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Nucleophile-Directed Selective Transformation of *cis*-1-Tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine into Aziridines, Azetidines, and Benzo-Fused Dithianes, Oxathianes, Dioxanes, and (Thio)morpholines

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Abstract: A five-step procedure for the synthesis of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine was developed, starting from 1-ethoxy-2,2,2-trifluoroethanol, involving imination, aziridination, ester reduction, hydrogenation, and *N*-,*O*-ditosylation steps. Further synthetic elaborations revealed a remarkable difference in the reactivity of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine with respect to aromatic sulfur and oxygen nucleophiles, thus enabling the selective deployment of this versatile substrate as a building block for the synthesis of functionalized aziridines, azetidines, and benzo-fused dithianes, oxathianes, dioxanes, and (thio)morpholines.

Keywords: aziridines · heterocycles · oxygen · ring expansion · sulfur

Introduction

Due to the inherent reactivity of their constrained ring system, aziridines have been widely employed as valuable building blocks in the synthesis of a large variety of functionalized cyclic and acyclic amines.[1] The class of 2-(trifluoromethyl)aziridines comprises an appealing—yet underexplored—subclass of these three-membered ring structures.[2,3] Owing to the specific chemical and physical properties of fluorine, that is, its high electronegativity and small van der Waals radius,[4] the incorporation of a trifluoromethyl group into biologically active compounds can strongly affect the activity (pK_a, lipophilicity, and metabolic stability) of these systems.[5] As a result, CF_3-substituted compounds are increasingly applied in the pharmaceutical and agrochemical industry.[6]

Herein, we report the preparation of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine and its application as a new building block in heterocyclic chemistry, starting from commercially available 1-ethoxy-2,2,2-trifluoroethanol. The high synthetic potential of this new aziridine is related to the presence of three electrophilic carbon atoms, which can undergo chemo-, regio-, and stereoselective manipulations toward the construction of specific target systems by using appropriate reagents and reaction conditions. Hence, the exploration of the reactivity profile of this new building block represents an important challenge, which will be carefully examined in this study.

Results and Discussion

In a first step toward the synthesis of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**), *N*-benzylimine **2** was prepared through the condensation of the commercially available latent aldehyde 1-ethoxy-2,2,2-trifluoroethanol (**1**) with benzylamine in toluene under Dean–Stark conditions.[7] Subsequently, imine **2** was treated with ethyl diazoacetate under Lewis acid catalysis in Et_2O, thereby yielding *cis*-ethyl 1-benzyl-3-(trifluoromethyl)aziridine-2-carboxylate (**3**) in 62% yield with excellent diastereoselectivity (d.r. > 99:1).[2g] The reduction of the ester moiety in aziridine **3** by using lithium aluminum hydride in THF at room temperature afforded *cis*-1-benzyl-2-hydroxymethyl-3-(trifluoromethyl)azir-

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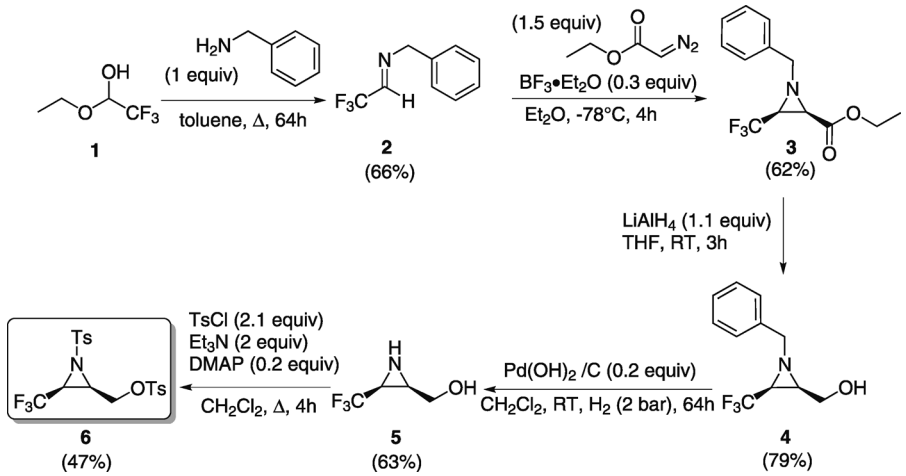


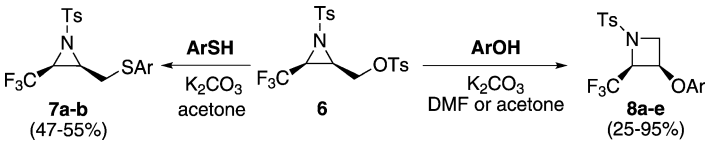
Scheme 1. Synthesis of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**). Ts = 4-toluenesulfonyl.

idine (**4**) in 79% yield.[8] In the next step, the hydrogenolysis of *N*-benzylaziridine **4** toward *cis*-2-hydroxymethyl-3-(trifluoromethyl)aziridine (**5**) was performed by using palladium hydroxide on carbon under a hydrogen atmosphere (2 bar). Finally, *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**) was obtained in 47% yield through the treatment of 2-(hydroxymethyl)aziridine **5** with 2.1 equivalents of tosyl chloride in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 (Scheme 1).

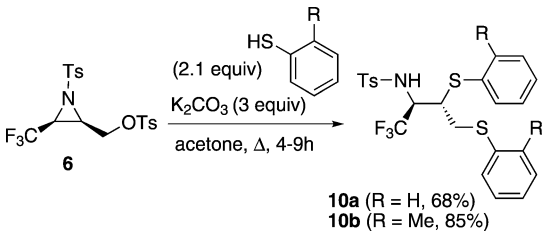
As mentioned above, *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**) holds great potential as a new synthon for the preparation of a variety of nitrogen-containing target compounds upon selective manipulation of the reactive sites. Therefore, in the next part of our investigation, the reactivity profile of functionalized aziridine **6** was explored toward different types of aromatic nucleophiles. As expected, the treatment of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**) with 0.9 equivalents of an arenethiol in the presence of potassium carbonate in acetone yielded *cis*-1-tosyl-2-arylthiomethyl-3-(trifluoromethyl)-aziridines **7a**,**b** (47–55% yield; Scheme 2 and Table 1, entries 1 and 2).[9] A subequimolar amount of arenethiol (0.9 equiv), as well as low reaction temperatures in the case of aziridine **7b**, appeared to be necessary to prevent ring opening of the initially formed 2-(arylthiomethyl)aziridine **7**. Indeed, when *N*-tosylaziridine **6** was treated with 2.1 equivalents of an arenethiol in acetone at reflux in the presence of potassium carbonate, the corresponding *N*-[2,3-bis(arylthio)-1-(trifluoromethyl)propyl]-4-methylbenzenesulfonamides (**10**) were formed in good yields (Scheme 3). It should be noted that the ring opening of the aziridines **7** occurred regio- and stereospecifically at the C2 position, which corroborates with the literature data on the ring opening of 2-(trifluoromethyl)aziridines.[3]

In view of the pronounced biological properties of compounds that contain a functionalized propane skeleton,[10] sulfonamides **10** might constitute useful new entities.

Based on the reactivity of aziridine **6** toward aromatic sulfur nucleophiles for the synthesis of functionalized aziridines, the same nucleophilic substitution reaction was envisaged with their oxygen analogues. However, by applying the same reaction conditions

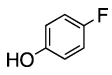
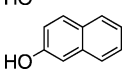
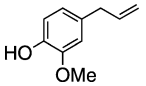


Scheme 2. Reactions of aziridine **6** with arenethiols and phenols.



Scheme 3. Synthesis of *N*-[2,3-bis(arylthio)-1-(trifluoromethyl)propyl]-4-(methylbenzene)sulfonamides (**10**).

Table 1. Reactions of aziridine **6** with arenethiols and phenols.

Entry	Nucleophile (ArSH/ArOH)	Reaction conditions[a]	Product	Yield [%]	Entry	Nucleophile (ArOH)	Reaction conditions[a]	Product	Yield [%]
1		A	**7a**	55	5		D	**8b**	73
2		B	**7b**	47	6		D	**8c**	95
3		C	**8a**	25	7		D	**8d**	87
4		C	**8b**	38	8		D	**8e**	56

[a] Reaction conditions: A = ArSH (0.9 equiv), K_2CO_3 (2 equiv), acetone, Δ, 5 h; B = ArSH (0.9 equiv), K_2CO_3 (2 equiv), acetone, RT, 42 h; C = ArOH (1.1 equiv), K_2CO_3 (2 equiv), acetone, 90 °C (pressure vial), 12–20 h; D = ArOH (1.2 equiv), K_2CO_3 (5 equiv), DMF, Δ, 4 h.

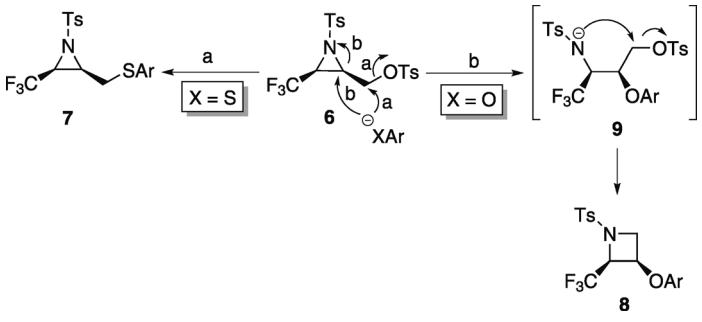
as for the reaction with thiophenol (treatment with phenol and potassium carbonate at reflux in acetone), no conversion of aziridine **6** could be obtained and, therefore, the reaction was performed at elevated temperatures in a pressure vial. Surprisingly, the reaction of aziridine **6** with 1.1 equivalents of a phenol in the presence of potassium carbonate in acetone at 90 °C in a pressure vial did not afford the anticipated *cis*-1-tosyl-2-aryloxymethyl-3-(trifluoromethyl)aziridines, although the reaction cleanly provided a single product. After detailed spectroscopic analysis, the obtained reaction product was identified as *cis*-3-aryloxy-1-tosyl-2-(trifluoromethyl)azetidine (**8**, Scheme 2). It should be noted that prolonged reaction times (12–20 h) only afforded 90% conversion and *cis*-3-aryloxy-1-tosyl-2-(trifluoromethyl)azetidines **8a**,**b** were obtained in rather low yields (25–38%; Scheme 2 and Table 1, entries 3 and 4). However, the treatment of aziridine **6** with 1.2 equivalents of a phenol and 5 equivalents of K_2CO_3 in DMF at reflux for 4 h afforded the corresponding *cis*-2-CF_3-azetidines (**8b**–**8e**) in significantly improved yields (56–95%; Table 1, entries 5–8).

From a mechanistic point of view, the unexpected formation of azetidines **8** can be rationalized by an initial regio- and stereospecific ring opening of the aziridine ring at the C2 position by the phenolate anion to produce intermediates **9** (Scheme 4, pathway b), followed by intramolecular displacement of the tosylate group to afford *cis*-2-CF_3-azetidines **8**. This selective approach stands in contrast to the treatment of aziridine **6** with an arenethiol, which leads to the clean formation of aziridines **7** through direct tosylate substitution (Scheme 4, pathway a).

The regiospecific ring opening of 1-tosyl-2-(tosyloxymethyl)aziridines by oxygen nucleophiles as an entry to azetidine synthesis is surprising and has not been described in the literature so far. Moreover, only a few reports on aziridine-to-azetidine ring expansions are known in the literature,[11] thus making this ring transformation a rare and peculiar one. In addition, the chemistry of 2-(trifluoromethyl)-azetidines comprises a scarcely investigated field of research,[12] both in terms of their synthesis and their reactivity, thus pointing to the significant value of this new approach toward azetidines **8**. Furthermore, the remarkable difference in reactivity of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**) toward aromatic oxygen and sulfur nucleophiles renders this aziridine a promising building block for the synthesis of different classes of α-CF_3-substituted compounds, including aziridines **7**, azetidines **8**, and sulfonamides **10**.

Having confirmed the ability to discriminate between two reactive sites within 3-CF_3-aziridine **6** with respect to phenols and arenethiols, the next step involved the evaluation of (thio)phenols that contained an additional nucleophilic group to effect ring expansion toward heterobicyclic systems through a domino ring-opening/cyclization procedure. Therefore, *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)-aziridine (**6**) was treated with 1.1 equivalents of benzene-1,2-dithiol in the presence of an excess of K_2CO_3 in acetone at reflux for 4 h, thus resulting in the formation of the corresponding 2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodithiin (**12a**) in a stereospecific manner (Table 2, entry 1). Considering the reactivity of substrate **6** toward S nucleophiles (Scheme 4), the nucleophilic substitution reaction to form aziridine **11** was expected to occur prior to its ring opening at the C2 position (Scheme 5). The reaction of aziridine **6** with 2-mercaptophenol, by applying the same procedure as mentioned above, resulted in the formation of 2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzoxathiin (**12b**; Table 2, entry 2). In this case, initial ring opening by an oxygen atom could not be excluded, because this would ultimately lead to the formation of the same reaction product (**12b**). In the case of 2-aminoarenethiols, the reaction proceeded more sluggishly and heating at elevated temperatures in a pressure vial appeared to be necessary to induce full conversion of the starting material toward 2,3-dihydro-1,4-benzothiazines (**12c**,**d**; Table 2, entries 3 and 4). When an excess of 2-amino-4-chlorothiophenol (2.4 equiv) was added to the reaction, the formation of benzothiazine **12d**, as well as the ring-opened product of compound **11d**, that is, *N*-[2,3-bis[(2-amino-4-chlorophenyl)thio]-1-(trifluoromethyl)propyl]-4-methylbenzenesulfonamide, was observed in a 1:1 ratio, again confirming that sulfur nucleophiles could induce ring opening of the aziridine moiety when added in excess.

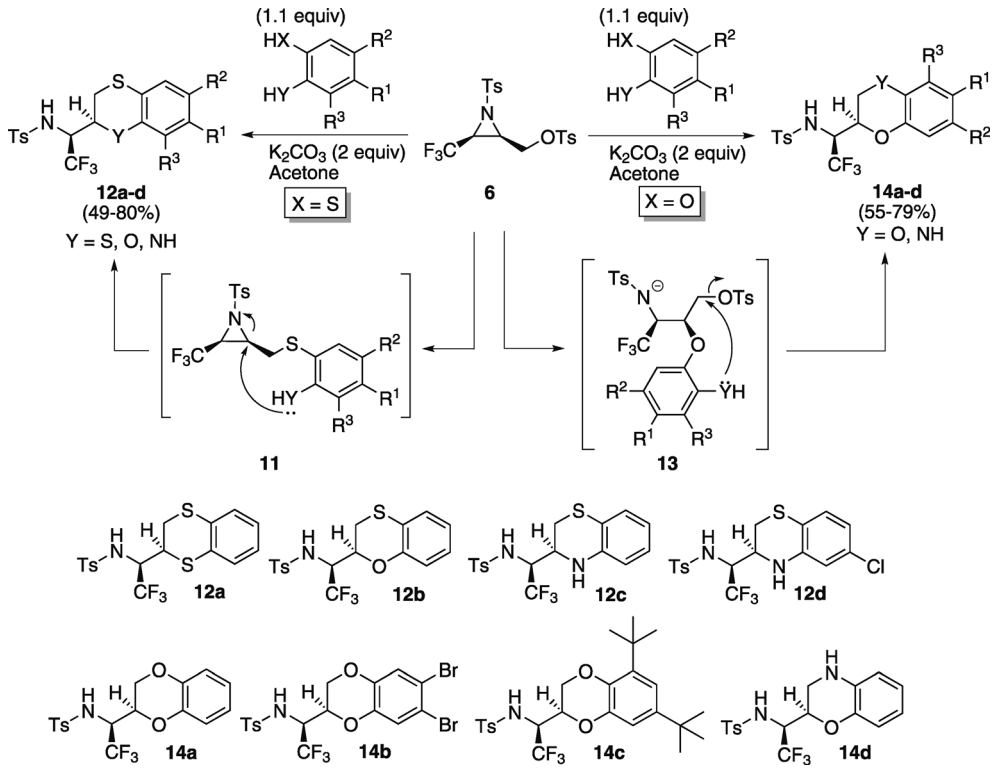
To validate its regioselective ring opening by oxygen nucleophiles, the reactions of aziridine **6** with a number of phenols that contained an additional nucleophilic group were



Scheme 4. Reaction mechanism for the synthesis of *cis*-1-tosyl-2-arylthio-3-(trifluoromethyl)aziridines (**7**) and *cis*-1-tosyl-3-aryloxy-2-(trifluoromethyl)azetidines (**8**).

Table 2. Reactions of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)-aziridine (**6**) with aromatic sulfur and oxygen nucleophiles that contain an additional nucleophilic group.

Entry	X	Y	R^1	R^2	R^3	Reaction conditions	Product	Yield [%]
1	S	S	H	H	H	Δ, 4 h	**12a**	80
2	S	O	H	H	H	Δ, 5 h	**12b**	49
3	S	NH	H	H	H	60 °C, 48 h (pressure vial)	**12c**	76
4	S	NH	Cl	H	H	150 °C, 16 h (pressure vial)	**12d**	68
5	O	O	H	H	H	Δ, 10 h	**14a**	79
6	O	O	Br	Br	H	Δ, 9 h	**14b**	58
7	O	O	H	*t*Bu	*t*Bu	Δ, 15 h	**14c**	55
8	O	NH	H	H	H	Δ, 4 h	**14d**	71



Scheme 5. Formation of heterobicycles **12** and **14** from *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**).

explored. Hence, aziridine **6** was treated with 1.1 equivalents of different benzene-1,2-diols in the presence of K_2CO_3 in acetone, thereby furnishing 2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodioxines **14a**,**b** in good yields (Table 2, entries 5 and 6). At this point, no conclusion could be made concerning the regioselectivity of the reaction, due to the use of symmetric nucleophiles. Therefore, 3,5-di-*tert*-butylbenzene-1,2-diol was used, thus resulting in the formation of 5,7-di-*tert*-butyl-2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodioxine (**14c**) in 55% yield (Table 2, entry 7). According to literature data, the least sterically hindered oxygen atom in 3,5-di-*tert*-butyl-1,2-benzenediol would react first with the electrophile,[13] which, based on the reactivity of aziridine **6** toward oxygen nucleophiles (Scheme 4), would furnish 1,4-benzodioxine **14c** as the resulting structure. Because the reaction outcome could not be solely determined by ^1H and ^{13}C NMR analysis, a single-crystal X-ray diffraction study was necessary to unambiguously assign the correct structure (see the Supporting Information), which was 5,7-di-*tert*-butyl-2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodioxine (**14c**). In this way, both the connectivity and the proposed relative stereochemistry within these new bicyclic systems were unequivocally established. Thus, we can conclude that these reactions proceed in a regio- and stereospecific manner in which the ring is selectively opened by the oxygen nucleophile at the C2 position through an S_N2-type approach (Scheme 5). Finally, also, 2-aminophenol was used as a nucleophile, thus affording 2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-2*H*-benzoxazine (**14d**) in 71% yield (Table 2, entry 8).

By means of these examples, the synthetic potential of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**) as a new building block was demonstrated, thus revealing a unique difference in reactivity toward aromatic O and S nucleophiles that allowed for the selective synthesis of a variety of CF_3-substituted aziridines (**7**), azetidines (**8**), sulfonamides (**10**), and heterobicyclic systems (**12** and **14**). In view of the known biological properties of compounds that contain a functionalized azetidine skeleton, azetidines **8** might constitute promising structures.[14] Moreover, oxa- and thia-heterobicyclic systems (**12** and **14**) represent an interesting class of compounds because they are known to possess a broad spectrum of biological activities, such as α-adrenergic blocking,[15] anxiolytic,[15d] hepatoprotective,[15d] antidiabetic,[15e] antimicrobial,[16] antioxidant,[17] and antiemetic activity.[18]

In summary, a straightforward synthesis of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine has been developed, starting from commercially available 1-ethoxy-2,2,2-trifluoroethanol. Moreover, the reactivity profile of this new α-CF_3-aziridine toward a number of aromatic nucleophiles was investigated, thus providing a convenient access to functionalized aziridines, azetidines, and biologically relevant benzo-fused dithianes, oxathianes, dioxanes, and (thio)morpholines. Surprisingly, this study revealed a remarkable difference between the reactivity of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine toward aromatic sulfur and oxygen nucleophiles. Whereas sulfur nucleophiles selectively attacked the exocyclic methylene carbon atom, thereby resulting in the direct displacement of the tosylate group,

oxygen nucleophiles induced ring opening of the three-membered ring in a regio- and stereospecific manner at the C2 position.

Experimental Section

Synthesis of *cis*-2-hydroxymethyl-3-(trifluoromethyl)aziridine (5): To a solution of *cis*-1-benzyl-2-hydroxymethyl-3-(trifluoromethyl)aziridine **4**[8] (1 g, 4.33 mmol) in CH_2Cl_2 (15 mL) was added $Pd(OH)_2/C$ (20% mass fraction, 176 mg, 0.87 mmol). The mixture was stirred at RT for 64 h under a H_2 atmosphere (2 bar) and subsequently filtered through a short pad of Celite. The pad was washed exhaustively with CH_2Cl_2 (5×10 mL) and the collected organic fractions were evaporated under reduced pressure. Recrystallization from CH_2Cl_2 afforded pure *cis*-2-hydroxymethyl-3-(trifluoromethyl)aziridine (**5**). M.p. 60–61 °C; recrystallized from CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.38 (br s, 1H), 2.09 (t, J = 5.5 Hz, 1H), 2.60–2.68 (m, 1H), 2.74–2.86 (m, 1H), 3.68–3.85 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 34.0 (q, J(C,F) = 39.6 Hz, *C*HCF$_3$), 36.7 (CH), 60.7 (CH_2), 124.7 ppm (q, J(C,F) = 273.4 Hz, CF_3); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −65.36 ppm (d, J(H,F) = 6.6 Hz); IR (ATR): $\tilde{\nu}$ = 3281, 3249 cm^{-1} (NH, OH); MS (70 eV): *m/z* (%): 142 (100) $[M+H]^+$; HRMS (ES-TOF): *m/z* calcd for $C_4H_7F_3NO$: 142.0480 $[M+H]^+$; found: 142.0476.

Synthesis of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (6): To a solution of *cis*-2-hydroxymethyl-3-(trifluoromethyl)aziridine **5** (1 g, 7.09 mmol) in CH_2Cl_2 (50 mL) at RT were added Et_3N (1.43 g, 14.18 mmol), TsCl (2.84 g, 14.89 mmol), and 4-dimethylaminopyridine (173 mg, 1.42 mmol). After heating the reaction mixture at reflux for 4 h, the solvent was evaporated in vacuo to afford the crude product. Recrystallization from CH_2Cl_2 afforded an analytically pure sample of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**). M.p. 64–65 °C; recrystallized from CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.45 (s, 3H), 2.47 (s, 3H), 3.26–3.40 (m, 2H), 4.07–4.19 (m, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 8.3 Hz, 2H), 7.80 ppm (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.7 (CH_3), 21.8 (CH_3), 39.7 (q, J(C,F) = 41.6 Hz, *C*HCF$_3$), 39.9 (CH), 65.0 (d, J = 2.3 Hz, CH_2), 122.1 (q, J(C,F) = 275.4 Hz, CF_3), 128.0 (2× CH), 128.4 (2×CH), 130.0 (2×CH), 130.1 (2×CH), 132.0 (C), 132.8 (C), 145.5 (C), 146.1 ppm (C); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −65.81 ppm (d, J(H,F) = 6.6 Hz); IR (ATR): $\tilde{\nu}$ = 1364, 1338, 1290, 1166, 1148, 1091, 984, 879, 740, 678, 666 cm^{-1}; MS (70 eV): *m/z* (%): 467 (100) $[M+NH_4]^+$; HRMS (ES-TOF): *m/z* calcd for $C_{18}H_{22}F_3N_2O_5S_2$: 467.0922 $[M+NH_4]^+$; found: 467.0923.

Synthesis of *cis*-2-phenylthiomethyl-1-tosyl-3-(trifluoromethyl)aziridine (7a): To a solution of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**, 90 mg, 0.20 mmol) in acetone (4 mL) were added benzenethiol (20 mg, 0.18 mmol) and potassium carbonate (55 mg, 0.40 mmol). After stirring the reaction mixture for 5 h at reflux, the reaction mixture was neutralized by using a saturated aqueous solution of $NaHCO_3$ (5 mL). Afterwards, the resulting reaction mixture was poured in water (10 mL) and extracted with EtOAc (3×5 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent in vacuo yielded *cis*-2-phenylthiomethyl-1-tosyl-3-(trifluoromethyl)aziridine (**7a**), which was purified by means of preparative TLC on silica gel (petroleum ether/EtOAc, 95:5). These reaction conditions only resulted in 64% conversion of aziridine **6**. However, these conditions appeared to be necessary to avoid ring opening of the prepared aziridine (**7a**) by benzenethiol. M.p. 67–68 °C; R_f = 0.14 (petroleum ether/EtOAc, 95:5); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.44 (s, 3H), 3.10–3.13 (m, 2H), 3.16–3.23 (m, 1H), 3.29 (dq, J = 6.1, 6.1 Hz, 1H), 7.21–7.36 (m, 7H), 7.79 ppm (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.7 (CH_3), 31.1 (CH), 41.1 (q, J(H,F) = 41.2 Hz, *C*HCF$_3$), 42.5 (CH_2), 122.8 (q, J(H,F) = 231.9 Hz, CF_3), 127.2 (CH), 128.3 (2×CH), 129.2 (2×CH), 129.9 (2×CH), 130.4 (2× CH), 133.2 (C), 134.0 (C), 145.6 ppm (C); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −65.18 ppm (3F, d, J(H,F) = 6.6 Hz); IR (ATR): $\tilde{\nu}$ = 3043, 1447, 1334, 1283, 1241, 1162, 1140, 1126, 1088, 1014, 886, 828, 819, 723, 686, 676 cm^{-1}; MS (70 eV): *m/z* (%): 388 (55) $[M+H]^+$, 337 (100); HRMS (ES-TOF): *m/z* calcd for $C_{17}H_{17}F_3NO_2S_2$: 388.0653 $[M+H]^+$; found: 388.0651.

Synthesis of *cis*-3-phenoxy-1-tosyl-2-(trifluoromethyl)azetidine (8b): To a solution of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**, 50 mg, 0.11 mmol) in dry DMF (5 mL) were added potassium carbonate (76 mg, 0.55 mmol) and phenol (12 mg, 0.13 mmol). After heating the reaction mixture at reflux for 4 h, water was added (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×5 mL). Afterwards, the combined organic phases were washed with a 10% aqueous solution of HCl (3×5 mL) and a 10% aqueous solution of $NaHCO_3$ (3×5 mL). Drying ($NaSO_4$), filtration of the drying agent, and evaporation of the solvent yielded *cis*-3-phenoxy-1-tosyl-2-(trifluoromethyl)aziridine (**8a**), which was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 92:8). M.p. 115–116 °C; R_f = 0.15 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.46 (s, 3H), 4.10 (dd, J = 9.7, 6.0 Hz, 1H), 4.46 (dd, J = 9.7, 8.0 Hz, 1H), 4.82 (dq, J = 7.3, 7.3 Hz, 1H), 5.07–5.11 (m, 1H), 6.74–6.75 (m, 1H), 7.01 (~t, J = 7.4 Hz, 1H), 7.27–7.29 (m, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.79 ppm (d, J = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 21.7 (CH_3), 57.2 (CH_2), 64.6 (q, J(C,F) = 33.0 Hz, *C*HCF$_3$), 65.4 (CH), 115.0 (2×CH), 122.6 (CH), 123.0 (q, J(C,F) = 285.8 Hz, CF_3), 128.0 (2×CH), 129.8 (2×CH), 129.9 (2×CH), 134.2 (C), 144.8 (C), 156.4 ppm (C); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −71.24 ppm (3F, d, J(H,F) = 7.9 Hz); IR (ATR): $\tilde{\nu}$ = 2930, 1598, 1495, 1358, 1250, 1155, 1101, 1029, 813, 689, 473 cm^{-1}; MS (70 eV): *m/z* (%): 372 (100) $[M+H]^+$; HRMS (ES-TOF): *m/z* calcd for $C_{17}H_{17}F_3NO_3S$: 372.0881 $[M+H]^+$; found: 372.0847.

Synthesis of *N*-[2,3-bis(phenylthio)-1-(trifluoromethyl)propyl]-4-methylbenzenesulfonamide (10a): To a solution of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**, 90 mg, 0.20 mmol) in acetone (4 mL) were added benzenethiol (46 mg, 0.42 mmol) and potassium carbonate (83 mg, 0.60 mmol). After stirring for 4 h at reflux, the reaction mixture was neutralized by using a saturated aqueous solution of $NaHCO_3$ (5 mL), poured in water (10 mL), and extracted with EtOAc (3×5 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent under reduced pressure afforded *N*-[2,3-bis(phenylthio)-1-(trifluoromethyl)propyl]-4-methylbenzenesulfonamide (**10a**), which was purified by preparative TLC on silica gel (petroleum ether/EtOAc, 95:5). M.p. 124–125 °C; R_f = 0.15 (petroleum ether/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.43 (s, 3H), 2.92 (dd, J = 14.6, 12.4 Hz, 1H), 3.20–3.25 (m, 2H), 4.73–4.80 (m, 1H), 5.52 (br s, 1H), 7.11–7.28 (m, 10H), 7.30 (d, J = 8.3 Hz, 2H), 7.79 ppm (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.6 (CH_3), 37.2 (CH_2), 48.0 (CH), 54.8 (q, J(C,F) = 31.5 Hz, *C*HCF$_3$), 124.2 (q, J(C,F) = 283.0 Hz, CF_3), 127.2 (3×CH), 128.3 (CH), 129.2 (2×CH), 129.3 (2× CH), 129.8 (2×CH), 130.7 (2×CH), 132.2 (C), 132.8 (2×CH), 133.6 (C), 137.4 (C), 144.0 ppm (C); ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −71.83 ppm (3F, d, J(H,F) = 6.6 Hz); IR (ATR): $\tilde{\nu}$ = 3240 cm^{-1} (NH); MS (70 eV): *m/z* (%): 496 (100) $[M-H]^-$; HRMS (ES-TOF): *m/z* calcd for $C_{23}H_{21}F_3NO_2S_3$: 496.0687 $[M-H]^-$; found: 496.0694.

Synthesis of oxaheterobicyclic (12) and thiaheterobicyclic systems (14): As a representative example, the synthesis of 2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodithiin (**12a**) is described. To a solution of *cis*-1-tosyl-2-tosyloxymethyl-3-(trifluoromethyl)aziridine (**6**, 100 mg, 0.22 mmol) in acetone (5 mL) were added benzene-1,2-dithiol (26 mg, 0.24 mmol) and potassium carbonate (61 mg, 0.44 mmol). After stirring for 4 h at reflux, the reaction mixture was poured in water (10 mL) and extracted with EtOAc (3×5 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent yielded 2-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodithiin (**12a**), which was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 92:8) to obtain an analytically pure sample. In the syntheses of 3-(1-tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzothiazines (**12c,d**), the reactions were performed in a pressure vial at 60 °C for 48 h and at 150 °C for 16 h, respectively. M.p. 131–132 °C; R_f = 0.27 (*n*-hexane/EtOAc, 85:15); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.41 (s, 3H), 2.63 (dd, J = 13.7, 10.6 Hz, 1H), 3.20 (dd, J = 13.7, 4.9 Hz, 1H), 4.23–4.30 (m, 2H), 5.65 (d, J = 9.6 Hz, 1H), 7.13–7.16 (m, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.28–

7.34 (m, 2H), 7.67 ppm (d, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C, TMS): δ=21.6 (CH_3), 32.8 (CH_2), 47.0 (CH), 57.3 (q, J(C,F)= 30.7 Hz, CHCF$_3$), 123.8 (q, J(C,F)=283.8 Hz, CF_3), 126.2 (CH), 126.9 (2×CH), 127.0 (CH), 129.2 (CH), 129.7 (2×CH), 130.2 (CH), 132.0 (C), 132.8 (C), 145.5 (C), 146.1 ppm (C); IR (ATR): $\tilde{\nu}$=3270 cm^{-1} (NH); MS (70 eV): m/z (%): 418 (100) [M−H]$^-$; HRMS (ES-TOF): m/z calcd for $C_{17}H_{17}F_3NO_5S_3$: 420.0374 [M+H]$^+$; found: 420.03734.

2-(1-Tosylamino-2,2,2-trifluoroethyl)-2,3-dihydro-1,4-benzodioxine (14a): M.p. 142–143 °C; R_f=0.19 (*n*-hexane/EtOAc, 98:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS): δ=2.44 (s, 3H), 4.06 (dd, J=11.6, 9.4 Hz, 1H), 4.17 (dq, J=8.0, 8.0 Hz, 1H), 4.29 (dd, J=11.6, 2.2 Hz, 1H), 4.51 (d, J= 9.2 Hz, 1H), 5.46 (d, J=9.7 Hz, 1H), 6.86–6.88 (m, 2H), 6.89–6.90 (m, 2H), 7.31 (d, J=8.2 Hz, 2H), 7.75 ppm (d, J=8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ=21.6 (CH_3), 54.6 (q, J(C,F)=30.7 Hz, CHCF$_3$), 65.2 (CH_2), 69.1 (CH), 117.4 (CH), 117.4 (CH), 121.9 (CH), 122.5 (CH), 123.6 (q, J(C,F)=283.2 Hz, CF_3), 127.0 (2×CH), 129.8 (2× CH), 137.4 (C), 142.1 (C), 142.7 (C), 144.2 ppm (C); IR (ATR): $\tilde{\nu}$= 3256 cm^{-1} (NH); MS (70 eV): m/z (%): 386 (100) [M−H]$^-$; HRMS (ES-TOF): m/z calcd for $C_{17}H_{17}F_3NO_4S$: 388.0830 [M+H]$^+$; found: 388.0830.

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