Stereoselective synthesis of *trans*- and *cis*-2-aryl-3-(hydroxymethyl)aziridines through transformation of 4-aryl-3-chloro-β-lactams and study of their ring opening

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trans- and *cis*-1-Alkyl-4-aryl-3-chloroazetidin-2-ones, prepared through cyclocondensation of chloroketene and the appropriate imines in a diastereoselective way, were transformed into the corresponding non-activated *trans*- and *cis*-2-aryl-3-(hydroxymethyl)aziridines *via* reductive ring contraction using $LiAlH_4$ in Et_2O. Furthermore, *trans*-2-aryl-3-(hydroxymethyl)aziridines were transformed into 2-amino-3-arylpropan-1-ols and *anti*-2-amino-3-aryl-3-methoxypropan-1-ols by means of an unprecedented ring opening by $LiAlH_4$ and by MeOH, respectively. *cis*-2-Aryl-3-(hydroxymethyl)aziridines were shown to be highly reluctant to undergo ring opening by $LiAlH_4$ and MeOH under similar reaction conditions.

Introduction

Aziridines have proven to be excellent building blocks for the synthesis of a large variety of ring opened and ring expanded amines due to the inherent reactivity of the constrained ring.[1] In particular, 2-(hydroxymethyl)aziridines are useful substrates for the preparation of amino alcohols through ring opening reactions, a class of compounds with a broad applicability in synthetic and medicinal chemistry.[2] Up to now, synthetic efforts in this field have been mainly limited to mono-substituted 2-(hydroxymethyl)aziridines,[3] and the study of for instance 2-aryl-3-(hydroxymethyl)aziridines has scarcely been reported in the literature.[4] However, the latter class of aziridines holds interesting potential for further elaboration towards *e.g.* aryl substituted amino alcohols, which are known to be of biological relevance as for example antibiotics,[5] antitumor agents,[6] *anti*-hypertensive agents,[7] herbicides[8] *etc*.

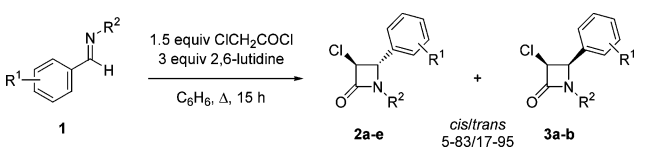
Moreover, the enhanced electrophilicity of the benzylic aziridine carbon atom can have a pronounced effect on the regiocontrol of ring opening reactions, leading to highly regioselective processes as compared to unsubstituted or 3-alkyl substituted 2-(hydroxymethyl)aziridines.

Also the constrained azetidin-2-one ring has been employed successfully in a large variety of different synthetic methodologies towards all kinds of nitrogen-containing target compounds.[9] One of these approaches comprises the synthesis of aziridines as useful synthons for further elaboration. Nevertheless, little effort has been devoted to the development of convenient and general methods for the conversion of β-lactams into aziridines,[10] especially with regard to the preparation of non-activated aziridine derivatives. Whereas a variety of methods is available for the preparation of aziridines,[1] the majority of these approaches involves the synthesis of activated aziridines, and the chemistry of non-activated aziridines has been explored to a limited extent up to now.

In the present paper, a straightforward and efficient new approach to non-activated *trans*- and *cis*-2-aryl-3-(hydroxymethyl)-aziridines is described through reductive ring opening and *in situ* cyclisation of the corresponding *trans*- and *cis*-4-aryl-3-chloro-β-lactams. Furthermore, the unprecedented ring opening of non-activated *trans*-2-aryl-3-(hydroxymethyl)aziridines by $LiAlH_4$ and MeOH towards 2-amino-3-arylpropan-1-ols and *anti*-2-amino-3-aryl-3-methoxypropan-1-ols, respectively, is discussed. On the other hand, *cis*-2-aryl-3-(hydroxymethyl)aziridines appeared to be highly reluctant to undergo ring opening by $LiAlH_4$ and MeOH under similar reaction conditions.

Results and discussion

N-(Arylmethylidene)alkylamines **1**, prepared in high yields through condensation of the corresponding benzaldehydes with the appropriate primary amines in CH_2Cl_2 in the presence of anhydrous $MgSO_4$, were used as substrates for the Staudinger synthesis of 3-chloro-β-lactams upon treatment with 1.5 equiv of chloroacetyl chloride and 3 equiv of 2,6-lutidine in benzene. In accordance with previous results,[11] the premised *trans*-4-aryl-3-chloro-β-lactams **2a–e** were obtained stereoselectively (*cis*/*trans* 5–8/92–95) after a reflux period of 15 h, and were isolated in pure form after crystallisation from EtOH or column chromatography on silica gel in good yields (Scheme 1, Table 1). The *trans*-stereochemistry of azetidin-2-ones **2** was unambiguously assigned based on the coupling constants between the protons at C3 and



Scheme 1

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Table 1 Staudinger synthesis of *trans*- and *cis*-4-aryl-3-chloroazetidin-2-ones **2** and **3**

Compound	R^1	R^2	*cis*/*trans*[a]	Isolated yield[b,c]
2a	H	iPr	5/95	56%[c]
2b	H	Bn	8/92	65%[c]
2c	4-Cl	Bn	7/93	65%[b]
2d	4-OMe	iBu	5/95	55%[c]
2e	2-F	nPr	5/95	64%[c]
3a	2-F	tBu	83/17	79%[b]
3b	2-OMe	tBu	69/31	55%[b]

[a] Based on ^{1}H NMR analysis of the reaction mixture. [b] Yields of pure compounds after crystallisation from EtOH. [c] Yields of pure compounds after column chromatography (SiO_2).

Table 2 Transformation of *trans*-3-chloro-β-lactams **2** into 2-amino-3-arylpropan-1-ols **4** and *trans*-2-aryl-3-(hydroxymethyl)aziridines **6**

Entry	R^1	R^2	Compound (yield)[a]	Compound (yield)[a,b,c]
1	H	iPr	**4a** (66%)	**6a** (55%)[a]
2	H	Bn	**4b** (44%)	**6b** (68%)[c]
3	4-Cl	Bn	**4c** (37%)	**6c** (56%)[a]
4	4-OMe	iBu	**4d** (60%)	**6d** (70%)[c]
5	2-F	nPr	**4e** (50%)	**6e** (44%)[b]

[a] After recrystallisation. [b] After column chromatography (SiO_2). [c] Crude yield (purity >95% based on NMR).

C4, as the observed *J*-values of 1.6–1.7 Hz (^{1}H NMR, $CDCl_3$) correspond well with those reported in the literature for *trans*-β-lactams.[12] Furthermore, it is known that the use of the Moore ketene (chloroketene) for the Staudinger synthesis of azetidin-2-ones favours the formation of the thermodynamically more stable *trans*-β-lactams through *E*/*Z*-isomerisation across the iminium bond in the zwitterionic intermediates,[13] although also other parameters such as reaction temperature and admission order of reagents are known to have an influence on the stereoselectivity.[14]

Surprisingly, the use of imines **1** bearing an *N*-*tert*-butyl group in combination with a substituent in the *ortho*-position on the aromatic ring afforded the corresponding *cis*-4-aryl-3-chloroazetidin-2-ones **3a, b** as the major stereoisomers (*cis*/*trans* 69–83/17–31) after condensation with chloroketene in benzene under the same reaction conditions (Scheme 1, Table 1). Again, the observed coupling constants between the protons at C3 and C4 were in accordance with literature data for *cis*-β-lactams (5.0–5.3 Hz, ^{1}H NMR, $CDCl_3$).[15] The unexpected formation of *cis*-azetidin-2-ones **3** can be explained by considering a hindered *E*/*Z*-isomerisation across the iminium bond in the zwitterionic intermediates due to a substantial steric interaction between the *N*-*tert*-butyl group and the *ortho*-substituted aromatic ring, resulting in a shift in the competition between isomerisation on the one hand and direct conrotatory ring closure on the other hand in favour of the latter.

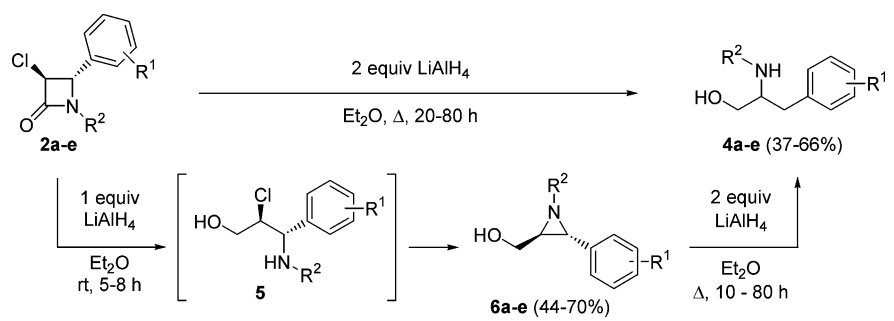
When the imine derived from benzaldehyde and *tert*-butylamine was used for the Staudinger synthesis of the corresponding 3-chloro-β-lactam, the latter compound was obtained as a mixture of *cis*/*trans* isomers in a 6/94 ratio, pointing to the necessity of the combination of a substituent in the *ortho*-position on the aromatic ring and an *N*-*tert*-butyl group for *cis*-stereoselectivity. Attempts to purify 1-*tert*-butyl-3-chloro-4-phenyl-β-lactam by recrystallization or column chromatography failed.

Other examples of *cis*-4-aryl-3-chloro-β-lactams have been described in the literature, although these compounds are usually obtained with lower diastereoselectivity and are mostly substituted with an aryl group at nitrogen.[16,17]

In previous work, the reductive ring opening of azetidin-2-ones by means of $LiAlH_4$ has been described as a suitable approach towards the synthesis of a variety of γ-amino alcohols.[18] In analogy, reductive ring opening of β-lactams **2** could lead to intermediate 3-amino-2-chloropropan-1-ols, which are prone to subsequent cyclization towards 2,3-disubstituted aziridines in basic medium. To date, only one literature report on the conversion of 3-chloro-β-lactams into aziridine derivatives is available, in which the transformation of *trans*-4-aryl-3-chloroazetidin-2-ones into 2-aryl-3-carbamoylaziridines is described upon treatment with primary amines.[10i]

Thus, *trans*-4-aryl-3-chloro-β-lactams **2** were subjected to a reductive ring opening utilizing two molar equiv of $LiAlH_4$ in Et_2O under reflux for 20–80 h, resulting in full conversion of the starting material. However, spectroscopic analysis of the obtained reaction products revealed a molecular structure different from the contemplated aziridines **6**, and finally these compounds were identified as 2-amino-3-arylpropan-1-ols **4** (Scheme 2, Table 2).[19] From a mechanistic point of view, the formation of the latter amino alcohols **4** can be rationalized considering the initial conversion of the starting β-lactams **2** into aziridines **6** *via* intermediate γ-amino alcohols **5**, followed by hydride-promoted ring opening of these aziridines **6** under the given reaction conditions.

The $LiAlH_4$-induced ring opening of aziridines without additional *N*-activation is surprising and has not been described before in the literature, apart from a recent paper in which the partial and non-regioselective $LiAlH_4$-promoted ring opening of 2-methyl-1-phenylaziridine is reported.[20] Besides that report, only indirect



Scheme 2

evidence for the reduction of aziridines by $LiAlH_4$, deduced from several experiments in which aziridines were assumed to be intermediates, is available in the literature.[21] The hydride-induced ring opening of aziridines is indeed peculiar, as several methods are known for the formation of aziridines by $LiAlH_4$ reduction of suitable substrates.[22]

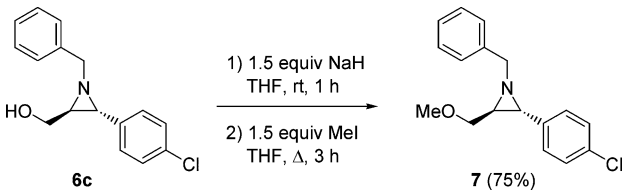
The observed reactivity can be explained considering the *in situ* activation of the aziridine moiety by the Lewis acid character of aluminium, resulting in a considerable weakening of the C2–N bond due to benzylic stabilisation of the developing carbenium ion. Subsequently, transfer of hydride to the C2 aziridine carbon atom results in the formation of β-amino alcohols **4** (Scheme 2). Furthermore, the presence of an internal hydrogen bond between the hydroxyl group and the aziridine nitrogen atom can account for additional activation of the aziridine ring,[23] facilitating its ring opening.

Alternatively, the aza-Payne rearrangement of intermediate 2-(aminomethyl)epoxides to aziridines **6** could be invoked due to the initial formation of highly reactive α-chloroaldehydes, which are known to afford epoxides under reductive reaction conditions.[24] However, this pathway would lead to *cis*-aziridines through double Walden inversion of the chlorinated carbon atom instead of *trans*-aziridines **6**, formed by cyclisation of β-chloroamines **5**. Furthermore, the intermediacy of γ-amino alcohols **5** in this transformation was acknowledged by ^{1}H NMR, IR and MS analysis of the reaction mixture obtained after treatment of β-lactam **2b** with two equiv of $LiAlH_4$ in Et_2O under reflux for three hours, pointing to the presence of the reactive β-chloroamine **5** as the major reaction component.

In order to prevent hydride-promoted ring opening of the desired aziridines **6**, milder reaction conditions were applied for the reduction of β-lactams **2**. Thus, treatment of *trans*-4-aryl-3-chloroazetidin-2-ones **2** with one equiv of $LiAlH_4$ in Et_2O at room temperature for 5–8 h afforded *trans*-2-aryl-3-(hydroxymethyl)aziridines **6** as the final reaction products (Scheme 2, Table 2). Treatment of aziridines **6** with two equiv of $LiAlH_4$ in Et_2O under reflux resulted in β-amino alcohols **4** (Scheme 2), supporting the intermediacy of aziridines **6** in the direct conversion of β-lactams **2** to 2-aminopropan-1-ols **4**. Furthermore, the latter experiments comprise the first example of $LiAlH_4$-mediated ring opening of 1-alkylaziridines.

Remarkably, *trans*-aziridines **6** appeared as mixtures of two invertomers (1/2–1/5) upon ^{1}H and ^{13}C NMR analysis, which is probably due to hindered *N*-inversion. These observations are in accordance with literature data.[4c,d] The *trans*-stereochemistry of aziridines **6** was assigned by means of comparison of the vicinal coupling constants (^{1}H NMR, $CDCl_3$) between both aziridine protons with those reported in the literature[4c,d,25] (3.3–3.9 Hz for the major invertomers, 2.2 Hz for the minor invertomers), and is a direct consequence of the relative stereochemistry as defined during the Staudinger synthesis of the starting β-lactams **2**.

In order to investigate the influence of an intramolecular hydrogen bridge between the free hydroxyl group and the basic nitrogen atom on the appearance of two invertomers, the alcohol was converted into the corresponding methyl ether through a Williamson ether synthesis. Thus, treatment of aziridine **6c** as a selected example with 1.5 equiv of sodium hydride, followed by the addition of 1.5 equiv of methyl iodide in THF under reflux for three hours resulted in the formation of methyl ether **7** (Scheme 3). Nonetheless, aziridine **7** also appeared as two distinct invertomers in NMR, albeit in a slightly changed ratio (**6c**: 1/2, **7**: 1/1.4).

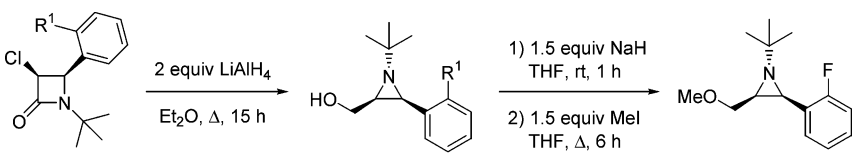


Scheme 3

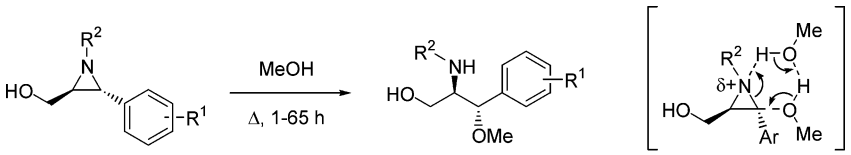
Because of the unexpected formation and isolation of *cis*-4-aryl-3-chloro-β-lactams **3**, their behaviour with respect to reductive ring opening with $LiAlH_4$ was evaluated. Surprisingly, treatment of azetidin-2-ones **3** with two equiv of $LiAlH_4$ in Et_2O under reflux for 15 h did not result in the isolation of the corresponding 2-amino-3-arylpropan-1-ols, but instead *cis*-2-aryl-3-(hydroxymethyl)aziridines **8** were obtained as the sole reaction products (Scheme 4).[26] Apparently, the hydride-induced ring opening of the latter aziridines **8** is disabled due to considerable steric hindrance by the aziridine substituents, preventing aziridine activation through coordination between the nitrogen atom and the Lewis acid.

Furthermore, *cis*-aziridines **8** appeared as single invertomers upon NMR analysis ($CDCl_3$), leading to the conclusion that *N*-inversion is completely blocked due to steric interactions. The same observations were made for the corresponding methyl ether **9**, prepared *via* Williamson ether synthesis upon treatment of aziridine **8a** with NaH and MeI in THF (Scheme 4). Again, the relative *cis*-stereochemistry controlled by the Staudinger synthesis of azetidin-2-ones **3** is transferred during the reductive ring opening, as demonstrated by analysis of the vicinal coupling constants between both aziridine protons in compounds **8** and **9** (6.1–6.4 Hz, ^{1}H NMR, $CDCl_3$).[4c,d,25]

Aziridines are generally recognized as valuable three-membered ring systems in organic chemistry because of their synthetic flexibility.[1] Consequently, the reactivity of 2-aryl-3-(hydroxymethyl)aziridines with respect to MeOH was evaluated



Scheme 4



10a (R^1 = H, R^2 = iPr, 45%, 24 h)
10b (R^1 = H, R^2 = Bn, 40% 1 h)
10c (R^1 = 4-Cl, R^2 = Bn, 39%, 8 h)
10d (R^1 = 4-OMe, R^2 = iBu, 38%, 24 h)
10e (R^1 = 2-F, R^2 = nPr, 52%, 65 h)

Scheme 5

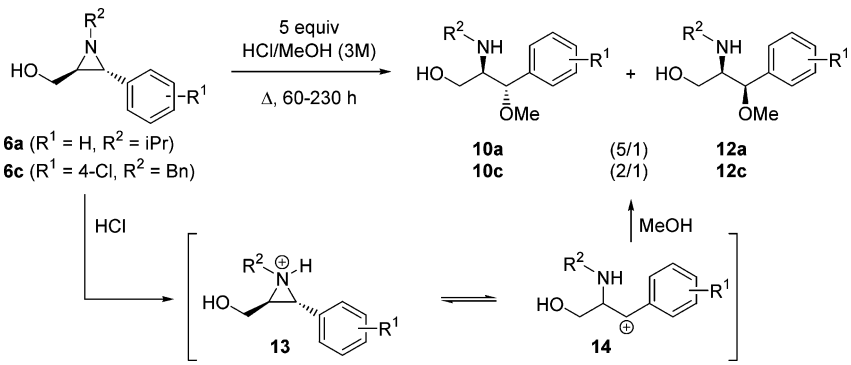
with the intention to provide a convenient entry into the biologically relevant class of 3-oxygenated aminopropanols.[5–8]

Interestingly, *trans*-aziridines **6** were transformed into the corresponding *anti*-2-amino-3-aryl-3-methoxypropan-1-ols **10** as the sole reaction products upon heating for 1–65 h in MeOH[27] under reflux (Scheme 5). In analogy with the reactivity of aziridines **6** with respect to $LiAlH_4$, their ring opening in MeOH can be explained considering the presence of an electrophilic aziridine carbon atom in the α-position of the aromatic ring in combination with the *in situ* activation of the aziridine moiety through coordination (hydrogen bridge formation) of the nitrogen atom with the acidic MeOH proton (intermediate **11**). This ring opening proceeded in a regio- and stereoselective way through a S_N2 reaction at the benzylic position. The formation of the other regio- and stereoisomers was excluded based on detailed spectroscopic analysis. It should be noted that 1-benzyl substituted aziridines **6b** and **6c** appeared to be considerably more reactive with regard to MeOH as compared to 1-alkylaziridines **6a**, **6d** and **6e**, as complete consumption of the substrates was observed after 1–8 h in the former and 24–65 h in the latter case.

Treatment of *trans*-2-aryl-3-(hydroxymethyl)aziridines **6** with NaOMe in MeOH (2 M) under reflux did not result in any conversion, and the starting material was recovered completely after every attempt (2, 8 or 24 h). Apparently, the strong nucleophilicity of methoxide as compared to MeOH does not compensate for the loss of aziridine activation through hydrogen bond formation because of the basic medium. The necessity of aziridine activation for ring opening was further supported by the reactivity of *trans*-aziridines **6** towards methanolic hydrogen chloride. Indeed, treatment of aziridines **6** with 5 equiv of HCl in MeOH (3 M) resulted in a mixture of *anti* and *syn* isomers **10** and **12** after reflux for 60–230 h (Scheme 6, *anti*/*syn* 2–5/1). Obviously, protonation of the aziridines **6** leads to the formation of aziridinium intermediates **13**, which (partially) can undergo ring opening towards stable benzylic carbenium ions **14**. Neutralisation of the planar carbenium ions **14** by MeOH results in a mixture of *anti* and *syn* isomers **10** and **12** (Scheme 6). Long reaction times (60–230 h) appeared to be necessary in order to drive the reaction to completion. This observation might indicate a substantial steric hindrance induced by the aziridine substituents, hampering protonation of the nitrogen atom.

Finally, the reactivity of *cis*-2-aryl-3-(hydroxymethyl)aziridines **8** with respect to MeOH was evaluated. However, the application of a variety of different reaction conditions did not lead to ring opening, and the starting compounds were recovered after every experiment (even after reflux for 90 h). Obviously, *cis*-aziridines **8** are highly reluctant to undergo ring opening by $LiAlH_4$ or MeOH, which can be attributed to the considerable steric hindrance induced by the aziridine substituents, in particular due to the bulky *N*-*tert*-butyl group. As a consequence, both faces of the three-membered ring are completely shielded, making any coordination or bonding interaction with the nitrogen lone pair impossible.

In conclusion, non-activated *trans*- and *cis*-1-alkyl-2-aryl-3-(hydroxymethyl)aziridines were prepared for the first time through reductive ring contraction of the corresponding *trans*- and *cis*-1-alkyl-4-aryl-3-chloroazetidin-2-ones upon treatment with $LiAlH_4$ in Et_2O. The synthetic applicability of *trans*-2-aryl-3-(hydroxymethyl)aziridines was demonstrated by means of the unprecedented ring opening by $LiAlH_4$ and by MeOH, thus affording a straightforward entry into 2-amino-3-arylpropan-1-ols and *anti*-2-amino-3-aryl-3-methoxypropan-1-ols, respectively. Furthermore, *cis*-2-aryl-1-*tert*-butyl-3-(hydroxymethyl)aziridines



Scheme 6

were shown to be highly reluctant to undergo ring opening under similar reaction conditions using $LiAlH_4$ or MeOH, pointing to a considerable steric hindrance due to the bulky substituents.

Experimental part

Synthesis of 1-alkyl-4-aryl-3-chloroazetidin-2-ones 2 and 3

General procedure: To a solution of *N*-(arylmethylidene)amine **1** (10 mmol) in dry benzene (50 mL) was added 2,6-lutidine (30 mmol, 3 equiv), and the resulting mixture was heated under reflux. Subsequently, chloroacetyl chloride (15 mmol, 1.5 equiv) was added to the boiling mixture, followed by a reflux period of 15 h. Afterwards, the resulting suspension was filtered in order to remove 2,6-lutidine hydrochloride, after which the filtrate was washed with an aqueous solution of 1 M HCl (2 × 15 mL). The organic phase was dried over $MgSO_4$, followed by removal of the drying agent and evaporation of the solvent *in vacuo*. The resulting crude compound was purified by means of recrystallization from absolute EtOH or column chromatography on silica gel.

trans-1-Benzyl-3-chloro-4-(4-chlorophenyl)azetidin-2-one 2c

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.83 (1H, d, J = 14.8 Hz); 4.35 and 4.52 (2 × 1H, 2 × d, J = 1.6 Hz); 4.83 (1H, d, J = 14.8 Hz); 7.10–7.18 and 7.29–7.37 (9H, 2 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.03, 63.15, 64.60, 128.02, 128.15, 128.44, 128.95, 129.46, 133.28, 134.08, 135.31, 163.37. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1767. MS (70 eV): m/z (%) 306/8/10 (M^+ + 1, 100). Recrystallization from absolute EtOH. Mp = 101.6 °C. Anal. Calcd for $C_{16}H_{13}Cl_2NO$: C 62.76, H 4.28, N 4.57. Found: C 62.93, H 4.57, N 4.42%.

trans-3-Chloro-1-isobutyl-4-(4-methoxyphenyl)azetidin-2-one 2d

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 and 0.94 (2 × 3H, 2 × d, J = 6.9 Hz); 1.76–1.90 (1H, m); 2.61 and 3.29 (2 × 1H, 2 × (d × d), J = 14.0, 8.6, 5.8 Hz); 3.83 (3H, s); 4.48 and 4.52 (2 × 1H, 2 × d, J = 1.6 Hz); 6.93–6.99 and 7.19–7.27 (2 × 2H, 2 × m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.14, 20.28, 27.38, 48.22, 55.29, 63.26, 66.37, 114.71, 126.80, 128.04, 160.61, 164.09. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1763. MS (70 eV): m/z (%) 268/70 (M^+ + 1, 100). R_f 0.18 (hexane–EtOAc 6/1). Anal. Calcd for $C_{14}H_{18}ClNO_2$: C 62.80, H 6.78, N 5.23. Found: C 63.01, H 7.02, N 5.33%.

trans-3-Chloro-4-(2-fluorophenyl)-1-propylazetidin-2-one 2e

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (3H, t, J = 7.5 Hz); 1.49–1.61 (2H, m); 2.82–2.91 and 3.42–3.52 (2 × 1H, 2 × m); 4.67 (1H, d, J = 1.6 Hz); 4.86 (1H, d, J = 1.6 Hz); 7.12–7.44 (4H, m). ^{19}F NMR (282 MHz, $CDCl_3$): δ (–118.37)–(–118.29) (m).^{13}C NMR (75 MHz, $CDCl_3$): δ 11.36, 20.83, 42.96, 60.15 (d, J = 3.5 Hz), 62.08, 116.31 (d, J = 20.8 Hz), 122.23 (d, J = 12.7 Hz), 124.95 and 128.00 (2 × d, J = 3.5, 3.4 Hz), 131.13 (d, J = 8.1 Hz), 161.13 (d, J = 248.1 Hz), 163.77. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1768. MS (70 eV): m/z (%) 242/4 (M^+ + 1, 100). R_f 0.18 (hexane–EtOAc 9/1). Anal. Calcd for $C_{12}H_{13}ClFNO$: C 59.63, H 5.42, N 5.80. Found: C 59.42, H 5.73, N 5.68%.

cis-1-*tert*-Butyl-3-chloro-4-(2-fluorophenyl)azetidin-2-one 3a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (9H, s); 5.04 and 5.42 (2 × 1H, 2 × d, J = 5.0 Hz); 7.07–7.13, 7.20–7.27, 7.32–7.40 and 7.45–7.47 (4H, 4 × m). ^{19}F NMR (282 MHz, $CDCl_3$): δ (–120.00) (s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.02, 52.63, 55.13, 59.03, 115.45 (d, J = 22.0 Hz), 122.79 (d, J = 11.6 Hz), 123.70, 129,57, 130,37 (d, J = 8.1 Hz), 161.62 (d, J = 248.1 Hz), 164.04. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1742. MS (70 eV): m/z (%) 256/8 (M^+ + 1, 100). Recrystallization from absolute EtOH. Mp = 102.6 °C. Anal. Calcd for $C_{13}H_{15}ClFNO$: C 61.06, H 5.91, N 5.48. Found: C 61.22, H 6.09, N 5.40%.

cis-1-*tert*-Butyl-3-chloro-4-(2-methoxyphenyl)azetidin-2-one 3b

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (9H, s); 3.85 (3H, s); 4.99 and 5.50 (2 × 1H, 2 × d, J = 5.3 Hz); 6.90–6.92, 6.98–7.05 and 7.29–7.41 (4H, 3 × m).^{13}C NMR (75 MHz, $CDCl_3$): δ 28.02, 53.88, 54.83, 55.48, 59.33, 110.34, 119.98, 123.82, 128.65, 129.58, 157.25, 164.73. IR (ATR, cm^{-1}): $\nu_{C=O}$ = 1751. MS (70 eV): m/z (%) 268/70 (M^+ + 1, 100). Recrystallization from absolute EtOH. Mp = 99.8 °C. Anal. Calcd for $C_{14}H_{18}ClNO_2$: C 62.80, H 6.78, N 5.23. Found: C 62.73, H 6.76, N 5.18%.

Synthesis of 2-amino-3-arylpropan-1-ols 4

General procedure. To an ice-cooled solution of *trans*-4-aryl-3-chloroazetidin-2-one **2** (2 mmol) in Et_2O (30 mL) was added $LiAlH_4$ (4 mmol, 2 molar equiv) in small portions. Subsequently, the resulting suspension was heated under reflux for 20–80 h, after which water (5 mL) was added at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterwards, the mixture was filtered through a pad of Celite®, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent afforded the crude product, which was purified by crystallization from absolute EtOH or hexane–EtOAc (1/30).

2-(*N*-Benzylamino)-3-(4-chlorophenyl)propan-1-ol 4c

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69–2.83 (2H, m); 2.89–2.96 (1H, m); 3.32 and 3.64 (2 × 1H, 2 × (d × d), J = 10.7, 4.9, 3.8 Hz); 3.75 and 3.80 (2 × 1H, 2 × d, J = 13.2 Hz); 7.07–7.10 and 7.20–7.34 (9H, 2 × m). ^{13}C NMR (75 MHz, $CDCl_3$): 37.36, 51.09, 59.16, 62.19, 127.21, 128.02, 128.53, 128.68, 130.53, 132.25, 136.91, 139.76. IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3263. MS (70 eV): m/z (%) 276/8 (M^+ + 1, 100). Recrystallization from absolute EtOH. Mp = 101.9 °C. Anal. Calcd for $C_{16}H_{18}ClNO$: C 69.68, H 6.58, N 5.08. Found: C 69.82, H 6.75, N 5.13%.

2-(*N*-Isobutylamino)-3-(4-methoxyphenyl)propan-1-ol 4d

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.85 and 0.86 (2 × 3H, 2 × d, J = 6.6 Hz); 1.56–1.70 (1H, m); 2.35 and 2.43 (2 × 1H, 2 × (d × d), J = 11.4, 6.9, 6.6 Hz); 2.62–2.73 (2H, m); 2.76–2.85 (1H, m); 3.28 and 3.59 (2 × 1H, 2 × (d × d), J = 10.5, 5.5, 3.8 Hz); 3.80 (3H, s); 6.84 and 7.09 (2 × 2H, 2 × d, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.58, 28.72, 37.24, 54.90, 55.26, 60.13, 62.20, 113.93, 130.10, 130.54, 158.16. IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3104. MS (70 eV): m/z (%) 238 (M^+ + 1, 100). Recrystallization from absolute EtOH. Mp = 102.3 °C. Anal. Calcd for $C_{14}H_{23}NO_2$: C 70.85, H 9.77, N 5.90. Found: C 70.92, H 9.83, N 5.87%.

3-(2-Fluorophenyl)-2-(*N*-propylamino)propan-1-ol 4e

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 7.2 Hz); 1.46 (2H, sextet, J = 7.2 Hz); 2.01–2.05 (2H, m); 2.50–2.79 (3H, m); 2.81–2.97 (2H, m); 3.28 and 3.59 (2 × 1H, 2 × (d × d), J = 10.6, 5.8, 3.9 Hz); 7.00–7.10 and 7.16–7.37 (4H, 2 × m). ^{19}F NMR (282 MHz, $CDCl_3$): δ (–117.73)–(–116.98) (m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.66, 23.41, 31.42, 48.81, 59.04, 62.46, 115.40 (d, J = 21.9 Hz), 124.12 (d, J = 3.5 Hz), 125.58 (d, J = 16.1 Hz), 128.24 (d, J = 8.1 Hz), 131.58 (d, J = 4.6 Hz), 161.34 (d, J = 244.6 Hz). IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3255. MS (70 eV): m/z (%) 212 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (1/30). Mp = 101.0 °C. Anal. Calcd for $C_{12}H_{18}FNO$: C 68.22, H 8.59, N 6.63. Found: C 68.39, H 8.76, N 6.71%.

Synthesis of *trans*-2-aryl-3-(hydroxymethyl)aziridines 6

General procedure: To an ice-cooled solution of *trans*-4-aryl-3-chloroazetidin-2-one **2** (8 mmol) in Et_2O (50 mL) was added $LiAlH_4$ (8 mmol, 1 equiv) in small portions. Subsequently, the resulting suspension was stirred at room temperature for 5–8 h, after which water (10 mL) was added at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterwards, the mixture was filtered through a path of Celite®, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent afforded the crude product, which was purified by recrystallization from absolute EtOH or column chromatography on silica gel.

trans-3-Hydroxymethyl-1-isopropyl-2-phenylaziridine 6a

Major invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.75 and 1.14 (2 × 3H, 2 × d, J = 5.9 Hz); 1.98 (1H, septet, J = 5.9 Hz); 2.39–2.44 (1H, m); 3.21 (1H, d, J = 5.9 Hz); 3.46–3.63 and 3.87–4.08 (2 × 1H, 2 × m); 7.20–7.35 (5H, m).^{13}C NMR (75 MHz, $CDCl_3$): δ 21.46; 22.45; 42.52; 44.30; 49.87; 62.45; 127.67; 127.85; 130.19; 132.97. IR (ATR, cm^{-1}): ν_{OH} = 3152. MS (70 eV): m/z (%) 192 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (4/6). Mp = 94.9 °C.

Minor invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 and 1.25 (2 × 3H, 2 × d, J = 6.1 Hz); 2.01 (1H, septet, J = 6.1 Hz); 2.39–2.45 (1H, m); 2.72 (1H, s(br)); 3.89–3.93 and 3.96–4.01 (2 × 1H, 2 × m); 7.28–7.32 (5H, m).^{13}C NMR (75 MHz, $CDCl_3$): δ 22.61, 23.15, 43.80, 48.37, 52.14, 58.66, 126.42, 126.83, 128.27, 140.27. IR (ATR, cm^{-1}): ν_{OH} = 3125. MS (70 eV): m/z (%) 192 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (1/30). Mp = 94.9 °C.

Anal. Calcd for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32. Found: C 75.26, H 9.11, N 7.37%.

trans-1-Benzyl-3-hydroxymethyl-2-phenylaziridine 6b

^{1}H NMR and MS data for the major and minor invertomer were in accordance with those reported in the literature.[4c,d]

Major invertomer. ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 44.21, 44.24, 55.57, 62.49, 127.15, 128.26, 128.35, 128.49, 128.57, 130.49, 133.19, 139.35. IR (ATR, cm^{-1}): ν_{OH} = 3323.

Minor invertomer. ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 45.60, 51.46, 55.66, 58.97, 126.41, 127.53, 127.73, 127.89, 128.73, 128.90, 139.15, 139.76. IR (ATR, cm^{-1}): ν_{OH} = 3323.

Anal. Calcd for $C_{16}H_{17}NO$: C 80.30, H 7.16, N 5.85. Found: C 80.44, H 7.35, N 5.97%.

trans-1-Benzyl-2-(4-chlorophenyl)-3-(hydroxymethyl)aziridine 6c

Major invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04–2.05 (1H, m); 2.37–2.39 (1H, m); 3.08 (1H, d, J = 13.8 Hz); 3.22 (1H, d, J = 3.3 Hz); 3.36 (1H, d, J = 13.8 Hz); 3.49–3.56 and 3.80–3.85 (2 × 1H, 2 × m); 7.10–7.35 (9H, m).^{13}C NMR (75 MHz, $CDCl_3$): δ 43.22, 43.90, 55.48, 62.13, 127.11, 127.53, 127.99, 128.42, 131.57, 131.78, 134.02, 139.08. IR (ATR, cm^{-1}): ν_{OH} = 3074. MS (70 eV): m/z (%) 274/6 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (1/30). Mp = 95.6 °C.

Minor invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (1H, s); 2.37–2.39 (1H, m); 2.48 (1H, s(br)); 3.80–3.85 (1H, m); 3.91 (2H, s); 3.97–4.03 (1H, m); 7.10–7.35 (9H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 44.52, 48.34, 55.48, 58.98, 127.11, 127.53, 127.99, 128.42, 131.57, 132.63, 138.22, 139.34. IR (ATR, cm^{-1}): ν_{OH} = 3074. MS (70 eV): m/z (%) 274/6 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (1/30). Mp = 95.6 °C.

Anal. Calcd for $C_{16}H_{16}ClNO$: C 70.20, H 5.89, N 5.12. Found: C 70.36, H 6.03, N 5.01%.

trans-2-(2-Fluorophenyl)-3-hydroxymethyl-1-propylaziridine 6e

Major invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.83 (3H, t, J = 7.5 Hz); 1.49 (2H, sextet, J = 7.5 Hz); 1.78–1.86 (1H, m); 2.27–2.38 (2H, m); 3.22 (1H, d, J = 3.9 Hz); 3.61–3.68 and 3.91–3.98 (2 × 1H, 2 × m); 7.06–7.13 and 7.16–7.35 (4H, 2 × m).^{19}F NMR (282 MHz, $CDCl_3$): δ (–114.41)–(–114.08) (m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.76, 22.87, 38.22 (d, J = 2.3 Hz), 44.28, 54.25, 62.39, 115.54 (d, J = 21.9 Hz), 121.28 (d, J = 15.0 Hz), 123.56 (d, J = 3.4 Hz), 129.73 (d, J = 8.1 Hz), 131.66 (d, J = 3.5 Hz), 162.96 (d, J = 248.1 Hz). IR (ATR, cm^{-1}): ν_{OH} = 3225. MS (70 eV): m/z (%) 210 (M^+ + 1, 100). R_f 0.13 (Et_2O–hexane 6/1).

Minor invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, J = 7.2 Hz); 1.61–1.75 (2H, m); 2.41 (1H, s(br)); 2.43–2.51 (1H, m); 2.64 (1H, d, J = 2.2 Hz); 2.89–2.97 (1H, m); 3.91–3.98 and 4.07–4.11 (2 × 1H, 2 × m); 7.00–7.13 and 7.16–7.35 (4H, 2 × m). ^{19}F NMR (282 MHz, $CDCl_3$): δ (–121.32)–(–118.00) (m).^{13}C NMR (75 MHz, $CDCl_3$): δ 11.97, 23.44, 39.15 (d, J = 4.6 Hz), 47.07, 54.,00, 58.69, 114.75 (d, J = 21.9 Hz), 124.21, 127.05, 127.28 (d, J = 3.5 Hz), 128.06 (d, J = 8.1 Hz), 161.49 (d, J = 244.6 Hz). IR (ATR, cm^{-1}): ν_{OH} = 3225. MS (70 eV): m/z (%) 210 (M^+ + 1, 100). R_f 0.13 (Et_2O–hexane 6/1).

Anal. Calcd for $C_{12}H_{16}FNO$: C 68.88, H 7.71, N 6.69. Found: C 68.74, H 7.87, N 6.58%.

Synthesis of *cis*-2-aryl-3-(hydroxymethyl)aziridines 8

General procedure: To an ice-cooled solution of *cis*-4-aryl-3-chloroazetidin-2-one **3** (2 mmol) in Et_2O (20 mL) was added $LiAlH_4$ (4 mmol, 2 equiv) in small portions. Subsequently, the resulting suspension was heated under reflux for 15 h, after which water (2 mL) was added at 0 °C in order to neutralize the excess of $LiAlH_4$. Afterwards, the mixture was filtered through a path of Celite®, and the filtrate was dried over $MgSO_4$. Removal of the drying agent through filtration and evaporation of the solvent

afforded the crude product, which was purified by recrystallization from hexane–EtOAc (1/30).

cis-1-*tert*-Butyl-2-(2-fluorophenyl)-3-(hydroxymethyl)aziridine 8a

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s); 2.35 (1H, d × d × d, J = 6.1, 6.1, 5.9 Hz); 3.05 (1H, d, J = 6.1 Hz); 3.15 and 3.42 (2 × 1H, 2 × (d × d), J = 11.4, 6.1, 5.9 Hz); 6.96–7.02, 7.05–7.10, 7.16–7.26 and 7.43–7.48 (4 × 1H, 4 × m). ^{19}F NMR (282 MHz, $CDCl_3$): δ (–119.17)–(–119.09) (m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.81, 33.78 (d, J = 3.4 Hz), 39.09, 52.93, 60.57, 114.71 (d, J = 20.7 Hz), 123.81 (d, J = 2.3 Hz), 124.94 (d, J = 13.8 Hz), 128.27 (d, J = 7.0 Hz), 130.00 (d, J = 3.5 Hz), 161.65 (d, J = 245.7 Hz). IR (ATR, cm^{-1}): ν_{OH} = 3292. MS (70 eV): m/z (%) 224 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (1/30). Mp = 101.7 °C. Anal. Calcd for $C_{13}H_{18}FNO$: C 69.93, H 8.13, N 6.27. Found: C 69.85, H 8.20, N 6.24%.

cis-1-*tert*-Butyl-3-hydroxymethyl-2-(2-methoxyphenyl)aziridine 8b

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (9H, s); 1.90 (1H, s(br)); 2.33 (1H, d × d × d, J = 6.7, 6.5, 6.5 Hz); 2.97 (1H, d, J = 6.5 Hz); 3.17 (1H, d × d, J = 11.0, 6.7 Hz); 3.28–3.33 (1H, m); 3.87 (1H, s); 6.85 (1H, d, J = 7.7 Hz); 6.94–7.45 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.93, 35.32, 38.86, 52.87, 55.35, 61.32, 109.85, 120.65, 126.05, 127.90, 129.87, 157.58. IR (ATR, cm^{-1}): ν_{OH} = 3314. MS (70 eV): m/z (%) 236 (M^+ + 1, 100). Recrystallization from hexane–EtOAc (1/30). Mp = 101.3 °C. Anal. Calcd for $C_{14}H_{21}NO_2$: C 71.46, H 8.99, N 5.95. Found: C 71.30, H 9.13, N 5.89%.

Synthesis of *anti*-2-amino-3-aryl-3-methoxypropan-1-ols 10

General procedure: A solution of *trans*-2-aryl-3-(hydroxymethyl)aziridine **6** (1 mmol) in MeOH (15 mL) was heated under reflux for 1–65 h, after which the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane–EtOAc).

anti-2-(*N*-Isopropylamino)-3-methoxy-3-phenylpropan-1-ol 10a

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 and 0.99 (2 × 3H, 2 × d, J = 6.6 Hz); 2.76–2.88 (2H, m); 3.27 (3H, s); 3.46 and 3.53 (2 × 1H, 2 × (d × d), J = 10.8, 5.5, 4.4 Hz); 4.28 (1H, d, J = 5.5 Hz); 7.29–7.41 (5H, m).^{13}C NMR (75 MHz, $CDCl_3$): δ 23.19, 23.44, 45.71, 57.53, 60.05, 60.75, 84.57, 126.91, 127.92, 128.56, 139.00. IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3423. MS (70 eV): m/z (%) 224 (M^+ + 1, 100). R_f 0.07 (hexane–EtOAc 1/2). Anal. Calcd for $C_{13}H_{21}NO_2$: C 69.92, H 9.48, N 6.27. Found: C 69.77, H 9.64, N 6.12%.

anti-2-(*N*-Benzylamino)-3-methoxy-3-phenylpropan-1-ol 10b

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (1H, d × d × d, J = 5.6, 5.1, 5.0 Hz); 3.25 (3H, s); 3.57 and 3.64 (2 × 1H, 2 × (d × d), J = 10.9, 5.1, 5.0 Hz); 3.71 and 3.78 (2 × 1H, 2 × d, J = 13.3 Hz); 4.32 (1H, d, J = 5.6 Hz); 7.16–7.40 (10H, m).^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 51.43, 57.51, 60.01, 62.79, 84.27, 127.19, 127.25, 128.22, 128.57, 128.77, 139.01, 140.09. IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3341. MS (70 eV): m/z (%) 272 (M^+ + 1, 100). R_f 0.10 (hexane–EtOAc 2/1). Anal. Calcd for $C_{17}H_{21}NO_2$: C 75.25, H 7.80, N 5.16. Found: C 75.16, H 7.97, N 5.03%.

anti-2-(*N*-Benzylamino)-3-(4-chlorophenyl)-3-methoxypropan-1-ol 10c

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.75 (1H, d × d × d, J = 5.8, 5.3, 4.6 Hz); 3.22 (3H, s); 3.55 and 3.62 (2 × 1H, 2 × (d × d), J = 11.1, 5.3, 4.6 Hz); 3.70 and 3.78 (2 × 1H, 2 × d, J = 13.3 Hz); 4.28 (1H, d, J = 5.8 Hz); 7.16–7.18 and 7.21–7.34 (9H, 2 × m).^{13}C NMR (75 MHz, $CDCl_3$): δ 51.24, 57.44, 59.70, 62.49, 83.47, 127.12, 128.02, 128.42, 128.45, 128.79, 133.72, 137.46, 139.78. IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3334. MS (70 eV): m/z (%) 306/8 (M^+ + 1, 100). R_f 0.16 (hexane–EtOAc 1/1). Anal. Calcd for $C_{17}H_{20}ClNO_2$: C 66.77, H 6.59, N 4.58. Found: C 66.91, H 6.84, N 4.70%.

anti-2-(*N*-Isobutylamino)-3-methoxy-3-(4-methoxyphenyl)propan-1-ol 10d

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 and 0.79 (2 × 3H, 2 × d, J = 6.9 Hz); 1.51–1.64 (1H, m); 2.33 and 2.34 (2 × 1H, 2 × d, J = 6.6 Hz); 2.69 (1H, d × d × d, J = 6.2, 5.2, 5.1 Hz); 3.22 (3H, s); 3.56 and 3.63 (2 × 1H, 2 × (d × d), J = 10.7, 5.2, 5.1 Hz); 3.82 (3H, s); 4.20 (1H, d, J = 6.2 Hz); 6.91 and 7.22 (2 × 2H, 2 × d, J = 8.5 Hz). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 20.50, 28.58, 55.34, 55.42, 57.11, 59.98, 63.75, 83.68, 114.09, 128.41, 130.92, 159.52. IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3423. MS (70 eV): m/z (%) 268 (M^+ + 1, 100). R_f 0.14 (hexane–EtOAc 1/2). Anal. Calcd for $C_{15}H_{25}NO_3$: C 67.38, H 9.42, N 5.24. Found: C 67.21, H 9.64, N 5.08%.

anti-3-(2-Fluorophenyl)-3-methoxy-2-(*N*-propylamino)propan-1-ol 10e

^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.5 Hz); 1.40–1.52 (2H, m); 2.51–2.60 and 2.62–2.70 (2 × 1H, 2 × m); 2.83 (1H, d × d × d, J = 5.9, 5.0, 4.9 Hz); 3.29 (3H, s); 3.47 and 3.51 (2 × 1H, 2 × (d × d), J = 10.9, 5.9, 4.9 Hz); 4.77 (1H, d, J = 5.0 Hz); 7.03–7.09, 7.16–7.21, 7.25–7.31 and 7.32–7.39 (4 × 1H, 4 × m).^{19}F NMR (282 MHz, $CDCl_3$): δ (–119.09)–(–119.00) (m).^{13}C NMR (75 MHz, $CDCl_3$): δ 11.63, 23.50, 49.15, 57.84, 59.97, 62.35, 77.49, 115.53 (d, J = 21.9 Hz), 124.35 (d, J = 3.4 Hz), 126.15 (d, J = 13.9 Hz), 127.76 (d, J = 4.6 Hz), 129.25 (d, J = 8.1 Hz), 160.80 (d, J = 245.8 Hz). IR (ATR, cm^{-1}): $\nu_{NH,OH}$ = 3408. MS (70 eV): m/z (%) 242 (M^+ + 1, 100). R_f 0.10 (hexane–EtOAc 1/2). Anal. Calcd for $C_{13}H_{20}FNO_2$: C 64.71, H 8.35, N 5.80. Found: C 64.50, H 8.58, N 5.64%.

Synthesis of 1-alkyl-2-aryl-3-(methoxymethyl)aziridines 7 and 9

General procedure: To an ice-cooled solution of 2-aryl-3-(hydroxymethyl)aziridine **6** or **8** (0.5 mmol) in dry THF (10 mL) was added NaH (0.75 mmol, 1.5 equiv, 60% dispersion in mineral oil), after which the resulting suspension was stirred for one hour at room temperature. Subsequently, MeI (0.75 mmol, 1.5 equiv) was added dropwise at 0 °C, followed by a reflux period of 6 h. The resulting mixture was poured in water (10 mL) and extracted with Et_2O (3 × 10 mL). Drying ($MgSO_4$), removal of the drying agent and evaporation of the solvent *in vacuo* afforded the crude product, which was purified by column chromatography on silica gel.

***trans*-1-Benzyl-2-(4-chlorophenyl)-3-(methoxymethyl)aziridine 7**

Major invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39–2.44 (1H, m); 3.19 (1H, d, J = 3.3 Hz); 3.40 (3H, s); 3.71 (1H, d, J = 14.3 Hz); 3.78–3.81 (2H, m); 4.12 (1H, d, J = 14.3 Hz); 7.17–7.36 (9H, m).^{13}C NMR (75 MHz, $CDCl_3$): δ 44.32, 46.12, 55.53, 58.60, 68.52, 126.76, 127.57, 128.30, 128.40, 131.60, 132.53, 138.57, 139.67. IR (ATR cm^{-1}): ν_{max} = 2923, 2873, 2853, 1493, 1452, 1104, 1090, 802, 732, 696. MS (70 eV): m/z (%) 288/90 (M^+ + 1, 100). R_f 0.25 (Et_2O–hexane 1/1).

Minor invertomer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.39–2.44 (1H, m); 2.57 (1H, d, J = 2.8 Hz); 3.36 (3H, s); 3.55 (2H, d, J = 4.4 Hz); 3.71 and 4.12 (2 × 1H, 2 × d, J = 14.3 Hz); 7.17–7.36 (9H, m).^{13}C NMR (75 MHz, $CDCl_3$): δ 42.46, 44.08, 55.82, 58.87, 74.29, 126.83, 127.57, 127.98, 128.22, 128.30, 132.10, 133.87, 139.17. IR (ATR, cm^{-1}): ν_{max} = 2923, 2873, 2853, 1493, 1452, 1104, 1090, 802, 732, 696. MS (70 eV): m/z (%) 288/90 (M^+ + 1, 100). R_f 0.25 (Et_2O–hexane 1/1).

Anal. Calcd for $C_{17}H_{18}ClNO$: C 70.95, H 6.30, N 4.87. Found: C 70.72, H 6.57, N 4.93%.

***cis*-1-*tert*-Butyl-2-(2-fluorophenyl)-3-(methoxymethyl)aziridine 9**

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (9H, s); 2.28 (1H, d × d × d, J = 6.1, 6.1, 5.9 Hz); 3.02 (1H, d, J = 6.1 Hz); 3.05 and 3.13 (2 × 1H, 2 × (d × d), J = 10.6, 6.1, 5.9 Hz); 3.19 (3H, s); 6.96–7.02, 7.05–7.10, 7.16–7.23 and 7.46–7.51 (4 × 1H, 4 × m). ^{19}F NMR (282 MHz, $CDCl_3$): δ (–119.11)–(–119.03) (m). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.70, 32.93 (d, J = 3.4 Hz), 37.53, 53.07, 58.64, 71.41, 114.60 (d, J = 20.7 Hz), 123.56 (d, J = 3.5 Hz), 125.31 (d, J = 13.9 Hz), 128.02 (d, J = 8.1 Hz), 130.01 (d, J = 4.6 Hz), 161.88 (d, J = 245.8 Hz). IR (ATR, cm^{-1}): ν_{max} = 2962, 2924, 2855, 1491, 1455, 1241, 1222, 1138, 1107, 1096, 757. MS (70 eV): m/z (%) 238 (M^+ + 1, 100). R_f 0.41 (hexane–EtOAc 9/1). Anal. Calcd for $C_{14}H_{20}FNO$: C 70.86, H 8.49, N 5.90. Found: C 71.05, H 8.64, N 5.82%.

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