofler bench, type WME Heizbank of Wagner & Munz.

The ozonolysis reaction was performed with an Ozonia Triogen Model LAB2B laboratory ozone generator, connected to a Bronkhorst Flow-Bus E-7000 type mass flow meter to control the dry air inflow and an Anseros Ozomat Model GM Non-Dispersive UV-analyzer to measure the ozone concentration.

### 3-Benzyloxy-4-(trifluoromethyl)azetidin-2-ones 2

The synthesis of 3-benzyloxy-4-(trifluoromethyl)azetidin-2-ones **2a**,**b** was reported in a previous study.[10] A slightly modified procedure for the synthesis of **2c**–**e** is described below.

### *cis*-3-Benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (2c); Typical Procedure

To a solution of 1-ethoxy-2,2,2-trifluoroethanol (**1**; 1.00 g, 0.82 mL, 6,94 mmol, 1 equiv) in toluene (30 mL) was added *p*-phenetidine (0.76 g, 0.71 mL, 5.55 mmol, 0.8 equiv) and PTSA as catalyst (13.2 mg, 0.07 mmol, 0.01 equiv). The resulting mixture was heated at reflux temperature for 3 h under Dean–Stark conditions, affording *N*-(4-ethoxyphenyl)-2,2,2-trifluoroethan-1-imine in high purity (>90% based on NMR analysis). Due to its hydrolytic instability, after evaporation of the crude mixture, the resulting product (1.23 g, 5.67 mmol, 1 equiv) was immediately dissolved in anhyd $CH_2Cl_2$ (50 mL) at 0 °C under argon atmosphere and $Et_3N$ (2.87 g, 3.95 mL, 28.4 mmol, 5 equiv) was added to the solution. Benzyloxyacetyl chloride (4.17 g, 3.57 mL, 22.68 mmol, 4 equiv) was then added dropwise to the reaction mixture. After stirring the mixture for 3 days under reflux, $H_2O$ (20 mL) was added to the mixture. Extraction with $CH_2Cl_2$ (3 × 20 mL), washing the combined organic layers with brine (3 × 20 mL), drying ($MgSO_4$), filtration, and evaporation of solvent afforded a mixture of two isomers *cis*/*trans* in a ratio of 78:22. The two isomers were separated by means of column chromatography on silica gel (PE/EtOAc 9:1), then recrystallization from EtOH was performed to obtain analytically pure **2c** and *trans*-3-benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one.

### 2c

Yield: 0.97 g (2.66 mmol, 47%); white crystals; mp 83 °C (EtOH); $R_f$ = 0.23 (PE/EtOAc 9:1).

IR (ATR): 1749, 1514, 1364, 1267, 1163, 1136, 1022, 922, 825, 735, 505 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 7 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 4.98 (d, *J* = 5.4 Hz, 1 H), 4.85 (d, *J* = 11.8 Hz, 1 H), 4.80 (d, *J* = 11.8 Hz, 1 H), 4.61 (quint, *J* = 5.4 Hz, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 163.8, 156.6, 136.1, 129.3, 128.6 (2 C), 128.3, 127.9 (2 C), 123.8 (q, *J* = 284.4 Hz), 119.4 (2 C), 115.0 (2 C), 80.2, 73.8, 63.7, 57.7 (q, *J* = 33.1 Hz), 14.8.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.37 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 366 ([$M^+$ + 1], 100).

***trans*-3-Benzyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one**

Yield: 0.20 g (0.55 mmol, 10%); white crystals; mp 71 °C (EtOH); $R_f$ = 0.49 (PE/EtOAc 9:1).

IR (ATR): 1763, 1514, 1398, 1281, 1244, 1148, 1113, 1045, 843, 735, 694 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.33–7.39 (m, 5 H), 7.32 (d, *J* = 8.9 Hz, 2 H), 6.88 (d, *J* = 8.9 Hz, 2 H), 4.88 (d, *J* = 1.1 Hz, 1 H), 4.82 (d, *J* = 11.5 Hz, 1 H), 4.76 (d, *J* = 11.5 Hz, 1 H), 4.41 (qd, *J* = 5.6, 1.1 Hz, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 162.5, 156.8, 135.9, 128.9, 128.7 (2 C), 128.5, 128.2 (2 C), 123.6 (q, *J* = 280.5 Hz), 120.1 (2 C), 115.0 (2 C), 82.0, 73.2, 63.7, 59.8 (q, *J* = 34.2 Hz), 14.8.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –71.38 (d, *J* = 5.6 Hz, 3 F).

MS (70 eV): *m*/*z* = 366 ([$M^+$ + 1], 100).

***cis*-3-Benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one (2d)**

Yield: 1.05 g (2.35 mmol, 35%); white crystals; mp 125 °C (EtOH); $R_f$ = 0.15 (PE/EtOAc 12:1).

IR (ATR): 1761, 1489, 1364, 1267, 1238, 1165, 1128, 816, 737, 694, 498 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.7 Hz, 2 H), 7.32–7.39 (m, 5 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 4.99 (d, *J* = 5.4 Hz, 1 H), 4.85 (d, *J* = 11.8 Hz, 1 H), 4.79(d, *J* = 11.8 Hz, 1 H), 4.64 (quint, *J* = 5.4 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.1, 138.2 (2 C), 135.9, 135.8, 128.7 (2 C), 128.4, 128.0 (2 C), 123.6 (q, *J* = 280.1 Hz), 119.4 (2 C), 89.0, 80.2, 73.9, 57.4 (q, *J* = 33.4 Hz).

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.21 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* (%) = 465 ([$M^+$ + 18], 100), 448 ([$M^+$ + 1], 55).

***trans*-3-Benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one**

Yield: 0.81 g (1.81 mmol, 27%); white crystals; mp 78 °C (EtOH); $R_f$ = 0.52 (PE/EtOAc 9:1).

IR (ATR): 1757, 1587, 1489, 1393, 1364, 1111, 1001, 696, 498 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.7 Hz, 2 H), 7.28–7.34 (m, 5 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 4.82 (d, *J* = 1.3 Hz, 1 H), 4.76 (d, *J* = 11.6 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.36 (qd, *J* = 5.6, 1.3 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 162.6, 138.3 (2 C), 135.6, 128.74 (2 C), 128.65, 128.2 (2 C), 123.4 (q, *J* = 280.2 Hz), 119.8 (2 C), 89.4, 82.2 (q, *J* = 1.5 Hz), 73.3, 59.6 (q, *J* = 34.5 Hz).

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –71.12 (d, *J* = 5.6 Hz, 3 F).

MS (70 eV): *m*/*z* = 448 ([$M^+$ + 1], 50).

***cis*-3-Benzyloxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one (2e)**

Yield: 0.63 g (1.88 mmol, 31%); white crystals; mp 113 °C (EtOH); $R_f$ = 0.25 (PE/EtOAc 9:1).

IR (ATR): 1769, 1514, 1360, 1265, 1167, 1130, 812, 760, 694, 494 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.33–7.40 (m, 7 H), 7.14 (d, *J* = 8.3 Hz, 2 H), 4.96 (d, *J* = 5.3 Hz, 1 H), 4.84 (d, *J* = 11.8 Hz, 1 H), 4.78 (d, *J* = 11.8 Hz, 1 H), 4.63 (quint, *J* = 5.3 Hz, 1 H), 2.31 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.0, 136.1, 135.3, 133.7, 129.8 (2 C), 128.6 (2 C), 128.3, 127.9 (2 C), 123.8 (q, *J* = 280.4 Hz), 117.7 (2 C), 80.2, 73.8, 57.4 (q, *J* = 33.2 Hz), 20.9.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.29 (d, *J* = 5.3 Hz, 3 F).

MS (70 eV): *m*/*z* = 336 ([$M^+$ + 1], 100).

***trans*-3-Benzyloxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one**

Yield: 0.25 g (0.75 mmol, 14%); white crystals; mp 62 °C (EtOH); $R_f$ = 0.52 (PE/EtOAc 9:1).

IR (ATR): 1759, 1512, 1391, 1348, 1277, 1163, 1138, 1109, 810, 739, 698, 509, 436 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.25–7.30 (m, 5 H), 7.22 (d, *J* = 8.3 Hz, 2 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 4.80 (d, *J* = 1.2 Hz, 1 H), 4.74 (d, *J* = 11.6 Hz, 1 H), 4.67 (d, *J* = 11.6 Hz, 1 H), 4.35 (qd, *J* = 5.6, 1.2 Hz, 1 H), 2.24 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 162.6, 135.9, 135.6, 133.4, 129.8 (2 C), 128.7 (2 C), 128.5, 128.2 (2 C), 123.6 (q, *J* = 280.4 Hz), 118.2 (2 C), 82.0 (q, *J* = 2.0 Hz), 73.2, 59.6 (q, *J* = 34.4 Hz), 21.0.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –71.22 (d, *J* = 5.6 Hz, 3 F).

MS (70 eV): *m*/*z* = 336 ([$M^+$ + 1], 100).

***cis*-3-Benzyloxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one (2f)**

To a solution of 1-ethoxy-2,2,2-trifluoroethanol (**1**; 1.00 g, 0.82 mL, 6,94 mmol, 1 equiv) in anhyd $CH_2Cl_2$ (20 mL) was added *i*-$PrNH_2$ (0.41 g, 0.60 mL, 6.94 mmol, 1 equiv) and $MgSO_4$ (1.67 g, 13.88 mmol, 2 equiv). After stirring for 2 h under reflux, $MgSO_4$ was removed by filtration. Evaporation of the solvent in vacuo gave 2,2,2-trifluoro-1-(isopropylamino)ethan-1-ol (0.76 g, 4.84 mmol, 70%) as white crystals. Benzyloxyacetyl chloride (3.56 g, 3.04 mL, 19.36 mmol, 4 equiv) was added dropwise to an ice-cooled solution of the latter *N*-isopropyl hemiaminal (0.76 g, 4.84 mmol, 1 equiv) and $Et_3N$ (2.44 g, 3.37 mL, 24.2 mmol, 5 equiv) in anhyd $CH_2Cl_2$ (30 mL). After stirring for 19 h under reflux, $H_2O$ (30 mL) was added to the reaction mixture and extracted with $CH_2Cl_2$ (2 × 25 mL). Drying the combined organic layers ($MgSO_4$), filtration, and removal of the solvent afforded a mixture of two isomers *cis*/*trans* in a ratio of 75:25. Pure **2f** (0.82 g, 2.86 mmol, 59%) was obtained by means of column chromatography on silica gel (PE/EtOAc 9:1); yield: 0.82 g (2.86 mmol, 59%); yellowish solid; mp 45 °C; $R_f$ = 0.11 (PE/EtOAc 9:1).

IR (ATR): 1763, 1393, 1354, 1277, 1161, 1138, 1113, 735, 696 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.28–7.36 (m, 5 H), 4.77 (d, *J* = 11.8 Hz, 1 H), 4.75 (d, *J* = 5.2 Hz, 1 H), 4.73 (d, *J* = 11.8 Hz, 1 H), 4.11 (qd, *J* = 6.1, 5.2 Hz, 1 H), 3.88 (sept, *J* = 6.8 Hz, 1 H), 1.29 (d, *J* = 6.8 Hz, 3 H), 1.25 (d, *J* = 6.8 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 166.1, 136.3, 128.5 (2 C), 128.2, 127.9 (2 C), 123.9 (q, *J* = 279.8 Hz), 80.0, 73.4, 56.5 (q, *J* = 33.1 Hz), 45.1, 21.1, 19.4.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –69.33 (d, *J* = 6.1 Hz, 3 F).

MS (70 eV): *m*/*z* = 288 ([$M^+$ + 1], 100).

***cis*-3-Benzyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one**

This product was obtained by hydrogenolysis of *cis*-3-benzyloxy-1-(4-iodophenyl)-4-(trifluoromethyl)azetidin-2-one (**2d**) by applying a literature procedure;[10] yield: 0.65 g (2.02 mmol, 86%); white crystals; mp 95 °C.

IR (ATR): 1757, 1499, 1366, 1167, 1138, 739, 752, 669, 490 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.1 Hz, 2 H), 7.31–7.41 (m, 7 H), 7.17 (t, *J* = 7.4 Hz, 1 H), 4.98 (d, *J* = 5.4 Hz, 1 H), 4.85 (d, *J* = 11.8 Hz, 1 H), 4.80 (d, *J* = 11.8 Hz, 1 H), 4.67 (quint, *J* = 5.4 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 164.2, 136.2, 136.1, 129.3 (2 C), 128.6 (2 C), 128.4, 128.0 (2 C), 125.5, 123.7 (q, *J* = 281.0 Hz), 117.6 (2 C), 80.1, 73.8, 57.4 (q, *J* = 33.3 Hz).

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –68.26 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 322 ([M$^+$ + 1], 100).

**3-Hydroxy-4-(trifluoromethyl)azetidin-2-ones 3; General Procedure**

The synthesis of 3-hydroxy-4-(trifluoromethyl)azetidin-2-ones **3c–f** was performed according to a procedure described in a previous study.[10]

***cis*-1-(4-Ethoxyphenyl)-3-hydroxy-4-(trifluoromethyl)azetidin-2-one (*cis*-3c)**

Yield: 0.54 g (1.96 mmol, 94%); white crystals; mp 144 °C (hexane/EtOAc 30:1).

IR (ATR): 3306, 1728, 1514, 1296, 1250, 1167, 1136, 1038, 860, 822, 652, 522 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 9.0 Hz, 2 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 5.31 (d, *J* = 5.5 Hz, 1 H), 4.63 (quint, *J* = 5.5 Hz, 1 H), 4.20 (s, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 165.6, 156.8, 129.1, 123.7 (q, *J* = 281.6 Hz), 119.5 (2 C), 115.0 (2 C), 75.2, 63.8, 58.2 (q, *J* = 32.0 Hz), 14.8.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –68.48 (d, *J* = 5.5 Hz, 3 F).

MS (70 eV): *m*/*z* = 276 ([M$^+$ + 1], 70).

***trans*-1-(4-Ethoxyphenyl)-3-hydroxy-4-(trifluoromethyl)azetidin-2-one (*trans*-3c)**

Yield: 0.11 g (0.40 mmol, 84%); white crystals; mp 102 °C (hexane/EtOAc 30:1).

IR (ATR): 3237, 1736, 1512, 1479, 1400, 1283, 1250, 1144, 1103, 1049, 876, 822, 696 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 9.0 Hz, 2 H), 6.85 (d, *J* = 9.0 Hz, 2 H), 5.03 (~s, 1 H), 4.93 (s, 1 H), 4.42 (qd, *J* = 5.7, 1.1 Hz, 1 H), 4.00 (q, *J* = 7.0 Hz, 2 H), 1.41 (t, *J* = 7.0 Hz, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 166.0, 157.1, 128.3, 123.5 (q, *J* = 280.3 Hz), 120.4 (2 C), 115.0 (2 C), 76.2 (q, *J* = 2.2 Hz), 63.8, 61.4 (q, *J* = 34.2 Hz), 14.7.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –71.72 (d, *J* = 5.7 Hz, 3 F).

MS (70 eV): *m*/*z* = 276 ([M$^+$ + 1], 100).

***cis*-3-Hydroxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one (3d)**

Yield: 0.42 g (1.82 mmol, 84%); white crystals; mp 164 °C (hexane/EtOAc 30:1).

IR (ATR): 2448, 1724, 1499, 1393, 1281, 1252, 1142, 758, 691, 664 cm$^{-1}$.

$^1$H NMR (400 MHz, $CD_3OD$): δ = 7.51 (d, *J* = 7.8 Hz, 2 H), 7.39 (t, *J* = 7.8 Hz, 2 H), 7.19 (t, *J* = 7.7 Hz, 1 H), 5.29 (d, *J* = 5.7 Hz, 1 H), 4.98 (quint, *J* = 5.7 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CD_3OD$): δ = 167.0, 136.7, 128.8 (2 C), 124.9, 124.3 (q, *J* = 279.7 Hz), 117.4 (2 C), 74.9, 57.8 (q, *J* = 31.5 Hz).

$^{19}$F NMR (376.5 MHz, $CD_3OD$): δ = –70.18 (d, *J* = 5.7 Hz, 3 F).

MS (70 eV): *m*/*z* = 249 ([M$^+$ + 18], 100).

***cis*-3-Hydroxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one (3e)**

Yield: 0.32 g (1.31 mmol, 87%); white crystals; mp 176 °C.

IR (ATR): 2455, 1732, 1512, 1389, 1281, 1248, 1167, 1082, 860, 810, 646, 471 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.3 Hz, 2 H), 7.17 (d, *J* = 8.3 Hz, 2 H), 5.28 (dd, *J* = 8.2, 5.5 Hz, 1 H), 4.66 (quint, *J* = 5.5 Hz, 1 H), 3.22 (br s, 1 H), 2.33 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CD_3OD$): δ = 166.8, 134.9, 134.1, 129.2 (2 C), 124.3 (q, *J* = 279.9 Hz), 117.5 (2 C), 74.9, 57.8 (q, *J* = 31.5 Hz), 19.5.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –68.41 (d, *J* = 5.5 Hz, 3 F).

MS (70 eV): *m*/*z* (%) = 263 ([M$^+$ + 18], 100), 246 ([M$^+$ + 1], 40).

***cis*-3-Hydroxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one (3f)**

Yield: 0.33 g (1.68 mmol, 97%); white crystals; mp 85 °C.

IR (ATR): 3240, 1719, 1580, 1385, 1371, 1217, 1153, 1119, 1053, 932, 854, 810, 646 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 5.07 (dd, *J* = 5.9, 5.1 Hz, 1 H), 4.61 (d, *J* = 5.9 Hz, 1 H), 4.12 (qd, *J* = 6.3, 5.1 Hz, 1 H), 3.87 (sept, *J* = 6.8 Hz, 1 H), 1.30 (d, *J* = 6.8 Hz, 3 H), 1.26 (d, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 168.6, 123.8 (q, *J* = 279.7 Hz), 74.7, 57.2 (q, *J* = 32.1 Hz), 45.4, 21.0, 19.3.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –69.44 (d, *J* = 6.3 Hz, 3 F).

MS (70 eV): *m*/*z* = 198 ([M$^+$ + 1], 70).

***trans*-3-Chloro-4-(trifluoromethyl)azetidin-2-ones 4; *trans*-3-Chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (4a); Typical Procedure**

To a solution of *cis*-3-hydroxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**3a**; (1.49 g, 5.71 mmol, 1 equiv) in $CCl_4$ (10 mL) at r.t. was added $Ph_3P$ (2.99 g, 11.42 mmol, 2 equiv) and $NaHCO_3$ as a catalyst (0.07 g, 0.86 mmol, 0.15 equiv). The mixture was heated under reflux for 10 h. Filtration of the heterogenous mixture through Celite and evaporation of the solvent in vacuo afforded **4a** (1.54 g, 5.52 mmol, 97%), which was purified by means of column chromatography on silica gel (PE/EtOAc 8:1); yield: 1.54 g (5.52 mmol, 97%), colorless solid; mp 52 °C; $R_f$ = 0.32 (PE/EtOAc 8:1).

IR (ATR): 1771, 1510, 1269, 1256, 1173, 1159, 1132, 1113, 1090, 1038, 878, 820, 800, 689, 588, 511, 424 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 9.1 Hz, 2 H), 6.91 (d, *J* = 9.1 Hz, 2 H), 4.93 (d, *J* = 1.8 Hz, 1 H), 4.55 (qd, *J* = 5.3, 1.8 Hz, 1 H), 3.80 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 159.0, 157.8, 128.7, 123.1 (q, *J* = 281.1 Hz), 120.1 (2 C), 114.6 (2 C), 61.8 (q, *J* = 34.9 Hz), 55.8 (q, *J* = 2.0 Hz), 55.5.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –72.36 (d, *J* = 5.3 Hz, 3 F).

MS (70 eV): *m*/*z* = 297 ([M$^+$ + 18], 100).

***trans*-3-Chloro-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one (4b)**

Yield: 2.10 g (7.17 mmol, 91%); yellowish oil; $R_f$ = 0.40 (PE/EtOAc 8:1).

IR (ATR): 1786, 1514, 1275, 1246, 1190, 1161, 1132, 1107, 1032, 835, 687, 621 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 4.86 (d, *J* = 15.0 Hz, 1 H), 4.81 (d, *J* = 1.4 Hz, 1 H), 3.96 (d, *J* = 15.0 Hz, 1 H), 3.811 (s, 3 H), 3.808 (qd, *J* = 5.7, 1.4 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 161.9, 159.8, 129.9 (2 C), 125.3, 123.1 (q, *J* = 280.2 Hz), 114.5 (2 C), 60.1 (q, *J* = 34.7 Hz), 55.9 (q, *J* = 2.4 Hz), 55.3, 45.6.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –73.72 (d, *J* = 5.7 Hz, 3 F).

MS (70 eV): *m*/*z* (%) = 294 ([M$^+$ + 1], 10), 311 ([M$^+$ + 18], 100).

### *trans*-3-Chloro-2-(trifluoromethyl)azetidines 5; *trans*-3-Chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine (5a); Typical Procedure

To an ice-cooled solution of $AlCl_3$ (0.38 g, 2.86 mmol, 2 equiv) in anhyd $Et_2O$ (10 mL), was carefully added a 1 M solution of $LiAlH_4$ in THF (2.86 mL, 0.11 g, 2.86 mmol, 2 equiv) dropwise. The reaction mixture was allowed to reach r.t., and then heated for 30 min at reflux temperature. Afterwards, the mixture was cooled to 0 °C and *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**4a**; 0.40 g, 1.43 mmol, 1 equiv) was added. After stirring for 5 min at r.t., the reaction was quenched with $H_2O$ (10 mL) and filtered through a short pad of Celite. Extraction with $Et_2O$ (3 × 10 mL), drying the combined organic layers ($MgSO_4$), filtration, and evaporation of the solvent afforded a crude mixture. The $^1$H NMR and $^{19}$F NMR of this mixture showed it to consist of product **5a** and the ring-opened product *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol in a ratio of 66:34. The mixture was separated by flash column chromatography (PE/EtOAc 12:1) to give pure **5a**; yield: 0.21 g (0.79 mmol, 54%); yellow solid; mp 50 °C; $R_f$ = 0.55 (PE/EtOAc 12:1).

IR (ATR): 1508, 1273, 1263, 1242, 1157, 1126, 1034, 824, 795, 692, 529 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 9.0 Hz, 2 H), 6.61 (d, *J* = 9.0 Hz, 2 H), 4.69 (ddd, *J* = 6.7, 6.7, 5.5 Hz, 1 H), 4.49 (dd, *J* = 7.9, 6.7 Hz, 1 H), 4.38 (q, *J* = 5.5 Hz, 1 H), 3.78 (dd, *J* = 7.9, 6.7 Hz, 1 H), 3.76 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 154.1, 143.6, 123.9 (q, *J* = 279.6 Hz), 114.8 (2 C), 114.0 (2 C), 73.0 (q, *J* = 33.4 Hz), 61.3, 55.7, 44.2 (q, *J* = 3.4 Hz).

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –75.70 (d, *J* = 5.5 Hz, 3 F).

MS (70 eV): *m*/*z* = 266 ([M$^+$ + 1], 100).

### *trans*-3-Chloro-1-(4-methoxybenzyl)-2-(trifluoromethyl)azetidine (5b)

Yield: 0.54 g (1.94 mmol, 78%); yellowish solid; mp 56 °C; $R_f$ = 0.78 (PE/EtOAc 12:1).

IR (ATR): 1514, 1283, 1250, 1236, 1161, 1142, 1123, 1082, 1032, 827, 781, 762, 696 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.6 Hz, 2 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 4.39 (q, *J* = 6.7 Hz, 1 H), 3.93 (d, *J* = 12.7 Hz, 1 H), 3.80 (s, 3 H), 3.69–3.75 (m, 2 H), 3.54 (d, *J* = 12.7 Hz, 1 H), 3.05 (t, *J* = 7.4 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 159.2, 130.1 (2 C), 127.8, 123.9 (q, *J* = 278.6 Hz), 113.9 (2 C), 72.7 (q, *J* = 32.3 Hz), 61.1, 60.2, 55.3, 43.6 (q, *J* = 3.5 Hz).

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –75.98 (d, *J* = 6.7 Hz, 3 F).

MS (70 eV): *m*/*z* = 280 ([M$^+$ + 1], 13).

### *anti*-2-Chloro-4,4,4-trifluoro-3-[*N*-(4-methoxybenzyl/phenyl)-*N*-methylamino]butyl Acetates 7; *anti*-2-Chloro-4,4,4-trifluoro-3-[*N*-(4-methoxyphenyl)-*N*-methylamino]butyl Acetate (7a); Typical Procedure

In a flame-dried flask under $N_2$ atmosphere, $Me_3OBF_4$ (0.11 g, 0.74 mmol, 2 equiv) was added to an ice-cooled solution of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine (**5a**; 0.10 g, 0.37 mmol, 1 equiv) in anhyd $CH_2Cl_2$ (5 mL). After stirring for 1 h at r.t., the solvent was evaporated and the resulting residue was redissolved in MeCN (5 mL), after which NaOAc (0.12 g, 1.48 mmol, 4 equiv) was added. After stirring at reflux temperature for 1 h, the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL) and the combined organic layers were washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration, and evaporation of the solvent afforded a crude mixture of product **7a** (0.05 g, 0.16 mmol, 43%) and the starting material **5a** (0.02 g, 0.08 mmol) in a ratio of 53:47, which were separated by means of preparative TLC (hexane/EtOAc 9:1) to obtain analytically pure compounds; yellowish solid; mp 48 °C; $R_f$ = 0.30 (hexane/EtOAc 9:1); yield: 0.05 g (0.16 mmol, 43%).

IR (ATR): 1734, 1514, 1252, 1227, 1163, 1140, 1107, 1045, 1034, 826 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.73–6.78 (m, 4 H), 4.33–4.43 (m, 3 H), 4.20–4.25 (m, 1 H), 3.70 (s, 3 H), 2.79 (q, *J* = 1.3 Hz, 3 H), 1.93 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 170.3, 153.6, 143.5, 125.5 (q, *J* = 289.4 Hz), 116.5 (2 C), 114.7 (2 C), 65.2, 64.7 (q, *J* = 27.2 Hz), 55.6, 52.5, 33.2, 20.5.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –64.59 (d, *J* = 6.1 Hz, 3 F).

MS (70 eV): *m*/*z* = 340 ([M$^+$ + 1], 100).

### *anti*-2-Chloro-4,4,4-trifluoro-3-[*N*-(4-methoxybenzyl)-*N*-methylamino]butyl Acetate (7b)

Yield: 0.02 g (0.06 mmol, 18%); yellowish solid; mp 47 °C; $R_f$ = 0.23 (hexane/EtOAc 10:1).

IR (ATR): 1744, 1512, 1233, 1169, 1119, 1107, 1061, 1034 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.6 Hz, 2 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 4.55 (dd, *J* = 11.8, 2.7 Hz, 1 H), 4.25–4.35 (m, 2 H), 3.82 (d, *J* = 12.8 Hz, 1 H), 3.80 (s, 3 H), 3.77 (d, *J* = 12.8 Hz, 1 H), 3.49 (dq, *J* = 9.1, 7.7 Hz, 1 H), 2.38 (q, *J* = 1.8 Hz, 3 H), 2.05 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 170.6, 159.1, 130.1 (2 C), 129.7, 126.6 (q, *J* = 293.4 Hz), 113.9 (2 C), 65.6, 65.0 (q, *J* = 24.9 Hz), 60.0, 55.3, 53.1, 36.5, 20.7.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –62.33 (d, *J* = 7.7 Hz, 3 F).

MS (70 eV): *m*/*z* = 371 ([M$^+$ + 18], 40).

### *anti*-$N^1$-(*tert*-Butyl)-2-chloro-4,4,4-trifluoro-$N^3$-(4-methoxybenzyl/phenyl)-$N^3$-methylbutane-1,3-diamines 8; *anti*-$N^1$-(*tert*-Butyl)-2-chloro-4,4,4-trifluoro-$N^3$-(4-methoxyphenyl)-$N^3$-methylbutane-1,3-diamine (8a); Typical Procedure

In a flame-dried flask under $N_2$ atmosphere, $Me_3OBF_4$ (0.11 g, 0.74 mmol, 2 equiv) was added to an ice-cooled solution of *trans*-3-chloro-1-(4-methoxyphenyl)-2-(trifluoromethyl)azetidine (**5a**; 0.10 g, 0.37 mmol, 1 equiv) in anhyd $CH_2Cl_2$ (5 mL). After stirring for 1 h at r.t., the solvent was evaporated and the resulting residue was redissolved in MeCN (5 mL), followed by the addition of *tert*-butylamine (0.11 g, 0.16 mL, 1.48 mmol, 4 equiv). After stirring at reflux temperature for 1 h, the mixture was extracted with $CH_2Cl_2$ (3 × 5 mL) and the combined organic layers were washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration, and evaporation of the solvent afforded a crude mixture of product **8a** (0.05 g, 0.14 mmol, 38%) and the recovery of the starting material **5a** (0.005 g, 0.02 mmol) in a ratio of 80:20, which were separated by means of preparative TLC (hexane/EtOAc 10:1) to obtain analytically pure samples; yellow oil, solidified in fridge; yield: 0.05 g (0.14 mmol, 38%); $R_f$ = 0.14 (hexane/EtOAc 10:1).

IR (ATR): 2959, 1512, 1246, 1225, 1165, 1132, 1101, 1038, 818, 698 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 9.3 Hz, 2 H), 6.76 (d, *J* = 9.3 Hz, 2 H), 4.53 (dq, *J* = 9.6, 7.5 Hz, 1 H), 4.32 (ddd, *J* = 9.6, 5.6, 3.2 Hz, 1 H), 3.70 (s, 3 H), 2.94 (dd, *J* = 12.3, 3.2 Hz, 1 H), 2.83 (dd, *J* = 12.3, 5.6 Hz, 1 H), 2.76 (q, *J* = 1.4 Hz, 3 H), 0.94 (s, 9 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 153.2, 144.0, 125.9 (q, *J* = 290.0 Hz), 116.5 (2 C), 114.5 (2 C), 64.7 (q, *J* = 26.5 Hz), 57.1, 55.6, 50.1, 45.5, 32.9, 29.0.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –64.15 (d, *J* = 7.5 Hz, 3 F).

MS (70 eV): *m*/*z* = 353 ([M$^+$ + 1], 100).

### *anti*-*N*$^1$-(*tert*-Butyl)-2-chloro-4,4,4-trifluoro-*N*$^3$-(4-methoxybenzyl)-*N*$^3$-methylbutane-1,3-diamine (8b)

Yield: 0.04 g (0.11 mmol, 11%); yellowish oil; $R_f$ = 0.25 (PE/EtOAc 12:1).

IR (ATR): 2967, 2928, 1512, 1244, 1169, 1103, 1034, 829, 814 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.6 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 3.80 (s, 3 H), 3.79 (d, *J* = 13.3 Hz, 1 H), 3.73 (d, *J* = 13.3 Hz, 1 H), 2.70 (quint, *J* = 8.3 Hz, 1 H), 2.44 (q, *J* = 1.2 Hz, 3 H), 2.02 (ddd, *J* = 8.3, 6.5, 3.1 Hz, 1 H), 1.63 (d, *J* = 6.5 Hz, 1 H), 1.49 (d, *J* = 3.1 Hz, 1 H), 0.98 (s, 9 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 158.8, 131.0, 129.6 (2 C), 127.2 (q, *J* = 290.9 Hz), 113.8 (2 C), 66.8 (q, *J* = 24.6 Hz), 58.9, 55.3, 53.2, 38.2, 29.4, 26.4, 24.5.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –67.19 (d, *J* = 8.3 Hz, 3 F).

MS (70 eV): *m*/*z* = 331 ([M$^+$ – 35], 100).

### *anti*-2-Chloro-4,4,4-trifluoro-3-[(4-methoxybenzyl/phenyl)amino]butan-1-ols 9;*anti*-2-Chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol (9a); Typical Procedure

To an ice-cooled solution of *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**4a**; 0.50 g, 1.79 mmol, 1 equiv) in $Et_2O$ (10 mL) was added a 1 M solution of $LiAlH_4$ in THF (1.79 mL, 0.07 g, 1.79 mmol, 1 equiv) in small portions whilst stirring. After stirring for 5 min at r.t., the 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 the combined organic layers ($MgSO_4$), filtration, and evaporation of the solvent afforded **9a**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 3:1) to obtain an analytically pure sample; yield: 0.49 g (1.73 mmol, 96%); yellowish oil; $R_f$ = 0.32 (hexane/EtOAc 3:1).

IR (ATR): 3387, 1510, 1233, 1171, 1125, 1032, 820 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, *J* = 8.9 Hz, 2 H), 6.70 (d, *J* = 8.9 Hz, 2 H), 3.92–4.29 (m, 5 H), 3.74 (s, 3 H), 2.43 (t, *J* = 6.4 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 153.6, 139.9, 125.1 (q, *J* = 284.8 Hz), 115.9 (2 C), 115.0 (2 C), 64.1 (q, *J* = 2.0 Hz), 60.8 (q, *J* = 28.5 Hz), 59.0, 55.7.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –71.30 (d, *J* = 6.6 Hz, 3 F).

MS (70 eV): *m*/*z* = 284 ([M$^+$ + 1], 100).

### *anti*-2-Chloro-4,4,4-trifluoro-3-[(4-methoxybenzyl)amino]butan-1-ol (9b)

Yield: 0.46 g (1.55 mmol, 90%); yellowish oil; $R_f$ = 0.43 (hexane/EtOAc 3:1).

IR (ATR): 3356, 1512, 1244, 1163, 1126, 1032, 831, 816 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.6 Hz, 2 H), 4.17 (q, *J* = 5.6 Hz, 1 H), 4.02 (d, *J* = 12.7 Hz, 1 H), 3.99 (dd, *J* = 12.3, 5.0 Hz, 1 H), 3.877 (dd, *J* = 12.3, 4.5 Hz, 1 H), 3.876 (d, *J* = 12.7 Hz, 1 H), 3.83 (s, 3 H), 3.54 (qd, *J* = 7.4, 5.6 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 159.2, 130.4, 129.8 (2 C), 125.6 (q, *J* = 285.6 Hz), 114.0 (2 C), 64.8 (q, *J* = 1.2 Hz), 62.3 (q, *J* = 27.1 Hz), 58.6, 55.3, 52.4.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –70.36 (d, *J* = 7.4 Hz, 3 F).

GC-MS: *m*/*z* (%) = 297 (M$^+$, 2), 174 (6), 136 (11), 121 (100), 78 (8).

### *trans*-5-Chloro-3-(4-methoxybenzyl/phenyl)-4-trifluoromethyl-1,3-oxazinanes 10; *trans*-5-Chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinane (10a); Typical Procedure

To a solution of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol (**9a**; 0.10 g, 0.35 mmol, 1 equiv) in THF (5 mL) in a pressure vial was added an excess of formaldehyde (37% solution in $H_2O$, 1 mL) at r.t. The resulting mixture was stirred for 3 h under reflux, after which $H_2O$ (5 mL) was added to the mixture. Extraction with EtOAc (3 × 7 mL), drying of the combined organic layers ($MgSO_4$), filtration, and evaporation of the solvent afforded **10a**, which was purified by means of preparative of TLC (hexane/EtOAc 10:1) to provide an analytically pure sample; yield: 0.06 g (0.20 mmol, 54%); yellowish solid; mp 64 °C; $R_f$ = 0.53 (hexane/EtOAc 10:1).

IR (ATR): 1508, 1238, 1223, 1182, 1167, 1136, 1109, 1074, 1051, 1034, 999, 972, 851, 833, 824, 785, 665, 530 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.22 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.04 (d, *J* = 11.7 Hz, 1 H), 4.98 (dq, *J* = 11.7, 1.4 Hz, 1 H), 4.26–4.33 (m, 2 H), 4.11–4.20 (m, 2 H), 3.81 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 155.7, 145.0, 124.8 (q, *J* = 284.8 Hz), 122.0 (2 C), 114.4 (2 C), 78.7 (q, *J* = 1.7 Hz), 69.4, 66.5 (q, *J* = 29.6 Hz), 55.5, 49.9.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –70.96 (d, *J* = 9.0 Hz, 3 F).

MS (70 eV): *m*/*z* = 296 ([M$^+$ + 1], 100).

### *trans*-5-Chloro-3-(4-methoxybenzyl)-4-trifluoromethyl-1,3-oxazinane (10b)

Yield: 0.04 g (0.13 mmol, 80%); white yellowish solid; mp 89 °C; $R_f$ = 0.41 (hexane/EtOAc 10:1).

IR (ATR): 1510, 1246, 1182, 1167, 1109, 1090, 1053, 1034, 999, 970, 837, 665, 515 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.7 Hz, 2 H), 6.87 (d, *J* = 8.7 Hz, 2 H), 4.59 (dq, *J* = 11.5, 1.1 Hz, 1 H), 4.38 (d, *J* = 11.5 Hz, 1 H), 4.30 (d, *J* = 13.3 Hz, 1 H), 4.20–4.25 (m, 3 H), 4.06 (dd, *J* = 14.2, 3.4 Hz, 1 H), 3.81 (s, 3 H), 3.65 (qd, *J* = 9.2, 2.3 Hz, 1 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 159.2, 130.4 (2 C), 129.5, 124.5 (q, *J* = 283.9 Hz), 113.8 (2 C), 80.2 (q, *J* = 1.2 Hz), 70.8, 62.6 (q, *J* = 29.0 Hz), 57.8, 55.3, 49.2.

$^{19}$F NMR (376 MHz, $CDCl_3$): δ = –69.60 (d, *J* = 9.2 Hz, 3 F).

GC-MS: *m*/*z* (%) = 309 (M$^+$, 8), 121 (100), 78 (8).

### *trans*-5-Chloro-3-(4-methoxybenzyl/phenyl)-4-trifluoromethyl-1,3-oxazinan-2-ones 11; *trans*-5-Chloro-3-(4-methoxyphenyl)-4-trifluoromethyl-1,3-oxazinan-2-one (11a); Typical Procedure

To a solution of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol (**9a**; 0.10 g, 0.35 mmol, 1 equiv) in anhyd $CH_2Cl_2$ (8 mL) was added $Et_3N$ (0.07 g, 0.1 mL, 0.70 mmol, 2 equiv) at 0 °C. Ethyl chloroformate (0.04 g, 0.04 mL, 0.35 mmol, 1 equiv) was added dropwise to the solution. The mixture was stirred at r.t. for 3 h,

after which the reaction mixture was extracted with $CH_2Cl_2$ (3 × 5 mL) and the combined organic layers were washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo afforded a mixture of **9a** and product **11a** in a ratio of 66:34. The mixture was redissolved in anhyd $CH_2Cl_2$ (5 mL) and an analogous procedure was repeated two more times. In this way, the starting material **9a** was completely converted into product **11a**, which was purified by means of preparative TLC (hexane/EtOAc 4:1) to obtain an analytically pure sample; yield: 0.03 g (0.10 mmol, 29%); white yellowish solid; mp 100 °C; $R_f$ = 0.12 (hexane/EtOAc 4:1).

IR (ATR): 1705, 1514, 1429, 1319, 1184, 1167, 1134, 1115, 1026, 827, 748, 665, 581 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.9 Hz, 2 H), 6.94 (d, *J* = 8.9 Hz, 2 H), 4.83 (dd, *J* = 13.3, 2.3 Hz, 1 H), 4.68 (q, *J* = 2.3 Hz, 1 H), 4.51 (d, *J* = 13.3 Hz, 1 H), 4.43 (qt, *J* = 6.5, 2.3 Hz, 1 H), 3.82 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 159.3, 150.2, 134.2, 128.7 (2 C), 123.1 (q, *J* = 285.7 Hz), 114.8 (2 C), 69.0 (q, *J* = 2.2 Hz), 67.0 (q, *J* = 29.9 Hz), 55.5, 46.8 (q, *J* = 1.2 Hz).

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –71.67 (d, *J* = 6.5 Hz, 3 F).

MS (70 eV): *m*/*z* = 310 ([$M^+$ + 1], 100).

### *trans*-5-Chloro-3-(4-methoxybenzyl)-4-trifluoromethyl-1,3-oxazinan-2-one (11b)

Yield: 0.07 g (0.22 mmol, 85%); yellow solid; mp 68 °C; $R_f$ = 0.21 (hexane/EtOAc 4:1).

IR (ATR): 1697, 1512, 1435, 1250, 1231, 1209, 1165, 1148, 1111, 1092, 1032, 1011, 750, 669, 588 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.5 Hz, 2 H), 6.89 (d, *J* = 8.5 Hz, 2 H), 5.54 (d, *J* = 14.8 Hz, 1 H), 4.68 (dd, *J* = 13.1, 2.4 Hz, 1 H), 4.45 (q, *J* = 2.4 Hz, 1 H), 4.31 (dq, *J* = 13.1, 1.1 Hz, 1 H), 3.96 (d, *J* = 14.8 Hz, 1 H), 3.91 (qt, *J* = 6.5, 2.4 Hz, 1 H), 3.81 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 159.8, 151.0, 130.8 (2 C), 125.9, 123.6 (q, *J* = 286.1 Hz), 114.2 (2 C), 68.3 (q, *J* = 2.0 Hz), 59.8 (q, *J* = 30.0 Hz), 55.3, 51.0 (q, *J* = 1.2 Hz), 46.3 (q, *J* = 1.2 Hz).

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –71.03 (d, *J* = 6.5 Hz, 3 F).

MS (70 eV): *m*/*z* = 324 ([$M^+$ + 1], 60).

### *trans*-2-Hydroxymethyl-1-(4-methoxybenzyl/phenyl)-3-(trifluoromethyl)aziridines 12; *trans*-2-Hydroxymethyl-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridine (12a); Typical Procedure

A 1 M solution of *t*-BuOK in THF (0.28 mL, 0.03 g, 0.28 mmol, 0.8 equiv) was added dropwise to a stirred solution of *anti*-2-chloro-4,4,4-trifluoro-3-[(4-methoxyphenyl)amino]butan-1-ol (**9a**; 0.10 g, 0.35 mmol, 1 equiv) in anhyd THF (5 mL), and the resulting suspension was stirred at r.t. under argon for 10 min. The reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration, and removal of the solvent in vacuo afforded **12a**, which was purified by means of preparative TLC (hexane/EtOAc 5:1) to obtain an analytically pure sample; yield: 0.02 g (0.08 mmol, 27%); orange solid; mp 53 °C; $R_f$ = 0.38 (hexane/EtOAc 5:1).

IR (ATR): 3374, 1514, 1258, 1231, 1165, 1148, 1125, 1111, 1034, 824, 764, 525 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 8.9 Hz, 2 H), 6.62 (d, *J* = 8.9 Hz, 2 H), 4.03–4.11 (m, 1 H), 3.74 (s, 3 H), 3.65 (d, *J* = 9.4 Hz, 1 H), 3.37–3.39 (m, 1 H), 2.79 (dd, *J* = 4.8, 4.2 Hz, 1 H), 2.68 (dd, *J* = 4.8, 2.6 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 153.3, 139.9, 125.4 (q, *J* = 284.0 Hz), 115.1 (2 C), 115.0 (2 C), 55.7, 55.6 (q, *J* = 29.3 Hz), 48.1 (q, *J* = 2.7 Hz), 42.3.

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –74.78 (d, *J* = 7.9 Hz, 3 F).

MS (70 eV): *m*/*z* = 248 ([$M^+$ + 1], 100).

### *trans*-2-Hydroxymethyl-1-(4-methoxybenzyl)-3-(trifluoromethyl)aziridine (12b)

Yield: 0.04 g (0.15 mmol, 61%); light yellow oil; $R_f$ = 0.46 (hexane/EtOAc 4:1).

IR (ATR): 3350, 1512, 1246, 1150, 1123, 1105, 1034, 831, 816 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 3.98 (d, *J* = 13.1 Hz, 1 H), 3.90 (d, *J* = 13.1 Hz, 1 H), 3.83 (s, 3 H), 3.17 (td, *J* = 4.3, 2.6 Hz, 1 H), 3.05 (qd, *J* = 7.3, 4.3 Hz, 1 H), 2.82 (dd, *J* = 5.1, 4.3 Hz, 1 H), 2.78 (dd, *J* = 5.1, 2.6 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 158.9, 131.2, 129.5 (2 C), 125.8 (q, *J* = 284.3 Hz), 113.9 (2 C), 59.1 (q, *J* = 27.5 Hz), 55.3, 51.0, 49.7 (q, *J* = 2.9 Hz), 43.6.

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –73.15 (d, *J* = 7.3 Hz, 3 F).

GC-MS: *m*/*z* (%) = 261 ($M^+$, 17), 136 (19), 121 (100), 78 (9).

### *trans*-2-Methoxycarbonyl-1-(4-methoxybenzyl/phenyl)-3-(trifluoromethyl)aziridines 13; *trans*-2-Methoxycarbonyl-1-(4-methoxyphenyl)-3-(trifluoromethyl)aziridine (13a); Typical Procedure

KOH (0.02 g, 0.36 mmol, 2 equiv) was added to a solution of *trans*-3-chloro-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**4a**; 0.05 g, 0.18 mmol, 1 equiv) in MeOH (6 mL). After stirring for 20 min under reflux, the reaction mixture was cooled to 0 °C, and quenched with $H_2O$ (5 mL). Extraction with EtOAc (3 × 5 mL), drying of the combined organic layers ($MgSO_4$), filtration, and evaporation of the solvent afforded **13a**, which was purified by means of preparative TLC (hexane/EtOAc 5:1) to provide white yellowish solid; yield: 0.04 g (0.14 mmol, 73%); mp 74 °C; $R_f$ = 0.40 (hexane/EtOAc 5:1).

IR (ATR): 1730, 1508, 1265, 1246, 1148, 1080, 1030, 1013, 872, 833, 696 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 6.71–6.76 (m, 4 H), 3.68 (s, 3 H), 3.57 (s, 3 H), 3.30–3.33 (m, 2 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 165.7, 156.2, 139.3, 122.9 (q, *J* = 273.9 Hz), 120.3 (2 C), 114.5 (2 C), 55.4, 52.8, 42.1 (q, *J* = 40.7 Hz), 39.2 (q, *J* = 1.9 Hz).

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –71.08 (~s, 3 F).

MS (70 eV): *m*/*z* = 276 ([$M^+$ + 1], 100).

### *trans*-1-(4-Methoxybenzyl)-2-methoxycarbonyl-3-(trifluoromethyl)aziridine (13b)

Yield: 0.02 g (0.07 mmol, 25%); light yellow oil; $R_f$ = 0.21 (hexane/EtOAc 5:1).

IR (ATR): 1736, 1514, 1344, 1246, 1207, 1175, 1144, 1032, 804 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.6 Hz, 2 H), 6.79 (d, *J* = 8.6 Hz, 2 H), 3.94 (d, *J* = 13.0 Hz, 1 H), 3.80 (d, *J* = 13.0 Hz, 1 H), 3.73 (s, 3 H), 3.66 (s, 3 H), 2.86–2.91 (m, 2 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 167.3, 159.0, 129.53 (2 C), 129.49, 123.0 (q, *J* = 273.9 Hz), 113.8 (2 C), 55.2, 53.8, 52.2, 43.7 (q, *J* =39.7 Hz), 37.3.

$^{19}F$ NMR (376 MHz, $CDCl_3$): δ = –71.28 (~s, 3 F).

GC-MS: *m*/*z* (%) = 290 ($M^+$, 4), 274 (10), 258 (8), 220 (17), 188 (16), 136 (16), 121 (100), 78 (7).

### *cis*-3-Allyloxy-4-(trifluoromethyl)azetidin-2-ones 14; *cis*-3-Allyloxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one (14b); Typical Procedure

To a solution of *cis*-3-hydroxy-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one (**3b**; 0.30 g, 1.09 mmol, 1 equiv), $Bu_4NI$ (0.003 g, 0.01 mmol, 0.01 equiv), and allyl bromide (0.21 g, 0.15 mL, 1.74 mmol, 1.6 equiv) in $CH_2Cl_2$ (10 mL) was added 50% aq NaOH (5 g, 10 mL). After stirring for 3 h at r.t., the reaction mixture was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered, and the solvent evaporated in vacuo to afforded **14b**, which was purified by means of column chromatography (hexane/EtOAc 5:1) to obtain an analytically pure sample; yield: 0.33 g (1.04 mmol, 95%); white crystals; mp 67 °C; $R_f$ = 0.27 (hexane/EtOAc 5:1).

IR (ATR): 1759, 1514, 1352, 1279, 1244, 1152, 1126, 1113, 1032, 920, 837, 669, 635, 590, 519 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.5 Hz, 2 H), 6.87 (d, *J* = 8.5 Hz, 2 H), 5.88 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1 H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1 H), 5.25 (d, *J* = 10.6 Hz, 1 H), 4.81 (d, *J* = 14.8 Hz, 1 H), 4.74 (d, *J* = 5.6 Hz, 1 H), 4.18 (d, *J* = 5.5 Hz, 2 H), 3.95 (d, *J* = 14.8 Hz, 1 H), 3.87 (quint, *J* = 5.6 Hz, 1 H), 3.80 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 166.4, 159.6, 132.9, 129.9 (2 C), 126.1, 123.9 (q, *J* = 280.2 Hz), 118.7, 114.4 (2 C), 81.1, 72.8, 56.4 (q, *J* = 32.7 Hz), 55.3, 44.5.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –69.33 (d, *J* = 5.6 Hz, 3 F).

MS (70 eV): *m*/*z* = 316 ([$M^+$ + 1], 100).

### *cis*-3-Allyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (14a)

Yield: 0.20 g (0.66 mmol, 94%); white crystals; mp 81 °C ($CH_2Cl_2$/$Et_2O$ 1:3); $R_f$ = 0.61 (hexane/EtOAc 2:1).

IR (ATR): 1759, 1516, 1389, 1273, 1134, 982, 837, 808, 642, 505 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 9.0 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 5.94 (ddt, *J* = 17.2, 10.6, 5.4 Hz, 1 H), 5.39 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.30 (dq, *J* = 10.6, 1.3 Hz, 1 H), 4.96 (d, *J* = 5.4 Hz, 1 H), 4.61 (quint, *J* = 5.4 Hz, 1 H), 4.22–4.32 (m, 2 H), 3.80 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 163.9, 157.2, 132.8, 129.4, 123.7 (q, *J* = 280.7 Hz), 119.4 (2 C), 118.9, 114.4 (2 C), 80.4, 73.1, 57.8 (q, *J* = 33.0 Hz), 55.5.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.52 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 302 ([$M^+$ + 1], 100).

### *cis*-3-Allyloxy-1-(4-ethoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (14c)

Yield: 0.31 g (0.98 mmol, 84%); white crystals; mp 83 °C ($CH_2Cl_2$/$Et_2O$ 1:3).

IR (ATR): 1757, 1518, 1391, 1258, 1136, 1111, 980, 922, 824, 650, 525 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 9.0 Hz, 2 H), 6.86 (d, *J* = 9.0 Hz, 2 H), 5.93 (ddt, *J* = 17.2, 10.7, 5.4 Hz, 1 H), 5.38 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.29 (dq, *J* = 10.7, 1.4 Hz, 1 H), 4.95 (d, *J* = 5.4 Hz, 1 H), 4.61 (quint, *J* = 5.4 Hz, 1 H), 4.21–4.30 (m, 2 H), 4.00 (q, *J* = 7.0 Hz, 2 H), 1.39 (t, *J* = 7.0 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.0, 156.6, 132.8, 129.3, 123.7 (q, *J* = 280.8 Hz), 119.4 (2 C), 118.8, 115.0 (2 C), 80.5, 73.0, 63.7, 57.8 (q, *J* = 33.0 Hz), 14.8.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.54 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 316 ([$M^+$ + 1], 100).

### *cis*-3-Allyloxy-1-phenyl-4-(trifluoromethyl)azetidin-2-one (14d)

Yield: 0.28 g (1.03 mmol, 77%); white yellowish solid; mp <45 °C; $R_f$ = 0.36 (PE/EtOAc 4:1).

IR (ATR): 1767, 1599, 1499, 1360, 1279, 1134, 989, 930, 752, 689, 490 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 7.7 Hz, 2 H), 7.36 (t, *J* = 7.7 Hz, 2 H), 7.18 (t, *J* = 7.7 Hz, 1 H), 5.94 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1 H), 5.40 (dq, *J* = 17.3, 1.5 Hz, 1 H), 5.31 (dq, *J* = 10.6, 1.3 Hz, 1 H), 4.98 (d, *J* = 5.4 Hz, 1 H), 4.67 (quint, *J* = 5.4 Hz, 1 H), 4.24–4.32 (m, 2 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.3, 136.2, 132.8, 129.3 (2 C), 125.5, 123.7 (q, *J* = 280.8 Hz), 119.0, 117.6 (2 C), 80.3, 73.1, 57.5 (q, *J* = 33.2 Hz).

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.41 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 272 ([$M^+$ + 1], 100).

### *cis*-3-Allyloxy-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one (14e)

Yield: 0.29 g (1.02 mmol, 71%); white crystals; mp 78 °C ($CH_2Cl_2$/$Et_2O$ 1:3).

IR (ATR): 1748, 1516, 1396, 1364, 1275, 1246, 1167, 1134, 1005, 816, 646, 482 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.2 Hz, 2 H), 7.09 (d, *J* = 8.2 Hz, 2 H), 5.87 (ddt, *J* = 17.2, 10.7, 5.5 Hz, 1 H), 5.32 (d, *J* = 17.2 Hz, 1 H), 5.23 (d, *J* = 10.7 Hz, 1 H), 4.89 (d, *J* = 5.4 Hz, 1 H), 4.57 (quint, *J* = 5.4 Hz, 1 H), 4.15–4.24 (m, 2 H), 2.25 (s, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.1, 135.3, 133.7, 132.8, 129.7 (2 C), 123.7 (q, *J* = 280.9 Hz), 118.9, 117.7 (2 C), 80.3, 73.1, 57.5 (q, *J* = 33.2 Hz), 20.9.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.46 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 286 ([$M^+$ + 1], 100).

### *cis*-3-Allyloxy-1-isopropyl-4-(trifluoromethyl)azetidin-2-one (14f)

Yield: 0.32 g (1.35 mmol, 79%); white yellowish oil, solidified in fridge; $R_f$ = 0.42 (PE/EtOAc 4:1).

IR (ATR): 1761, 1281, 1213, 1148, 1123, 1009, 928, 660 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 5.90 (dqt, *J* = 17.2, 10.6, 5.4 Hz, 1 H), 5.35 (dq, *J* = 17.2, 1.6 Hz, 1 H), 5.26 (dq, *J* = 10.6, 1.4 Hz, 1 H), 4.74 (d, *J* = 4.8 Hz, 1 H), 4.15–4.24 (m, 2 H), 4.11 (qd, *J* = 6.0, 4.8 Hz, 1 H), 3.88 (sept, *J* = 6.8 Hz, 1 H), 1.29 (d, *J* = 6.8 Hz, 3 H), 1.26 (d, *J* = 6.8 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 166.2, 133.0, 123.9 (q, *J* = 279.8 Hz), 118.5, 80.2, 72.7, 56.6 (q, *J* = 33.0 Hz), 45.1, 21.1, 19.3.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –69.49 (d, *J* = 6.0 Hz, 3 F).

MS (70 eV): *m*/*z* = 238 ([$M^+$ + 1], 100).

### 3-(2-Hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-ones 15; *cis*-3-(2-Hydroxyethoxy)-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (15a); Typical Procedure

In a 250 mL flame-dried flask, *cis*-3-allyloxy-1-(4-methoxyphenyl)-4-(trifluoromethyl)azetidin-2-one (**14a**; 0.12 g, 0.40 mmol, 1 equiv)

was dissolved in a mixture of anhyd $CH_2Cl_2$ (15 mL) and anhyd MeOH (10 mL). A small pinch of Sudan III indicator was added to the reaction mixture. The mixture was sparged with $O_3$ at –78 °C until the red color of the reaction mixture dissipated. The mixture was stirred for 1 h at r.t. in the presence of $Me_2S$ (0.06 g, 0.07 mL, 1 mmol, 2.5 equiv), after which the mixture was extracted with $H_2O$ (10 mL). The aqueous phase was then extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic extracts were washed with brine (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure, affording a crude mixture. To the crude mixture in anhyd THF (6 mL) at 0 °C was added gradually $BH_3$ (1 M in $Et_2O$, 1 mL, 1 mmol, 2.5 equiv). The temperature was allowed to rise to r.t. and the reaction mixture was stirred for 3 h at this temperature. The mixture was extracted with EtOAc (3 × 8 mL) and the combined extracts were washed with brine (3 × 5 mL). Drying ($MgSO_4$), filtration, and evaporation of the solvent in vacuo afforded **15a**, which was purified by means of column chromatography (hexane/EtOAc 3:1) to obtain an analytically pure sample; yield: 0.09 g (0.30 mmol, 72%); yellow oil; $R_f$ = 0.14 (hexane/EtOAc 3:1).

IR (ATR): 3393, 1744, 1512, 1233, 1128, 1032, 822, 681 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 9.0 Hz, 2 H), 4.95 (d, *J* = 5.4 Hz, 1 H), 4.60 (quint, *J* = 5.4 Hz, 1 H), 3.85–3.91 (m, 1 H), 3.75–3.80 (m, 3 H), 3.73 (s, 3 H), 2.67 (t, *J* = 5.7 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.6, 157.4, 129.1, 123.6 (q, *J* = 281.0 Hz), 119.6 (2 C), 114.5 (2 C), 82.2, 74.9, 62.2, 58.0 (q, *J* = 33.1 Hz), 55.5.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.42 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 306 ([$M^+$ + 1], 100).

### *cis*-3-(2-Hydroxyethoxy)-1-(4-methoxybenzyl)-4-(trifluoromethyl)azetidin-2-one (15b)

Yield: 0.10 g (0.31 mmol, 77%); yellowish oil; *Rf* = 0.15 (hexane/EtOAc 1:1).

IR (ATR): 3431, 1759, 1514, 1279, 1246, 1159, 1130, 1030, 800, 664, 513 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.16 (d, *J* = 8.6 Hz, 2 H), 6.88 (d, *J* = 8.6 Hz, 2 H), 4.81 (d, *J* = 14.5 Hz, 1 H), 4.80 (d, *J* = 4.9 Hz, 1 H), 3.97 (d, *J* = 14.5 Hz, 1 H), 3.94 (qd, *J* = 6.1, 4.9 Hz, 1 H), 3.82–3.88 (m, 1 H), 3.81 (s, 3 H), 3.71–3.79 (m, 3 H), 2.89 (t, *J* = 6.6 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 167.2, 159.6, 129.9 (2 C), 125.8, 123.8 (q, *J* = 280.2 Hz), 114.4 (2 C), 82.7, 74.8, 62.2, 56.7 (q, *J* = 32.9 Hz), 55.3, 44.6.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –69.26 (d, *J* = 6.1 Hz, 3 F).

MS (70 eV): *m*/*z* = 320 ([$M^+$ + 1], 100).

### *cis*-1-(4-Ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one (15c)

Yield: 0.12 g (0.38 mmol, 72%); white solid; mp 81 °C; $R_f$ = 0.10 (PE/EtOAc 2:1).

IR (ATR): 3399, 1759, 1510, 1391, 1250, 1169, 1146, 1121, 1043, 841, 824, 656 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 9.0 Hz, 2 H), 6.88 (d, *J* = 9.0 Hz, 2 H), 5.02 (d, *J* = 5.4 Hz, 1 H), 4.67 (quint, *J* = 5.4 Hz, 1 H), 4.01 (q, *J* = 7.0 Hz, 2 H), 3.91–395 (m, 1 H), 3.77–3.89 (m, 3 H), 2.93 (t, *J* = 6.2 Hz, 1 H), 1.40 (t, *J* = 7.0 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.6, 156.8, 129.0, 123.6 (q, *J* = 280.9 Hz), 119.5 (2 C), 115.0 (2 C), 82.1, 74.9, 63.8, 62.1, 58.0 (q, *J* = 33.1 Hz), 14.8.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.44 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 320 ([$M^+$ + 1], 100).

### *cis*-3-(2-Hydroxyethoxy)-1,4-bis(4-methoxyphenyl)azetidin-2-one (19)

Yield: 0.06 g (0.17 mmol, 51%); white crystals; mp 105 °C; $R_f$ = 0.10 (PE/EtOAc 1:1).

IR (ATR): 3273, 1736, 1510, 1396, 1298, 1236, 1175, 1132, 1028, 835, 800, 540 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.6 Hz, 2 H), 7.19 (d, *J* = 9.0 Hz, 2 H), 6.84 (d, *J* = 8.6 Hz, 2 H), 6.71 (d, *J* = 9.0 Hz, 2 H), 5.11 (d, *J* = 4.8 Hz, 1 H), 4.85 (d, *J* = 4.8 Hz, 1 H), 3.72 (s, 3 H), 3.66 (s, 3 H), 3.30–3.55 (m, 4 H), 2.32 (t, *J* = 6.7 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.5, 160.0, 156.5, 130.4, 129.3 (2 C), 125.1, 118.9 (2 C), 114.3 (2 C), 114.1 (2 C), 83.9, 73.4, 62.0, 61.9, 55.4, 55.3.

MS (70 eV): *m*/*z* = 344 ([$M^+$ + 1], 100).

### *trans*-1-(4-Ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one (21)

Yield: 0.02 g (0.06 mmol, 11%); colorless oil; $R_f$ = 0.42 (PE/EtOAc 1:1).

IR (ATR): 3447, 1755, 1512, 1395, 1246, 1159, 1115, 1045, 829, 700, 515 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.9 Hz, 2 H), 6.89 (d, *J* = 8.9 Hz, 2 H), 4.87 (d, *J* = 1.3 Hz, 1 H), 4.45 (qd, *J* = 5.6, 1.3 Hz, 1 H), 4.02 (q, *J* = 7.0 Hz, 2 H), 3.78–3.93 (m, 4 H), 2.77 (t, *J* = 5.5 Hz, 1 H), 1.41 (t, *J* = 7.0 Hz, 3 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 163.2, 157.0, 128.6, 123.5 (q, *J* = 280.3 Hz), 120.2 (2 C), 115.1 (2 C), 83.3 (q, *J* = 1.5 Hz), 73.6, 63.8, 61.9, 60.1 (q, *J* = 34.3 Hz), 14.8.

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –71.48 (d, *J* = 5.6 Hz, 3 F).

MS (70 eV): *m*/*z* = 320 ([$M^+$ + 1], 100).

### *cis*-3-(2-Hydroxyethoxy)-1-phenyl-4-(trifluoromethyl)azetidin-2-one (15d)

Yield: 0.06 g (0.22 mmol, 95%); yellowish oil; $R_f$ = 0.31 (PE/EtOAc 1:1).

IR (ATR): 3428, 1761, 1599, 1499, 1360, 1277, 1136, 752, 689, 486 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 7.8 Hz, 2 H), 7.31 (t, *J* = 7.8 Hz, 2 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 4.97 (d, *J* = 5.4 Hz, 1 H), 4.67 (quint, *J* = 5.4 Hz, 1 H), 3.72–3.92 (m, 4 H), 2.55 (t, *J* = 5.6 Hz, 1 H).

$^{13}C$ NMR (100.6 MHz, $CDCl_3$): δ = 164.9, 136.0, 129.3 (2 C), 125.7, 123.6 (q, *J* = 280.2 Hz), 117.7 (2 C), 82.1, 74.9, 62.2, 57.7 (q, *J* = 33.3 Hz).

$^{19}F$ NMR (376.5 MHz, $CDCl_3$): δ = –68.31 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 276 ([$M^+$ + 1], 100).

### *cis*-3-(2-Hydroxyethoxy)-1-(4-methylphenyl)-4-(trifluoromethyl)azetidin-2-one (15e)

Yield: 0.10 g (0.35 mmol, 63%); white crystals; mp 79 °C; $R_f$ = 0.14 (PE/EtOAc 2:1).

IR (ATR): 3358, 1753, 1514, 1398, 1366, 1275, 1244, 1140, 1028, 814, 646, 494 $cm^{-1}$.

$^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.3 Hz, 2 H), 7.10 (d, *J* = 8.3 Hz, 2 H), 4.95 (d, *J* = 5.4 Hz, 1 H), 4.63 (quint, *J* = 5.4 Hz, 1 H), 3.73–3.91 (m, 4 H), 2.65 (br s, 1 H), 2.26 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 164.8, 135.6, 133.5, 129.8 (2 C), 123.6 (q, *J* = 281.0 Hz), 117.8 (2 C), 82.1, 74.9, 62.2, 57.8 (q, *J* = 33.1 Hz), 21.0.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –68.36 (d, *J* = 5.4 Hz, 3 F).

MS (70 eV): *m*/*z* = 290 ([M$^+$ + 1], 100).

### *cis*-3-(2-Hydroxyethoxy)-1-isopropyl-4-(trifluoromethyl)azetidin-2-one (15f)

Yield: 0.07 g (0.29 mmol, 47%); yellow oil; $R_f$ = 0.15 (PE/EtOAc 1:1).

IR (ATR): 3428, 1755, 1281, 1217, 1148, 1042, 849, 660 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 4.79 (d, *J* = 4.9 Hz, 1 H), 4.17 (qd, *J* = 6.1, 4.9 Hz, 1 H), 3.71–3.91 (m, 5 H), 3.12 (t, *J* = 6.4 Hz, 1 H), 1.31 (d, *J* = 6.8 Hz, 3 H), 1.27 (d, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 167.2, 123.7 (q, *J* = 279.8 Hz), 81.8, 74.8, 62.2, 56.9 (q, *J* = 33.1 Hz), 45.4, 21.0, 19.4.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –69.40 (d, *J* = 6.1 Hz, 3 F).

MS (70 eV): *m*/*z* = 242 ([M$^+$ + 1], 100).

### 3-[2,2,2-trifluoro-1-(arylamino)ethyl]-1,4-dioxan-2-ones 16; 3-{1-[(4-Ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one (16c); Typical Procedure

A solution of *cis*-1-(4-ethoxyphenyl)-3-(2-hydroxyethoxy)-4-(trifluoromethyl)azetidin-2-one (**15c**; 0.05 g, 0.16 mmol, 1 equiv) in toluene was heated with an excess of $K_2CO_3$ at reflux temperature for 28 h. The reaction mixture was then filtered through a small pad of Celite and concentrated under reduced pressure, resulting in a crude mixture. The $^{19}$F NMR of this mixture showed it to consist of *syn*-3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one and *anti*-3-{1-[(4-ethoxyphenyl)amino]-2,2,2-trifluoroethyl}-1,4-dioxan-2-one (**16c**) in a ratio of 72:28. The mixture was purified by means of preparative TLC (PE/EtOAc 6:1), providing a pure but inseparable mixture of *syn*- and *anti*-**16c** (*syn*/*anti* = 72:28); yield: 0.04 g (0.13 mmol, 86%); yellow crystals; mp 108 °C; $R_f$ = 0.08 (PE/EtOAc 6:1).

The spectral data given below correspond to a mixture of diastereomers.

IR (ATR): 3374, 3352, 1721, 1520, 1231, 1105, 1049, 949, 926, 808, 694, 521 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.71–6.83 (m, 4 H), 4.54–4.74 (m, 3 H), 4.39–4.42 (m, 1 H), 3.80–4.11 (m, 5 H), 1.38 and 1.37 (t, *J* = 7.1 and 6.9 Hz, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 166.2 and 165.9, 153.3, 138.8 and 137.9, 124.9 and 124.5 (q, *J* = 285.9 and 283.5 Hz), 116.8 and 116.5 (2 C), 115.9 and 115.6 (2 C), 75.4 and 74.1 (q, *J* = 1.9 and 1.5 Hz), 68.5, 63.95 and 63.86, 62.8 and 62.7, 59.2 and 59.0 (q, *J* = 28.3 and 29.0 Hz), 14.9.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –70.00 and –72.21 (d, *J* = 6.9 and 7.7 Hz, 3 F).

MS (70 eV): *m*/*z* = 320 ([M$^+$ + 1], 100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{17}F_3NO_4^+$: 320.1104; found: 320.1094.

### 3-{2,2,2-Trifluoro-1-[(4-methoxyphenyl)amino]ethyl}-1,4-dioxan-2-one (16a)

Yield: 0.03 g (0.10 mmol, 81%); *syn*/*anti* = 78:22; yellow oil; $R_f$ = 0.18 (PE/EtOAc 3:1).

The spectral data given below correspond to a mixture of diastereomers.

IR (ATR): 3393, 2922, 1721, 1520, 1458, 1244, 1233, 1140, 1123, 1074, 826, 694, 519 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 6.65–6.77 (m, 4 H), 4.47–4.67 (m, 3 H), 4.32–4.36 (m, 1 H), 3.73–4.05 (m, 3 H), 3.69 and 3.68 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 166.2 and 165.9, 154.0, 138.9 and 138.0, 124.9 (q, *J* = 285.9 Hz), 116.8 and 116.5 (2 C), 115.1 and 114.8 (2 C), 75.4 and 74.1 (q, *J* = 1.9 and 1.5 Hz), 68.55 and 68.53, 62.8 and 62.7, 59.0 (q, *J* = 28.8 Hz), 55.7 and 55.6.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –69.98 and –72.22 (d, *J* = 6.9 and 7.5 Hz, 3 F).

MS (70 eV): *m*/*z* = 306 ([M$^+$ + 1], 100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO_4^+$: 306.0948; found: 306.0935.

### 3-[2,2,2-Trifluoro-1-(phenylamino)ethyl]-1,4-dioxan-2-one (16d)

Yield: 0.02 g (0.07 mmol, 71%); *syn*/*anti* = 69:31; yellowish solid; mp 85 °C; $R_f$ = 0.38 (PE/EtOAc 2:1).

The spectral data given below correspond to a mixture of diastereomers.

IR (ATR): 3385, 1722, 1603, 1254, 1167, 1140, 1111, 1074, 930, 750, 691, 505 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.27 and 6.71–6.89 (m, 5 H), 4.56–4.89 (m, 3 H), 4.41–4.44 (m, 1 H), 3.75–4.29 (m, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 166.0 and 165.7, 145.0 and 144.2, 129.7 and 129.4 (2 C), 124.8 and 124.4 (q, *J* = 285.7 and 282.2 Hz), 120.11 and 120.10, 114.6 and 114.4 (2 C), 75.3 and 74.4 (q, *J* = 1.9 and 1.5 Hz), 68.6 and 68.5, 62.9 and 62.8, 57.6 and 57.1 (q, *J* = 28.8 and 29.5 Hz).

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –70.00 and –72.51 (d, *J* = 6.8 and 7.2 Hz, 3 F).

MS (70 eV): *m*/*z* = 276 ([M$^+$ + 1], 100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}F_3NO_3^+$: 276.0842; found: 276.0846.

### 3-{2,2,2-Trifluoro-[1-(4-methylphenyl)amino]ethyl}-1,4-dioxan-2-one (16e)

Yield: 0.01 g (0.03 mmol, 98%); *syn*/*anti* 75:25; white solid; mp 109 °C; $R_f$ = 0.38 (PE/EtOAc 2:1).

The spectral data given below correspond to a mixture of diastereomers.

IR (ATR): 3383, 3360, 1721, 1526, 1252, 1159, 1125, 1105, 1070, 1047, 930, 812, 692, 519 cm$^{-1}$.

$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.05 and 6.69 (d, *J* = 8.4 Hz, 2 H), 7.01 and 6.68 (d, *J* = 8.3 Hz, 2 H), 4.70–4.83 and 4.54–4.61 (m, 3 H), 4.39–4.43 (m, 1 H), 3.79–4.16 (m, 3 H), 2.26 and 2.24 (s, 3 H).

$^{13}$C NMR (100.6 MHz, $CDCl_3$): δ = 166.1 and 165.8, 142.7 and 141.8, 130.2 and 129.9 (2 C), 129.6 and 129.5, 124.9 and 124.5 (q, *J* = 285.8 and 283.6 Hz), 115.0 and 114.8 (2 C), 75.3 and 74.2 (q, *J* = 1.8 and 1.2 Hz), 68.5, 62.8 and 62.7, 58.2 and 57.8 (q, *J* = 28.8 and 29.3 Hz), 20.45 and 20.43.

$^{19}$F NMR (376.5 MHz, $CDCl_3$): δ = –70.00 and –72.41 (d, *J* = 6.9 and 7.0 Hz, 3 F).

MS (70 eV): *m*/*z* = 290 ([M$^+$ + 1], 100).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}F_3NO_3^+$: 290.0999; found: 290.0985.

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## Supporting Information

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