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Systematic Study of Halide-Induced Ring Opening of 2-Substituted Aziridinium Salts and Theoretical Rationalization of the Reaction Pathways

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Dedicated to Professor Carmen Nájera on the occasion of her 60th birthday

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The ring-opening reactions of 2-alkyl-substituted 1,1-bis(arylmethyl)- and 1-methyl-1-(1-phenylethyl)aziridinium salts with fluoride, chloride, bromide and iodide in acetonitrile have been evaluated for the first time in a systematic way. The reactions with fluoride afforded regioisomeric mixtures of primary and secondary fluorides, whereas secondary β-chloro, β-bromo and β-iodo amines were obtained as the sole reaction products from the corresponding halides by regiospecific ring opening at the substituted position. Both experimental and computational results revealed that the reaction outcomes in the cases of chloride, bromide and iodide were dictated by product stability through thermodynamic control involving rearrangement of the initially formed primary halides to the more stable secondary halides. The ring opening of the same aziridinium salts with fluoride, however, was shown to be mediated by steric interactions (kinetic control), with the corresponding primary β-fluoro amines being obtained as the main reaction products. Only for 2-acylaziridinium ions was the reaction outcome shown to be under full substrate control, affording secondary β-fluoro, β-chloro, β-bromo and β-iodo amines through exclusive attack at the activated α-carbonyl carbon atom.

Introduction

The aziridine moiety represents one of the most valuable three-membered ring systems in organic chemistry[1] and the regiocontrolled ring opening of *C*-substituted aziridines is a powerful approach towards the preparation of a large variety of functionalized nitrogen-containing target compounds. The ring opening of activated aziridines, that is, aziridines bearing an electron-withdrawing group at the nitrogen atom, has been widely reported in the literature.[1d]

However, non-activated aziridines, that is, aziridines with an electron-donating substituent at the nitrogen atom, have to be activated prior to ring opening, but so far this has only been evaluated to a limited extent. Nevertheless, the reactivity and applications of non-activated aziridines are different and often complementary to those of activated aziridines and epoxides, providing interesting opportunities for the selective synthesis of a variety of functionalized amines. The most commonly applied methodology in this respect involves the formation of highly electrophilic aziridinium intermediates by *N*-alkylation, *N*-acylation, *N*-protonation or *N*-complexation with Lewis acids, which can then easily be opened by different types of nucleophiles.

The ring opening of aziridinium salts with halides is a convenient approach towards β-halo amines, which are generally recognized as useful building blocks in organic chemistry[2] and valuable targets in medicinal chemistry (nitrogen mustards, chemotherapy agents).[3] If 2-substituted aziridines are used for the synthesis of the corresponding β-halo amines, the issue of regioselectivity in the ring opening of the intermediate aziridinium salts becomes important as two regioisomeric β-halo amines can be obtained. As depicted in Scheme 1, the ring opening of aziridinium salts **1** can occur at either the unsubstituted (path a) or substituted aziridine carbon atom (path b), leading either to primary halides **2** (path a) or secondary halides **3** (path b).

A number of reports on the synthesis of β-halo amines by the ring opening of aziridinium salts with halides are

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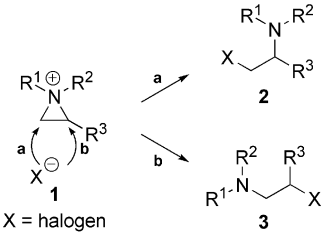


Scheme 1. Regioselectivity in the ring opening of 2-subsitituted aziridinium salts **1**.

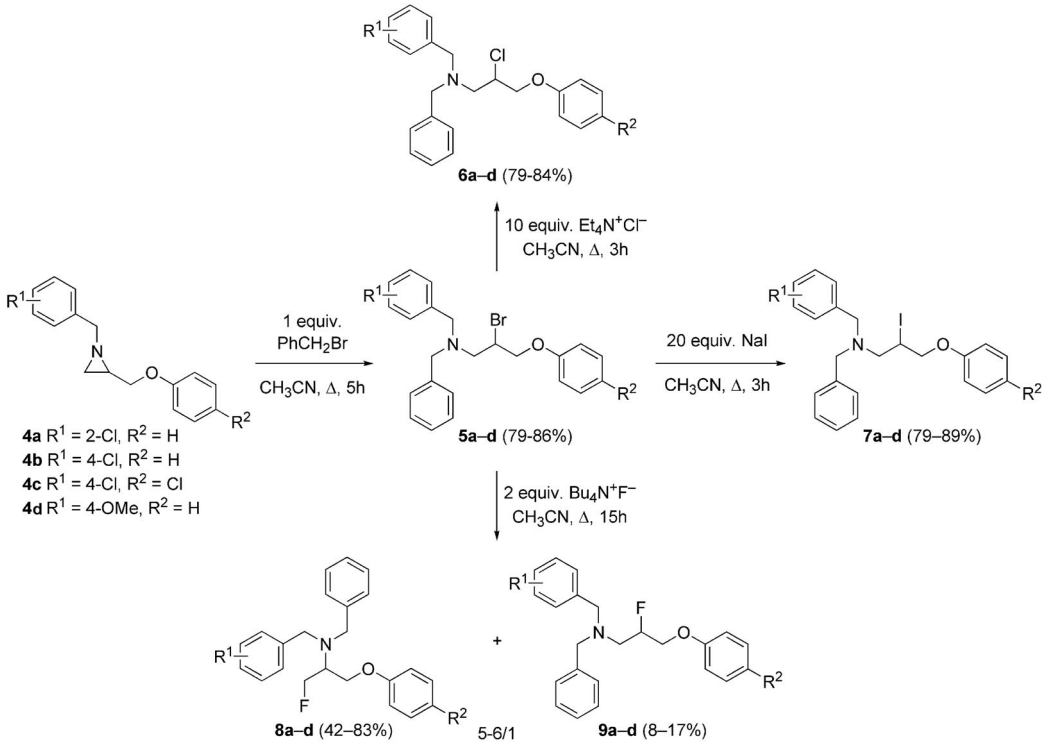
available in the literature.[4] In most cases, 2-vinyl- and 2-arylaziridinium salts have been evaluated in which the regioselectivity is substrate-dictated due to the presence of a pronounced electrophilic centre at the substituted aziridine carbon atom. The use of 2-alkyl-substituted aziridinium ions has somewhat been neglected in this respect, probably because of the potential influence of different parameters such as the type of nucleophile, substrate and solvent on the reaction outcome.

Although the issue of regioselectivity has been addressed in a number of reports, no systematic study has been performed up to now in which aziridinium substrates have been subjected to ring opening with fluoride, chloride, bromide and iodide. In the work reported herein two different types of 2-substituted aziridinium salts, namely in situ generated and preformed aziridinium ions, were used as electrophiles in a systematic study of ring opening with fluoride, chloride, bromide and iodide in acetonitrile. As a continuation of our interest in the study of the ring-opening reactions of 2-substituted aziridinium salts,[5] the influence of the nucleophile and substrate on the regioselectivity of these ring-opening reactions has been investigated and the observed reaction paths have been rationalized by detailed computational analysis.

Results and Discussion

In a first approach, the systematic study of halide-induced ring opening of intermediate 2-aryloxymethyl-1,1-bis(arylmethyl)aziridinium salts was contemplated. As reported before, 2-(aryloxymethyl)aziridines **4** can be prepared in high yields and purity upon treatment of the corresponding 2-(bromomethyl)aziridines[6] with 2 equiv. of the appropriate potassium phenolate in a DMF/acetone (1:1) solvent system at reflux for 10–20 h.[7] Subsequent treatment of the aziridines **4** with 1 equiv. of benzyl bromide in acetonitrile is known to afford secondary bromides **5** as the sole reaction products in high yields after heating at reflux for 5 hours.[7] To provide an entry to the corresponding fluorides, chlorides and iodides as well, β-bromo amines **5** were treated with different halide sources. Thus, both novel β-chloro amines **6** and β-iodo amines **7** were prepared as the sole reaction products by heating either with 10 equiv. of tetraethylammonium chloride or with 20 equiv. of sodium iodide, respectively, at reflux in acetonitrile for 3 hours (Scheme 2, Table 1). Detailed spectroscopic analysis ruled out the formation of other regioisomers.

The conversion of β-bromo amines **5** into β-chloro amines **6** using 20 equiv. of NaCl instead of tetraethylammonium chloride in acetonitrile proceeded very sluggishly; no conversion occurred after heating at reflux for 4 h and



Scheme 2. Synthesis of β-bromo amines **5**, β-chloro amines **6**, β-iodo amines **7** and β-fluoro amines **8** and **9**.

Table 1. Synthesis of β-bromo amines **5**, β-chloro amines **6**, β-iodo amines **7** and β-fluoro amines **8** and **9**.

Entry	R^1	R^2	**5** (% yield)	**6** (% yield)	**7** (% yield)	**8** (% yield)	**9** (% yield)	Ratio[a] **8/9**
1	2-Cl	H	**5a** (71)	**6a** (82)	**7a** (89)	**8a** (54)	**9a** (10)	5:1
2	4-Cl	H	**5b** (86)	**6b** (79)	**7b** (88)	**8b** (42)	**9b** (8)	5:1
3	4-Cl	Cl	**5c** (85)	**6c** (83)	**7c** (82)	**8c** (60)	**9c** (10)	6:1
4	4-OMe	H	**5d** (84)	**6d** (84)	**7d** (79)	**8d** (61)	**9d** (14)	6:1

[a] Ratio determined by ^{1}H NMR analysis.

only partial conversion was observed after 60 h. On the other hand, the reaction of β-bromo amines **5** with 10 equiv. of tetrabutylammonium iodide in acetonitrile appeared to be less successful in comparison with the use of sodium iodide as only 50% conversion took place after heating at reflux for 7 h. If 15 equiv. of sodium iodide were used instead of 20 equiv., a longer reaction time (5 h) was required to drive the reaction to completion.

When β-bromo amines **5** were treated with 2 equiv. of tetrabutylammonium fluoride in acetonitrile, however, a mixture of regioisomeric fluorides **8** and **9** was obtained after heating at reflux for 15 h (Scheme 2, Table 1).[5c] In this case, primary fluorides **8** were formed as the major reaction products in addition to minor amounts of secondary fluorides **9** (ratio **8/9** 5–6:1). To test the reaction outcome as a function of reaction time and temperature, prolonged reaction times and elevated temperatures were also evaluated. In particular, heating at reflux for 3 d instead of 15 h did not affect the isomeric distribution (ratio **8/9**: 5–6:1) and the same conclusion was drawn after heating at reflux for 25 h in DMF. These observations indicate that the product distribution between primary and secondary fluorides **8** and **9** is not under thermodynamic control.

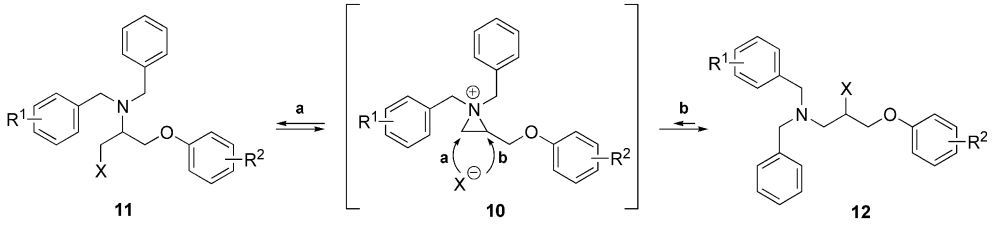
From a mechanistic point of view, the formation of β-bromo amines **5**, β-chloro amines **6**, β-iodo amines **7** and β-fluoro amines **8** and **9** proceeds through the ring opening of the same intermediate aziridinium salts **10** with different halides (Scheme 3).

As observed and investigated before, quaternization and subsequent ring opening of 2-(aryloxymethyl)aziridines **4** using benzyl bromide produces β-bromo amines **12** through the regiospecific ring opening of aziridinium salts **10** at the substituted aziridine carbon atom (X = Br, path b, Scheme 3).[5b,5i,7] Furthermore, in addition to preliminary findings using other types of substrates,[5c] the ring opening of aziridinium intermediates **10** with fluoride afforded a mixture of regioisomers in which primary fluorides **11** are predominant (X = F, path a, Scheme 3), which indicates a change in regioselectivity in comparison with bromide. In previous theoretical studies, it was demonstrated that product stabilities in the case of bromide seem to dictate the outcome of the reaction through thermodynamic control, whereas in the case of fluoride differences in barriers were shown to be mainly due to the differences in interaction energies, which indicates that steric interactions dictate the reaction outcome.[5i]

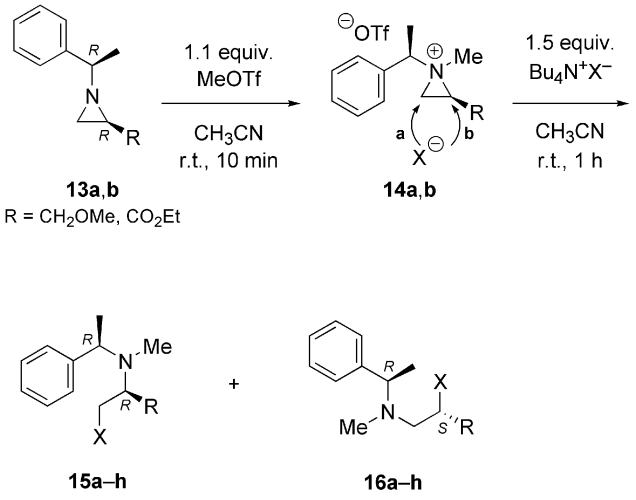
Apparently, the chloride-[8] and iodide-promoted ring opening of aziridinium ions **10** is controlled by the same factors as those influencing the bromide-induced ring opening with attack at the substituted position (X = Cl and I, path b, Scheme 3). Thus, it can be concluded that chloride-, bromide- and iodide-promoted ring opening of aziridinium ions **10** is under thermodynamic control, eventually leading to the more stable secondary halides **12** as the final reaction products. On the other hand, ring opening with fluoride is kinetically controlled, which can be attributed to the poor leaving-group capacity of fluoride in comparison with the other halides, which prevents thermodynamic equilibration.

To provide an insight into the potential role of the substrate in the above ring-opening reactions, the synthesis of another type of aziridinium salt was devised. In addition to non-isolable aziridinium intermediates **10**, stable 1-methylaziridinium triflates **14** were prepared by *N*-methylation of chiral aziridines **13** by treatment with 1.1 equiv. of methyl trifluoromethanesulfonate in acetonitrile for 10 min (Scheme 4). These were then evaluated as electrophiles for the halide-induced ring-opening reactions. Chiral substrates **13a**,**b** were prepared starting from the corresponding commercially available (*R*)-2-hydroxymethyl-1-[(*R*)-1-phenylethyl]aziridine according to literature protocols.[5c,5g,5h]

In this work, different tetrabutylammonium halides were used as halide sources for the ring opening of the aziridinium triflates **14**. First, the reactions of 2-(methoxymethyl)-aziridinium **14a** (R = CH_2OMe) with 1.5 equiv. of tetrabutylammonium fluoride, chloride, bromide or iodide in acetonitrile at room temperature for 1 hour afforded the corresponding β-halo amines in good yields. Interestingly, the



Scheme 3. Regioselectivity in the ring opening of aziridinium salts **10** with different halides.



Scheme 4. Ring opening of 1-methylaziridinium triflates **14** with tetrabutylammonium halides.

same conclusions were drawn as described above in relation to the selective synthesis of secondary bromide **16a**, iodide **16b** and chloride **16d** as the sole reaction products and the regioisomeric mixture of primary and secondary fluorides **15c** and **16c** (3:1; Scheme 4, Table 2). These observations further confirm the nucleophile-dependency of the ring-opening reactions of 1,1,3-trialkylaziridinium ions with halides, showing chloride-, bromide- and iodide-mediated ring opening under thermodynamic control and fluoride-induced ring opening under kinetic control.

Table 2. Ring opening of 1-methylaziridinium triflates **14** with tetrabutylammonium halides.

Entry	Substrate	R	X^-	Product	% Yield
1	**14a**	CH_2OMe	Br^-	**16a**	47
2	**14a**	CH_2OMe	I^-	**16b**	52
3	**14a**	CH_2OMe	F^-	**15c** + **16c**	77 (3:1)
4	**14a**	CH_2OMe	Cl^-	**16d**	73
5	**14b**	CO_2Et	Br^-	**16e**	92[a]
6	**14b**	CO_2Et	I^-	**16f**	90[a]
7	**14b**	CO_2Et	F^-	**16g**	71
8	**14b**	CO_2Et	Cl^-	**16h**	83

[a] Compounds decomposed during chromatographic purification.

Nonetheless, the nucleophile-dependency of the aziridinium ring-opening reactions is over-ruled by substrate control if an activated aziridine carbon atom is present in the substrate. For example, with the 2-(ethoxycarbonyl)aziridinium salt **14b** (R = CO_2Et), only the corresponding secondary halides were obtained by ring opening at the activated α-carbonyl atom after reaction with 1.5 equiv. of tetrabutylammonium halide in acetonitrile at room temperature, and no primary halides were retrieved (Scheme 4, Table 2). Thus, α-halo esters **16e**–**h** were formed through regiospecific ring opening of aziridinium salts **14b** at the substituted aziridine carbon atom (path b, Scheme 4).

Interestingly, when aziridinium triflate **14a** was treated with 1.5 equiv. of NaCl in acetonitrile (20 h, room temp.) instead of $Bu_4N^+Cl^-$, a different reaction product was initially observed upon chromatographic analysis (TLC), which underwent slow conversion into the secondary β-chloro amine **16d** upon standing at room temperature. Although purification by column chromatography on silica gel failed, the initially formed reaction product could be identified as 2-amino-3-chloro-1-methoxypropane **15d** by ^{1}H NMR analysis. Clearly this primary chloride comprises the kinetically controlled reaction product obtained through ring opening of the aziridinium ion **14a** at the unsubstituted position (path a, Scheme 4), which then rearranges into the more stable secondary chloride through a thermodynamic equilibrium. The same observation was made by careful analysis of the reaction between aziridinium triflate **14a** and 1.5 equiv. of $Me_4N^+Cl^-$. The product distribution between aziridinium ion **14a**, primary chloride **15d** and secondary chloride **16d** was evaluated by ^{1}H NMR spectroscopy ($CDCl_3$; Figure 1). Note that these findings comprise the first experimental proof of the occurrence of a thermodynamic equilibrium in the halide-induced ring opening of 2-alkyl-substituted aziridinium salts.

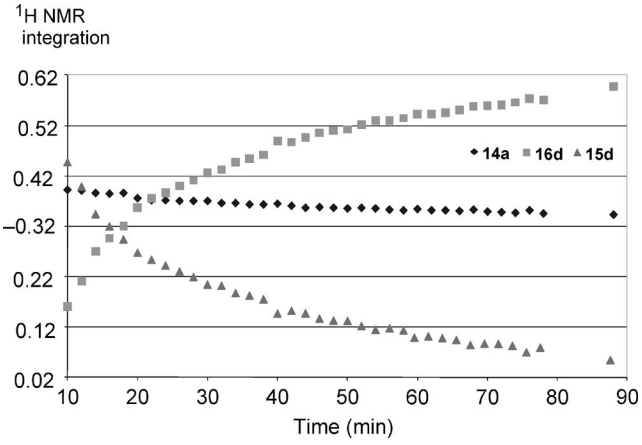
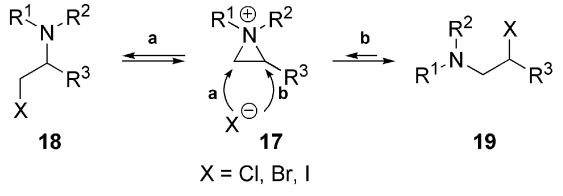


Figure 1. Product distribution between **14a**, **15d** and **16d** as a function of reaction time.

From these experiments it can be concluded that the ring-opening reactions of 2-alkyl-substituted aziridinium salts **17** with chloride, bromide and iodide proceed under thermodynamic control, with product stabilities dictating the outcome of the reactions. Thus, the initially formed kinetic primary halides **18** undergo rearrangement into the thermodynamically more stable secondary halides **19** (Scheme 5). Fluoride-mediated ring opening, however, is under kinetic control, with the reaction outcome only being dictated by steric interactions.



Scheme 5. Thermodynamic control for chloride-, bromide- and iodide-induced ring-opening reactions of aziridinium salts.

Theoretical Rationalization

Computational studies have previously been performed on fluoride- and bromide-mediated ring-opening reactions of various *N*,*N*-dibenzylaziridinium ions,[5b,5d,5i,5j] however, a systematic evaluation is necessary for the rationalization of the observed trend in the halide series. To elucidate the factors causing the differences in regioselectivity, a thorough computational analysis was performed on the halide-mediated ring opening of **14a**. Iodide-induced ring-opening reactions have been excluded from this study because they show similar experimental regioselectivity to bromide, and the main aim of this computational study was to elucidate the factors causing the difference in experimental regioselectivities.

Computational Methodology

Reaction pathways for the nucleophilic attack of halides on aziridinium ion **14a** were obtained at the B3LYP/6-31++G(d,p) level of theory.[9,10] Stationary points were characterized as minima or first-order saddle points from frequency calculations. Intrinsic reaction coordinate (IRC)[11] calculations followed by full geometry optimizations were used to verify the reactant complexes (ion–dipole complex) and products yielded by each transition state. Energies were further refined by MPW1B95[12] single-point calculations as this method was recently shown to successfully reproduce SCS-MP2[13] results in the ring opening of aziridines with benzyl bromide.[5i] The effect of a polar environment has been taken into account by the use of self-consistent reaction field (SCRF) theory.[14] Solvation free energies in acetonitrile (ε = 35.688) were obtained by using the conductor-like polarizable continuum (C-PCM) model.[15] All DFT calculations were carried out with the Gaussian 03 program package.[16]

Explicit acetonitrile molecules were used to solvate halide ions as calculations of gas-phase systems, in which bare halide ions attack the electrophilic aziridinium ion, were previously shown to give unrealistic results and were incapable of representing the real system at hand.[4i] Accordingly, previous modelling studies on the bromide-induced ring opening of aziridinium ions effectively made use of explicit solvent molecules as this had previously been shown to be vital in reproducing realistic potential energy surfaces.[5d,5i] The use of discrete solvent molecules to stabilize chemically active species in reactions is a well-established methodology[5b,5d,5i,5j,17] and was used by us in a recent study, which successfully pointed to the correct regioselective outcome in aziridinium ring-opening reactions.[4i] However, this approach only accounts for short-range interactions such as in ion–dipole complexes and does not take into account potential long-range interactions with solvent molecules, which are likely to be significant when anionic nucleophiles are involved, as is the case herein. In view of this, the supermolecule was also placed in a dielectric continuum,[18] which led to a mixed implicit/explicit solvent model.[19] A recent comparative study has shown that mixed models should be used with caution as they may give unreliable results.[20] Nonetheless, the mixed implicit/explicit solvent model has been employed in addition to the supermolecule approach for comparative purposes.

Nucleophilic Ring-Opening Mechanisms

Nucleophilic ring opening can occur by attack at the unhindered (path a) or hindered (path b) aziridine carbon atoms (Scheme 1). Both reaction pathways were modelled for fluoride, chloride and bromide. Subsequent comparison of the reaction barriers and relative stabilities of the products should help us to understand the factors controlling regioselectivity. Halide-induced ring openings were modelled with the use of explicit solvent molecules; three acetonitrile molecules have been used to solvate the fluoride, chloride and bromide ions that attack the aziridinium ring as this was previously shown to be adequate for the solvation of the halide ion.[5i]

The transition-state geometries for the S_N2 attack of halides on both aziridine carbon atoms of **14a** are illustrated in Figure 2. Acetonitrile molecules stabilize the halide ions through charge–dipole interactions; typical X···H_3C–CN distances for fluoride, chloride and bromide are 2.0, 2.6 and 2.75 Å, respectively. These critical distances provide a measure of the ring opening within the aziridine as well as nucleophile-to-aziridine attack and are considerably different for both pathways and for all halides.

The relative energies show that the barrier for path a is systematically lower than that for path b for all three halides studied, that is, the kinetically favoured pathway is always the unhindered one as the steric properties would suggest. Differences in the activation energies between paths a (unhindered) and b (hindered) are shown in Table 3. On the other hand, the differences in reaction energies show that path b leads to the thermodynamically more stable product in all three cases. As mentioned earlier, the supermolecule (Figure 3) has also been embedded in a dielectric continuum to take into account long-range interactions with the bulk solvent. This mixed implicit/explicit solvent approach is shown to have the same trend as the discrete continuum model (supermolecule), which is solely solvated by explicit solvent molecules.

The potential energy surfaces (PES) for the halide-induced nucleophilic ring opening of **14a** through paths a (unhindered) and b (hindered) for all three halides are illustrated in Figure 3. There is a substantial barrier difference between the two pathways for fluoride attack that favours the unhindered route (path a), which also leads to the experimentally observed major product F-P-a (**15c**). Although F-P-b (**16c**) is shown to be thermodynamically more stable (Figure 3), because fluoride is a rather poor leaving group, thermodynamic equilibration requires a back-reaction barrier of approximately 130 kJ/mol to be overcome. This explains the mixture of products (**15c** and **16c**) observed for the fluoride-mediated ring opening of **14a**. For chloride, reaction barriers for both pathways are approximately 15 kJ/mol lower than in the fluoride case, which is consistent with

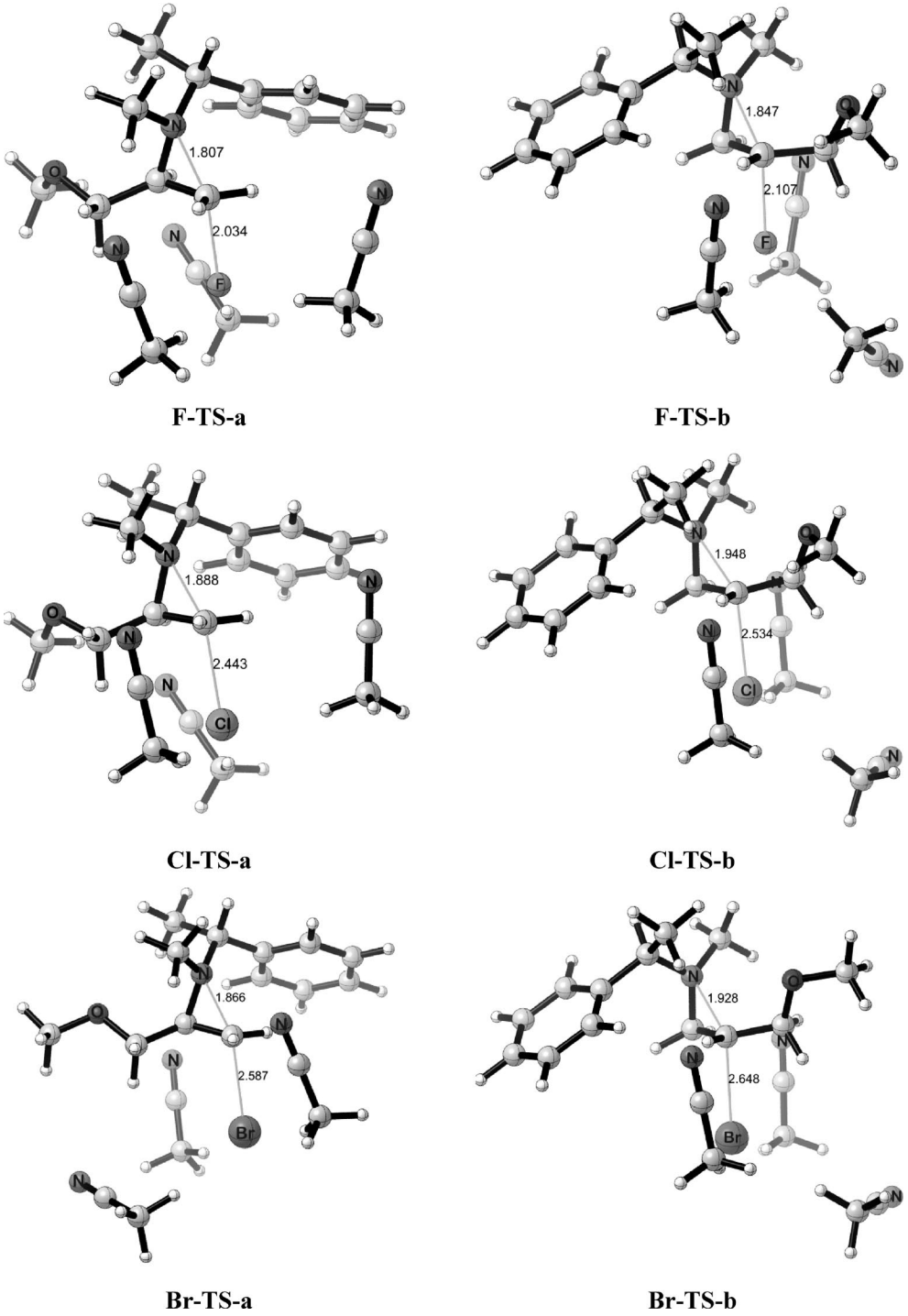


Figure 2. Transition-state geometries optimized at the B3LYP/6-31++G(d,p) level of theory for halide-induced nucleophilic ring opening of aziridinium ion **14a** through paths a and b. Some critical distances are given in units of Å.

the strength of the nucleophile; the softer the nucleophile the lower the barrier for attack. The reaction energies are also significantly different; this is in line with relative leaving-group abilities. For chloride, Cl-P-b (**16d**) is more stable than Cl-P-a (**15d**) by 20 kJ/mol, whereas Cl-TS-a is more feasible than Cl-TS-b by the same amount. Once again the kinetic route suggests path a, leading to **15d** (Cl-P-a), however, the back-reaction barriers are reasonably low (approximately 75 kJ/mol) and thermodynamic equilibration is feasible, leading to the energetically more stable final product Cl-P-b (**16d**). This explains the initial observation of **15d** during the ring-opening reaction with chloride. For bromide, the difference in energy between Br-TS-a and Br-TS-b is smaller than for the corresponding chlorides. Product stabilities favour path b and again the back-reaction barriers are quite low, easily allowing equilibration to yield the

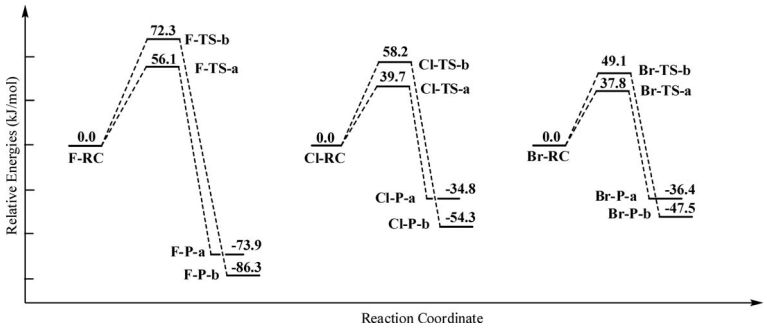


Figure 3. Free-energy surfaces (FES) for the halide-induced nucleophilic ring opening of **14a** through paths a (unhindered) and b (hindered) determined at the MPW1B95/6-31++G(d,p)//B3LYP/6-31++G(d,p) level of theory. Relative energies are given in kJ/mol.

Table 3. Differences in electronic ($\Delta\Delta E^{\ddagger}$) and free ($\Delta\Delta G^{\ddagger}$) energies of activation and electronic ($\Delta\Delta E^{rxn}$) and free ($\Delta\Delta G^{rxn}$) energies of reaction for halide-induced nucleophilic ring opening of **14a** by paths a (unhindered) and b (hindered).[a,b]

	MPW1B95/6-31++G(d,p)[c]				CPCM[e] (ε = 36.6)			
	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta G^{\ddagger}$[d]	$\Delta\Delta E^{rxn}$	$\Delta\Delta G^{rxn}$[d]	$\Delta\Delta E^{\ddagger}$	$\Delta\Delta G^{\ddagger}$[f]	$\Delta\Delta E^{rxn}$	$\Delta\Delta G^{rxn}$[f]
F^-	23.9	16.2	–17.2	–12.3	10.8	10.2	–16.7	–23.3
Cl^-	21.4	18.5	–18.0	–19.5	15.8	8.7	–20.1	–24.3
Br^-	12.0	11.3	–12.5	–11.1	16.3	11.1	–18.6	–15.8

[a] Energies in kJ/mol. [b] $\Delta\Delta E(G)^{\ddagger} = \Delta E(G)_b^{\ddagger} - \Delta E(G)_a^{\ddagger}$; $\Delta\Delta E(G)^{rxn} = \Delta E(G)_b^{rxn} - \Delta E(G)_a^{rxn}$. [c] B3LYP/6-31++G(d,p) geometries. [d] Thermal free-energy corrections from B3LYP/6-31++G(d,p) calculations at 1 atm and 298 K. [e] Bond radii with explicit hydrogen spheres. [f] Non-electrostatic terms included.

more stable product Br-P-b (**16a**; Table 3). Because Br-TS-b is lower in energy than Cl-TS-b, it is likely that equilibration takes place much faster with the bromide and the kinetic product Br-P-a (**15a**) is therefore not experimentally observed.

The overall picture for halide-induced ring opening shows that the unhindered route (path a) is always kinetically preferred, however, the hindered route leads to the thermodynamic product. The eventual outcome depends on the softness and leaving-group ability of the nucleophile (halide). If the nucleophile is a good leaving group (soft nucleophile, bromide), back-reaction barriers are sufficiently low to allow equilibration and the thermodynamic product will prevail. If the nucleophile is a poor leaving group (hard nucleophile, fluoride), the back reaction is unlikely and the kinetic route will dictate the reaction outcome. In the case of bromide, equilibration is so rapid that the initial formation of the kinetic product (Br-P-a) is not observed. In the case of chloride, however, equilibration is slower and therefore the kinetic product (**15d**) is initially observed during the reaction. Theoretical results are in perfect agreement with experimental findings and also in accord with the well-known trend in nucleophile strength and leaving-group ability of the halide series.

Distortion/Interaction Model

Efforts to rationalize the experimentally observed reaction outcomes also led to a comparative analysis of the transition-state structures by using the distortion/interaction model. To further verify the relationship between the structural distinctions and differences in the relative free energies of the transition states the activation strain model of chemical reactivity by Bickelhaupt,[21] also known as the distortion/interaction model by Houk,[22]was employed.

The distortion/interaction model breaks down the activation energy ($\Delta E^{\ddagger}$) into the distortion ($\Delta E^{\ddagger}_{dist}$) and interaction ($\Delta E^{\ddagger}_{int}$) energies between the distorted fragments [Equation (1)]; the former is associated with the strain caused by deforming the individual reactants and the latter is the favourable interaction between the deformed reactants. The fragment distortion and interaction energies determined at the MPW1B95/6-31++G(d,p) level are given in Table 4.

$$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{dist} + \Delta E^{\ddagger}_{int} \quad (1)$$

Table 4. Differences in the reaction barriers ($\Delta\Delta E^{\ddagger}$) and the distortion ($\Delta\Delta E^{\ddagger}_{dist}$) and interaction energies ($\Delta\Delta E^{\ddagger}_{int}$) between paths a and b for the hydride and halide-induced nucleophilic ring opening of **14a** as determined at the MPW1B95/6-31++G(d,p) level of theory.[a,b]

	$\Delta\Delta E^{\ddagger}$ [kJ/mol]	$\Delta\Delta E^{\ddagger}_{dist}$ [kJ/mol]	$\Delta\Delta E^{\ddagger}_{int}$ [kJ/mol]
F^-	23.9	7.5	16.4
Cl^-	21.4	9.5	11.9
Br^-	12.0	13.0	–1.1

[a] $\Delta\Delta E^{\ddagger} = \Delta E_b^{\ddagger} - \Delta E_a^{\ddagger}$. [b] B3LYP/6-31++G(d,p) geometries.

The distortion energy is shown to increase on going from fluoride to bromide. The penalty for distorting the aziridinium ring increases as the nucleophile gets larger, which is also reflected in the difference in elongation in the aziridinium ring (Figure 2) and is an indication of the difference in progression along the reaction coordinate; the transition state is increasingly product-like going down the halide series. There is a substantial difference in $\Delta\Delta E^{\ddagger}_{dist}$ for the halides studied even though the substrate is the same in all three cases. This indicates that transition states occur at different positions along the reaction coordinate, which in turn also explains the stronger TS interaction $\Delta\Delta E^{\ddagger}_{int}$, as suggested earlier by Bickelhaupt.[23]

Distortion/interaction calculations have revealed that for bromide the main contribution to the difference in activation barriers comes from the strain caused by the deformation of the reactant, whereas no difference in orbital in-

teractions between the competing pathways was present. However, for fluoride and chloride, the differences in the energy barriers of the two competing pathways are significantly affected by the differences in the interaction energies between the two transition states, which indicates that fluoride and chloride ions are much more influenced by the steric constraints around the aziridine carbon under attack. This is certainly not the case for bromide, which is considerably further from the aziridinium moiety in the transition state (bromide–aziridine carbon distances in the transition state are approximately 2.6 Å, Figure 2), which suggests that bromide is not affected by the difference in steric effects.

Conclusions

The ring-opening reactions of both non-isolable and stable 2-alkyl-substituted aziridinium salts with fluoride, chloride, bromide and iodide have been studied for the first time in a systematic way and the results indicate an inherent difference in reactivity between the reactions of fluoride on the one hand and chloride, bromide and iodide on the other. Both experimental and computational evidence shows that product stabilities dictate the reaction outcome through thermodynamic control in the cases of chloride, bromide and iodide by rearrangement of the initially formed primary halides to the more stable secondary halides through a thermodynamic equilibrium. The ring opening of the same aziridinium salts with fluoride, however, was shown to be mediated by steric interactions (kinetic control) as the difference in the activation barriers was mainly due to differences in interaction energies. For 2-acylaziridinium ions, the reactions were shown to occur under full substrate control to afford secondary β-halo amines by attack at the activated α-carbonyl carbon atom regardless of the nature of the halide.

Experimental Section

Synthesis of 1-Arylmethyl-2-(aryloxymethyl)aziridines 4:[7] As a representative example, the synthesis of 1-[(4-methoxyphenyl)-methyl]-2-(phenoxymethyl)aziridine (**4d**) is described here. 2-Bromomethyl-1-[(4-methoxyphenyl)methyl]aziridine[6] (1.28 g, 5 mmol) was added to a mixture of phenol (1.03 g, 2.2 equiv.) and K_2CO_3 (3.45 g, 5 equiv.) in a solvent mixture containing acetone and DMF (50 mL, 1:1 v/v) and the resulting mixture was heated at reflux for 15 h. Afterwards the reaction mixture was poured into brine (50 mL) and extracted with Et_2O (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-[(4-methoxyphenyl)methyl]-2-(phenoxymethyl)aziridine (**4d**), which was purified by column chromatography on silica gel (hexane/EtOAc, 4:1) to give an analytically pure sample (87% yield, 1.17 g).

1-[(4-Chlorophenyl)methyl]-2-(phenoxymethyl)aziridine (4b): Yield 85%, yellow liquid. R_f = 0.28 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (d, J = 6.6 Hz, 1 H), 1.85 (d, J = 3.3 Hz, 1 H), 1.94–2.03 (m, 1 H), 3.43 and 3.49 (2 d, J = 13.8 Hz, 2 H), 3.89 and 3.99 (2 dd, J = 10.3, 6.3, 5.0 Hz, 2 H), 6.86–6.96 and 7.22–7.33 (2 m, 3 H and 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8, 38.0, 63.5, 70.0, 114.6, 120.9, 128.5, 129.3, 129.4, 132.8, 137.4, 158.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2921, 1599, 1491, 1240, 1086, 1034, 1015, 805, 752, 691 cm^{-1}. MS (70 eV): m/z (%) = 274/6 (100) [M + 1]$^+$. $C_{16}H_{16}ClNO$ (273.76): calcd. C 70.20, H 5.89, N 5.12; found C 70.31, H 6.04, N 5.21.

2-[(4-Chlorophenoxy)methyl]-1-[(4-chlorophenyl)methyl]aziridine (4c): Yield 82%, yellow liquid. R_f = 0.10 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55 (d, J = 6.6 Hz, 1 H), 1.84 (d, J = 3.3 Hz, 1 H), 1.91–1.98 (m, 1 H), 3.42 and 3.48 (2 d, J = 13.2 Hz, 2 H), 3.83 and 3.99 (2 dd, J = 10.4, 6.6, 4.4 Hz, 2 H), 6.77–6.80, 7.18–7.21 and 7.27–7.32 (3 × m, 2 H, 2H and 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.7, 37.9, 63.5, 70.4, 115.9, 125.8, 128.5, 129.29, 129.34, 133.0, 137.3, 157.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2986, 2923, 2830, 1596, 1489, 1284, 1240, 1171, 1089, 1015, 822, 806, 668 cm^{-1}. MS (70 eV): m/z (%) = 308/10/12 (100) [M + 1]$^+$. $C_{16}H_{15}Cl_2NO$ (308.21): calcd. C 62.35, H 4.91, N 4.54; found C 62.42, H 5.23, N 4.45.

1-[(4-Methoxyphenyl)methyl]-2-(phenoxymethyl)aziridine (4d): Yield 87%, light-yellow crystals. R_f = 0.11 (hexane/EtOAc, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.52 (d, J = 6.6 Hz, 1 H), 1.79 (d, J = 3.3 Hz, 1 H), 1.86–1.97 (m, 1 H), 3.37 and 3.44 (2 d, J = 13.2 Hz, 2 H), 3.76 (s, 3 H), 3.91 (d, J = 5.5 Hz, 2 H), 6.81–6.93 and 7.19–7.28 (2 m, 5 H and 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8, 37.8, 55.2, 63.6, 70.1, 113.8, 114.6, 120.8, 129.3, 129.4, 130.0, 158.7, 158.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2933, 2836, 1609, 1511, 1457, 1243, 1173, 1030, 1018, 809, 760 cm^{-1}. MS (70 eV): m/z (%) = 270 (100) [M + 1]$^+$. $C_{17}H_{19}NO_2$ (269.34): calcd. C 75.81, H 7.11, N 5.20; found C 75.67, H 7.27, N 5.08.

Synthesis of *N*-(3-Aryloxy-2-bromopropyl)amines 5: As a representative example the synthesis of *N*-benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-chlorobenzyl)amine (**5b**) is described here. Benzyl bromide (1.71 g, 1 equiv.) was added to a solution of 1-[(4-chlorophenyl)methyl]-2-(phenoxymethyl)aziridine (**4b**; 2.73 g, 10 mmol) in acetonitrile (50 mL) at room temperature whilst stirring and the resulting mixture was heated at reflux for 5 h. Afterwards the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-chlorobenzyl)amine (**5b**), which was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to obtain an analytically pure sample (86% yield, 3.83 g).

***N*-Benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-chlorobenzyl)amine (5b):** Yield 86%, colourless oil. R_f = 0.76 (hexane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 and 3.10 (2 dd, J = 13.8, 7.2, 5.5 Hz, 2 H), 3.53–3.71 (m, 4 H), 4.07–4.23 (m, 3 H), 6.77–6.80, 6.94–6.99 and 7.22–7.36 (3 m, 2 H, 1 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.9, 57.8, 58.5, 59.2, 70.0, 114.6, 121.2, 127.4, 128.4, 128.5, 129.0, 129.5, 130.3, 132.9, 137.3, 138.5, 158.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2925, 2826, 1736, 1598, 1587, 1491, 1453, 1240, 1088, 801, 752, 692 cm^{-1}. MS (70 eV): m/z (%) = 364/6 (100), 444/6/8 (15) [M + 1]$^+$. $C_{23}H_{23}BrClNO$ (444.80): calcd. C 62.11, H 5.21, N 3.15; found C 62.29, H 5.41, N 3.04.

***N*-Benzyl-*N*-[2-bromo-3-(4-chlorophenoxy)propyl]-*N*-(4-chlorobenzyl)amine (5c):** Yield 85%, colourless oil. R_f = 0.74 (hexane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.90 and 3.08 (2 dd, J = 13.8, 7.4, 5.8 Hz, 2 H), 3.52–3.72 (m, 4 H), 4.02–4.14 (m, 3 H), 6.67–6.71 and 7.20–7.38 (2 m, 2 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 48.5, 57.7, 58.6, 59.4, 70.2, 115.9, 126.2, 127.4, 128.45, 128.53, 129.0, 129.4, 130.3, 133.0, 137.3, 138.5, 156.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2920, 2826, 1596, 1490, 1453, 1240, 1090, 821, 801, 740, 697 cm^{-1}. MS (70 eV): m/z (%) = 398/400/402

(100) $[M + 1]^+$. $C_{23}H_{22}BrCl_2NO$ (479.24): calcd. C 57.64, H 4.63, N 2.92; found C 57.79, H 4.95, N 2.81.

***N*-Benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine (5d):** Yield 84%, colourless oil. R_f = 0.76 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.91 and 3.08 (2 dd, J = 13.8, 8.3, 5.4 Hz, 2 H), 3.49–3.74 (m, 4 H), 3.77 (s, 3 H), 4.01–4.24 (m, 3 H), 6.78–6.83, 6.92–6.97 and 7.15–7.39 (3 m, 4 H, 1 H and 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 49.3, 55.2, 57.8, 58.6, 59.3, 70.2, 113.7, 114.7, 121.1, 127.2, 128.3, 129.0, 129.4, 130.2, 130.8, 138.9, 158.3, 158.9 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2932, 2833, 1599, 1509, 1495, 1453, 1241, 1172, 1034, 813, 752, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 360 (100), 440/2 (30) $[M + 1]^+$. $C_{24}H_{26}BrNO_2$ (440.38): calcd. C 65.46, H 5.95, N 3.18; found C 65.62, H 6.13, N 3.14.

Synthesis of *N*-(2-Chloro-3-aryloxypropyl)amines 6: As a representative example the synthesis of *N*-benzyl-*N*-(2-chloro-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine (**6d**) is described here. Tetraethylammonium chloride (1.66 g, 10 equiv.) was added to a solution of *N*-benzyl-*N*-(2-bromo-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine (**5d**; 0.44 g, 1 mmol) in acetonitrile (20 mL) at room temperature whilst stirring and the resulting mixture was heated at reflux for 3 h. Afterwards the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2-chloro-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine (**6d**), which was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to obtain an analytically pure sample (84% yield, 0.33 g).

***N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-chloro-3-phenoxypropyl)amine (6a):** Yield 82%, colourless oil. R_f = 0.78 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.87 and 3.06 (2 dd, J = 13.8, 7.2, 5.5 Hz, 2 H), 3.61–3.84 (m, 4 H), 3.90–3.96 (m, 1 H), 4.10–4.18 (m, 2 H), 6.76–6.78, 6.92–6.97, 7.13–7.39 and 7.51–7.54 (4 m, 2 H, 1 H, 10 H and 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.0, 56.5, 57.5, 59.6, 69.9, 114.6, 121.1, 126.7, 127.3, 128.3, 128.4, 129.1, 129.4, 129.6, 131.0, 134.3, 136.4, 138.5, 158.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2923, 2849, 1599, 1495, 1453, 1241, 1037, 749, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 400/2/4 (100) $[M + 1]^+$, 364/6 (75). $C_{23}H_{23}Cl_2NO$ (400.35): calcd. C 69.00, H 5.79, N 3.50; found C 69.17, H 5.97, N 3.72.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-(2-chloro-3-phenoxypropyl)amine (6b):** Yield 79%, colourless oil. R_f = 0.79 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.81 and 3.02 (2 dd, J = 13.8, 7.2, 6.0 Hz, 2 H), 3.55 and 3.68 (2 d, J = 13.5 Hz, 2 H), 3.59 and 3.64 (2 d, J = 13.8 Hz, 2 H), 3.96–4.01 (m, 1 H), 4.05–4.18 (m, 2 H), 6.76–6.79, 6.93–6.98 and 7.21–7.38 (3 m, 2 H, 1 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.1, 57.4, 58.7, 59.4, 70.0, 114.7, 121.3, 127.5, 128.5, 128.6, 129.1, 129.6, 130.4, 133.0, 137.5, 138.7, 158.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2924, 2828, 1599, 1588, 1491, 1453, 1241, 1088, 801, 751, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 400/2/4 (100) $[M + 1]^+$, 364/6 (60). $C_{23}H_{23}Cl_2NO$ (400.35): calcd. C 69.00, H 5.79, N 3.50; found C 68.92, H 5.94, N 3.55.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-[2-chloro-3-(4-chlorophenoxy)-propyl]amine (6c):** Yield 83%, colourless oil: R_f = 0.80 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 and 3.00 (2 dd, J = 13.6, 7.4, 5.5 Hz, 2 H), 3.51–3.71 (m, 4 H), 3.91–3.96 (m, 1 H), 4.02–4.13 (m, 2 H), 6.65–6.68 and 7.18–7.31 (2 m, 2 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 56.7, 57.1, 58.7, 59.4, 70.0, 115.8, 126.1, 127.4, 128.4, 128.5, 128.9, 129.3, 130.2, 132.9, 137.3, 138.5, 156.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2925, 2828, 2359, 1596, 1490, 1453, 1285, 1241, 1090, 821, 801, 740, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 434/36/38/40 (100) $[M + 1]^+$, 398/400 (90). $C_{23}H_{22}Cl_3NO$ (434.79): calcd. C 63.54, H 5.10, N 3.22; found C 63.78, H 5.41, N 3.38.

***N*-Benzyl-*N*-(2-chloro-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine (6d):** Yield 84%, colourless oil. R_f = 0.75 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.80 and 3.00 (2 dd, J = 13.6, 8.0, 5.5 Hz, 2 H), 3.48–3.75 (m, 4 H), 3.77 (s, 3 H), 3.86–3.95 (m, 1 H), 4.09–4.17 (m, 2 H), 6.78–6.84, 6.92–6.97 and 7.21–7.32 (3 m, 4 H, 1 H and 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.2, 57.2, 58.7, 59.3, 70.0, 113.7, 114.7, 121.1, 127.2, 128.3, 129.0, 129.4, 130.1, 130.8, 138.9, 158.3, 158.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2932, 2833, 2342, 1599, 1510, 1495, 1454, 1241, 1172, 1035, 813, 752, 741, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 360 (100), 396/8 (49) $[M + 1]^+$. $C_{24}H_{26}ClNO_2$ (395.93): calcd. C 72.81, H 6.62, N 3.54; found C 72.94, H 6.82, N 3.40.

Synthesis of *N*-(2-Iodo-3-aryloxypropyl)amines (7): As a representative example the synthesis of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-iodo-3-phenoxypropyl)amine (**7a**) is described here. Sodium iodide (3.00 g, 20 equiv.) was added to a solution of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine (**5a**; 0.44 g, 1 mmol) in acetonitrile (20 mL) at room temperature whilst stirring and the resulting mixture was heated at reflux for 3 h. Afterwards the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-iodo-3-phenoxypropyl)amine (**7a**), which was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to obtain an analytically pure sample (89% yield, 0.40 g).

***N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-iodo-3-phenoxypropyl)amine (7a):** Yield 89%, colourless oil. R_f = 0.76 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.01 and 3.07 (2 dd, J = 14.0, 8.5, 6.9 Hz, 2 H), 3.63 and 3.70 (2 d, J = 13.2 Hz, 2 H), 3.74 and 3.81 (2 d, J = 14.1 Hz, 2 H), 4.05–4.18 (m, 2 H), 4.22–4.30 (m, 1 H), 6.76–6.79, 6.93–6.97, 7.12–7.41 and 7.54–7.57 (4 m, 2 H, 1 H, 10 H and 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.7, 56.1, 59.4, 59.6, 71.0, 114.8, 121.1, 126.7, 127.3, 128.3, 128.4, 129.2, 129.4, 129.5, 131.2, 134.2, 136.3, 138.4, 158.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2921, 2849, 1598, 1494, 1453, 1239, 1029, 749, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 492/4 (5) $[M + 1]^+$. $C_{23}H_{23}ClINO$ (491.80): calcd. C 56.17, H 4.71, N 2.85; found C 55.96, H 4.83, N 3.01.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-(2-iodo-3-phenoxypropyl)amine (7b):** Yield 88%, colourless oil. R_f = 0.77 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.93 and 3.00 (2 dd, J = 13.8, 7.7, 7.2 Hz, 2 H), 3.54 and 3.63 (2 d, J = 13.8 Hz, 2 H), 3.59 (d, J = 7.7 Hz, 2 H), 4.08–4.20 (m, 2 H), 4.22–4.32 (m, 1 H), 6.77–6.81, 6.94–6.99 and 7.21–7.42 (3 m, 2 H, 1 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.7, 58.3, 59.0, 59.3, 71.1, 114.8, 121.3, 127.5, 128.5, 128.6, 129.1, 129.6, 130.4, 133.0, 137.4, 138.5, 158.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2924, 2803, 1598, 1587, 1491, 1453, 1239, 1088, 800, 751, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 492/4 (8) $[M + 1]^+$. $C_{23}H_{23}ClINO$ (491.80): calcd. C 56.17, H 4.71, N 2.85; found C 56.19, H 4.88, N 3.04.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-[3-(4-chlorophenoxy)-2-iodopropyl]-amine (7c):** Yield 82%, colourless oil. R_f = 0.77 (hexane/EtOAc, 1:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.92 and 2.99 (2 dd, J = 14.0, 8.0, 6.9 Hz, 2 H), 3.52 and 3.64 (2 d, J = 13.5 Hz, 2 H), 3.58 (s, 2 H), 3.38–3.70 (m, 4 H), 4.03–4.14 (m, 2 H), 4.18–4.26 (m, 1 H), 6.67–6.70 and 7.18–7.38 (2 m, 2 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.0, 58.3, 59.0, 59.1, 71.1, 115.9, 126.1, 127.4, 128.4, 128.5, 129.0, 129.3, 130.3, 132.9, 137.2, 138.4, 156.6 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2924, 2804, 2361, 1596, 1489, 1452, 1238, 1090, 821, 800, 737, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = no

[M]$^+$, 398/400/402 (100) [M – I]$^+$. $C_{23}H_{22}Cl_2INO$ (526.24): calcd. C 52.49, H 4.21, N 2.66; found C 52.36, H 4.18, N 2.53.

***N*-Benzyl-*N*-(2-iodo-3-phenoxypropyl)-*N*-(4-methoxybenzyl)amine (7d):** Yield 79%, colourless oil. R_f = 0.77 (hexane/EtOAc, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.95 and 3.01 (2 dd, J = 13.9, 8.5, 6.6 Hz, 2 H), 3.48–3.72 (m, 4 H), 3.76 (s, 3 H), 4.01–4.29 (m, 3 H), 6.78–6.83, 6.92–6.97 and 7.22–7.35 (3 m, 4 H, 1 H and 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.1, 55.2, 58.3, 58.9, 59.3, 71.1, 113.7, 114.7, 121.1, 127.2, 128.3, 129.0, 129.4, 130.2, 130.7, 138.8, 158.2, 158.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 2928, 2833, 1598, 1509, 1495, 1240, 1171, 1033, 812, 752, 734, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 360 (100), 488 (10) [M + 1]$^+$. $C_{24}H_{26}INO_2$ (487.38): calcd. C 59.14, H 5.38, N 2.87; found C 59.30, H 5.62, N 3.00.

Synthesis of 2-Amino-3-aryloxy-1-fluoropropanes 8 and *N*-(2-Fluoro-3-aryloxypropyl)amines 9: As a representative example the synthesis of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane (**8a**) and *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine (**9a**) is described here. TBAF (2.61 g, 2 equiv.) was added to a solution of *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-bromo-3-phenoxypropyl)amine (**5a**; 2.22 g, 5 mmol) in acetonitrile (30 mL) at room temperature whilst stirring and the resulting mixture was heated at reflux for 15 h. Extraction with Et_2O (3 × 50 mL), drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2-[*N*-benzyl-*N*-(2-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane (**8a**) and *N*-benzyl-*N*-(2-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)-amine (**9a**) in a ratio of 5:1. The two isomers were separated by column chromatography (hexane/EtOAc, 97:3) to furnish compounds **8a** (54% yield, 1.04 g) and **9a** (10% yield, 0.19 g) as analytically pure samples.

2-[*N*-Benzyl-*N*-(2-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane (8a): Yield 54%, colourless oil. R_f = 0.17 (hexane/EtOAc, 97:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.31–3.44 (m, 1 H), 3.88 and 4.01 (2 s, 4 H), 4.20 (d, J = 6.1 Hz, 2 H), 4.77 (dd, J = 47.4, 5.5 Hz, 2 H), 6.86–6.89, 6.91–6.97, 7.12–7.38 and 7.61–7.63 (4 m, 2 H, 1 H, 10 H and 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.2, 55.5, 57.2 (d, J = 18.4 Hz), 65.3 (d, J = 5.8 Hz), 82.4 (d, J = 170.7 Hz), 114.4, 121.0, 126.8, 127.1, 128.1, 128.3, 128.7, 129.4, 129.5, 130.5, 134.0, 137.1, 139.6, 158.5 ppm. ^{19}F NMR (CCl_3F): δ = –227.32 (td, J = 48.0, 23.7 Hz) ppm. IR (neat): $\tilde{\nu}_{max}$ = 3062, 3029, 2954, 1599, 1495, 1470, 1241, 1037, 751, 734, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 384/6 (100) [M + 1]$^+$. $C_{23}H_{23}ClFNO$ (383.89): calcd. C 71.96, H 6.04, N 3.65; found C 71.82, H 6.19, N 3.56.

***N*-Benzyl-*N*-(2-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine (9a):** Yield 10%, colourless oil. R_f = 0.10 (hexane/EtOAc, 97:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84–2.93 (m, 2 H), 3.71 and 3.82 (2 s, 4 H), 3.92–4.06 (m, 2 H), 4.80–4.87 and 4.96–5.03 (2 m, 1 H), 6.78–6.81, 6.92–6.97, 7.15–7.40 and 7.52–7.55 (4 m, 2 H, 1 H, 10 H and 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.0 (d, J = 21.9 Hz), 56.5, 59.6, 68.3 (d, J = 23.1 Hz), 90.9 (d, J = 174.2 Hz), 114.6, 121.2, 126.8, 127.4, 128.5, 129.1, 129.5, 129.6, 129.7, 131.0, 134.3, 136.7, 138.9, 158.5 ppm. ^{19}F NMR (CCl_3F): δ = –188.68 to –188.2 (m) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2923, 2850, 1598, 1588, 1494, 1443, 1242, 1049, 1037, 750, 690 cm^{-1}. MS (70 eV): *m*/*z* (%) = 384/6 (82) [M + 1]$^+$.

2-[*N*-Benzyl-*N*-(4-chlorobenzyl)amino]-1-fluoro-3-phenoxypropane (8b): Yield 42%, colourless oil. R_f = 0.35 (hexane/EtOAc, 96:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.28–3.43 (m, 1 H), 3.82 and 3.83 (2 s, 4 H), 4.16 (d, J = 6.1 Hz, 2 H), 4.72 (dd, J = 47.4, 5.0 Hz, 2 H), 6.85–6.88, 6.94–6.99 and 7.22–7.38 (3 m, 2 H, 1 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.7, 55.3, 56.4 (d, J = 18.5 Hz), 65.4 (d, J = 6.9 Hz), 82.5 (d, J = 172.0 Hz), 114.4, 121.0, 127.2, 128.4, 128.5, 128.6, 129.5, 130.0, 132.7, 138.4, 139.6, 158.4 ppm. ^{19}F NMR (CCl_3F): δ = –227.30 (td, J = 47.3, 22.3 Hz) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2928, 2833, 1599, 1588, 1491, 1470, 1241, 1088, 1014, 907, 753, 730, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 384/6 (77) [M + 1]$^+$. $C_{23}H_{23}ClFNO$ (383.89): calcd. C 71.96, H 6.04, N 3.65; found C 71.89, H 6.18, N 3.67.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-(2-fluoro-3-phenoxypropyl)amine (9b):** Yield 8%, colourless oil. R_f = 0.28 (hexane/EtOAc, 96:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75–2.95 (m, 2 H), 3.65 and 3.67 (2 s, 4 H), 3.91–4.06 (m, 2 H), 4.80–4.86 and 4.93–5.02 (2 m, 1 H), 6.79–6.82, 6.94–6.99 and 7.22–7.38 (3 m, 2 H, 1 H and 11 H) ppm. ^{13}C NMR (75 MHz, ref. = $CDCl_3$): δ = 53.7 (d, J = 21.9 Hz), 58.7, 59.4, 68.2 (d, J = 23.1 Hz), 90.9 (d, J = 174.3 Hz), 114.6, 121.3, 127.4, 128.5, 128.6, 129.0, 129.6, 130.3, 132.9, 137.7, 138.9, 158.4 ppm. ^{19}F NMR (CCl_3F): –188.58 to –188.18 (m) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2924, 2829, 1598, 1588, 1490, 1453, 1242, 1088, 1014, 801, 752, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 364/6 (100), 384/6 (55) [M + 1]$^+$.

2-[*N*-Benzyl-*N*-(4-chlorobenzyl)amino]-3-(4-chlorophenoxy)-1-fluoropropane (8c): Yield 60%, colourless oil. R_f = 0.33 (hexane/EtOAc, 96:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.25–3.40 (m, 1 H), 3.81 and 3.82 (2 s, 4 H), 4.11 (d, J = 6.0 Hz, 2 H), 4.71 (dd, J = 47.3, 4.9 Hz, 2 H), 6.75–6.80 and 7.19–7.37 (2 m, 2 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.7, 55.3, 56.4 (d, J = 18.5 Hz), 66.0 (d, J = 7.0 Hz), 82.3 (d, J = 171.9 Hz), 115.7, 125.9, 127.2, 128.4, 128.5, 128.6, 129.4, 129.9, 132.7, 138.3, 139.4, 157.0 ppm. ^{19}F NMR (CCl_3F): δ = –227.31 (td, J = 47.3, 22.3 Hz) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2930, 2831, 1596, 1588, 1490, 1470, 1241, 1090, 1014, 1006, 821, 737, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 418/20/22 (100) [M + 1]$^+$. $C_{23}H_{22}Cl_2FNO$ (418.34): calcd. C 66.04, H 5.30, N 3.35; found C 66.11, H 5.54, N 3.57.

***N*-Benzyl-*N*-(4-chlorobenzyl)-*N*-[3-(4-chlorophenoxy)-2-fluoropropyl]amine (9c):** Yield 10%, colourless oil. R_f = 0.27 (hexane/EtOAc, 96:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.74–2.96 (m, 2 H), 3.64 and 3.66 (2 s, 4 H), 3.90–4.05 (m, 2 H), 4.75–4.82 and 4.91–5.03 (2 m, 1 H), 6.69–6.72 and 7.20–7.37 (2 m, 2 H and 11 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.4 (d, J = 21.9 Hz), 58.7, 59.4, 68.5 (d, J = 24.2 Hz), 90.7 (d, J = 175.4 Hz), 115.7, 127.3, 128.4, 128.5, 128.9, 129.3, 129.6, 130.2, 132.9, 137.5, 138.7, 156.9 ppm. ^{19}F NMR (CCl_3F): δ = –188.96 to –188.73 (m) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2925, 2828, 1594, 1488, 1452, 1240, 1090, 1014, 907, 822, 732, 698 cm^{-1}. MS (70 eV): *m*/*z* (%) = 418/20/22 (100) [M + 1]$^+$.

2-[*N*-Benzyl-*N*-(4-methoxybenzyl)amino]-1-fluoro-3-phenoxypropane (8d): Yield 61%, colourless oil. R_f = 0.13 (hexane/EtOAc, 97:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29–3.44 (m, 1 H), 3.78 (s, 5 H), 3.84 (s, 2 H), 4.15 (d, J = 6.6 Hz, 2 H), 4.71 (dd, J = 47.6, 5.2 Hz, 2 H), 6.83–6.87, 6.92–6.97 and 7.20–7.39 (3 m, 4 H, 1 H and 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 54.7, 55.1, 55.2, 56.2 (d, J = 18.5 Hz), 65.5 (d, J = 7.0 Hz), 82.6 (d, J = 171.9 Hz), 113.7, 114.4, 120.9, 127.0, 128.3, 128.6, 129.5, 129.8, 131.8, 140.0, 158.5, 158.7 ppm. ^{19}F NMR (CCl_3F): δ = –227.27 (td, J = 47.4, 23.7 Hz) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2917, 2849, 1599, 1510, 1495, 1454, 1241, 1171, 1035, 831, 819, 753, 737, 691 cm^{-1}. MS (70 eV): *m*/*z* (%) = 380 (100) [M + 1]$^+$. $C_{24}H_{26}FNO_2$ (379.47): calcd. C 75.96, H 6.91, N 3.69; found C 75.77, H 7.03, N 3.51.

***N*-Benzyl-*N*-(2-fluoro-3-phenoxypropyl)-*N*-(4-methoxybenzyl)-amine (9d):** Yield 14%, colourless oil. R_f = 0.09 (hexane/EtOAc, 97:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.73–2.94 (m, 2 H), 3.61 and 3.67 (2 s, 4 H), 3.78 (s, 3 H), 3.94–4.04 (m, 2 H), 4.77–4.83 and 4.93–5.00 (2 m, 1 H), 6.78–6.85, 6.93–6.98 and 7.22–7.36 (3 m, 4 H, 1 H and 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.6 (d,

J = 23.1 Hz), 55.3, 58.8, 59.4, 68.5 (d, J = 23.1 Hz), 91.0 (d, J = 174.2 Hz), 113.8, 114.6, 121.1, 127.2, 128.4, 129.0, 129.5, 130.2, 131.1, 139.3, 158.5, 158.8 ppm. ^{19}F NMR (CCl_3F): δ = –188.52 to –188.05 (m) ppm. IR (neat): $\tilde{\nu}_{max}$ = 2951, 2834, 1599, 1510, 1495, 1453, 1243, 1172, 1035, 812, 752, 742, 691 cm^{-1}. MS (70 eV): m/z (%) = 380 (100) $[M + 1]^+$.

General Procedure for the Synthesis of Chiral β-Halo Amines 15 and 16: Methyl trifluoromethanesulfonate (1.1 equiv.) was added to a solution of either (*R*)-2-methoxymethyl-1-[(*R*)-1-phenylethyl]aziridine (**13a**) or ethyl (*R*)-1-[(*R*)-1-phenylethyl]aziridine-2-carboxylate (**13b**) in CH_3CN (3 M) at room temperature under nitrogen in oven-dried glassware. This solution was stirred for 10 min at room temperature before the addition of tetra-*n*-butylammonium halide (1.5 equiv.) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h. Subsequently the reaction mixture was extracted with CH_2Cl_2 and water and the combined organic layers were dried with anhydrous $MgSO_4$. Filtration of the drying agent and removal of the solvent in vacuo afforded the crude product, which was purified by column chromatography on silica gel to provide an analytically pure sample.

***N*-[(*S*)-2-Bromo-3-methoxypropyl]-*N*-methyl-*N*-[(*R*)-1-phenylethyl]-amine (16a):** Yield 47%, colourless oil. $[\alpha]_D^{25}$ = +13 (c = 0.722, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.8 Hz, 3 H), 2.21 (s, 3 H), 2.69 (dd, J = 13.6, 6.0 Hz, 1 H), 2.93 (dd, J = 13.2, 8.8 Hz, 1 H), 3.38 (s, 3 H), 3.6–3.67 (m, 2 H), 3.67 (dd, J = 10.8, 4.1 Hz, 1 H), 4.06–4.12 (m, 1 H), 7.22–7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4, 38.9, 51.0, 58.3, 58.9, 63.5, 74.7, 127.0, 127.7, 128.1, 143.2 ppm. MS: m/z (%) = 287 (0.3), 285 (0.3), 270 (1), 272 (1), 148 (75), 105 (100). HRMS (ESI): calcd. for $C_{13}H_{20}BrNONa$ $[M + Na]^+$ 308.0626; found 308.0624.

***N*-[(*S*)-2-Iodo-3-methoxypropyl]-*N*-methyl-*N*-[(*R*)-1-phenylethyl]-amine (16b):** Yield 52%, colourless oil. $[\alpha]_D^{25}$ = –4 (c = 3.26, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.8 Hz, 3 H), 2.17 (s, 3 H), 2.72–2.87 (m, 2 H), 3.38 (s, 3 H), 3.61–3.73 (m, 3 H), 4.16–4.22 (m, 1 H), 7.21–7.37 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 31.8, 38.9, 59.0, 60.0, 63.6, 75.9, 127.2, 128.0, 128.4, 143.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{20}INONa$ $[M + Na]^+$ 356.0487; found 356.0488.

***N*-[(*R*)-1-Fluoromethyl-2-methoxyethyl]-*N*-methyl-*N*-[(*R*)-1-phenylethyl]amine (15c):** Yield 58%, colourless oil. $[\alpha]_D^{25}$ = +51 (c = 0.758, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (d, J = 6.8 Hz, 3 H), 2.32 (s, 3 H), 3.09–3.26 (m, 1 H), 3.29 (s, 3 H), 3.39–3.52 (m, 2 H), 3.87 (q, J = 6.8 Hz, 1 H), 4.36 (ddd, J = 46.8, 9.6, 4.6 Hz, 1 H), 4.40 (ddd, J = 46.8, 9.6, 4.6 Hz, 1 H), 7.17–7.37 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.8, 34.2, 57.4, 57.8, 58.9, 62.4, 69.9, 70.1, 81.4, 84.8, 126.8, 127.3, 128.3, 145.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{20}FNONa$ $[M + Na]^+$ 248.1427; found 248.1424.

***N*-[(*S*)-2-Fluoro-3-methoxypropyl]-*N*-methyl-*N*-[(*R*)-1-phenylethyl]-amine (16c):** Yield 19%, colourless oil. $[\alpha]_D^{25}$ = +25 (c = 0.86, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.37 (d, J = 6.8 Hz, 3 H), 2.27 (s, 3 H), 2.45–2.77 (m, 2 H), 3.36 (s, 3 H), 3.42–3.68 (m, 3 H), 4.53–4.87 (m, 1 H), 7.20–7.36 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.9, 39.6, 39.6, 54.5, 54.9, 59.3, 63.8, 73.0, 73.4, 90.2, 93.6, 126.9, 127.7, 128.1, 143.3 ppm. HRMS (ESI): calcd. for $C_{13}H_{20}FNONa$ $[M + Na]^+$ 248.1427; found 248.1422.

***N*-[(*R*)-1-Chloromethyl-2-methoxyethyl]-*N*-methyl-*N*-[(*R*)-1-phenylethyl]amine (15d):** Spectral data derived from the crude reaction mixture. Colourless oil. ^{1}H NMR (400 MHz, CD_3CN): δ = 1.36 (d, J = 6.8 Hz, 3 H), 2.39 (s, 3 H), 3.30 (s, 3 H), 3.23 (q, J = 6.8 Hz, 1 H), 3.48–3.68 (m, 3 H), 4.08–4.14 (m, 1 H), 7.21–7.35 (m, 5 H) ppm.

***N*-[(*S*)-2-Chloro-3-methoxypropyl]-*N*-methyl-*N*-[(*R*)-1-phenylethyl]-amine (16d):** Yield 73%, colourless oil. $[\alpha]_D^{25}$ = +22 (c = 1.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.8 Hz, 3 H), 2.44 (s, 3 H), 2.57 (dd, J = 13.6, 6.0 Hz, 1 H), 2.86 (dd, J = 13.2, 8.4 Hz, 1 H), 3.38 (s, 3 H), 3.53 (dd, J = 10.8, 6.4 Hz, 1 H), 3.66 (q, J = 6.8 Hz, 1 H), 3.73 (dd, J = 10.4, 4.0 Hz, 1 H), 3.99–4.05 (m, 1 H), 7.21–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 39.4, 58.1, 58.6, 59.3, 63.9, 74.9, 127.2, 127.9, 128.4, 143.4 ppm. HRMS (ESI): calcd. for $C_{13}H_{20}ClNONa$ $[M + Na]^+$ 264.1131; found 264.1129.

Ethyl (*S*)-2-Bromo-3-{*N*-methyl-*N*-[(*R*)-1-phenylethyl]amino}-propionate (16e): This compound was isolated with a small amount of the dehydrobrominated product. Yield 92%, colourless oil. $[\alpha]_D$ = +32 (c = 0.524, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 6 H), 2.16 (s, 3 H), 2.70–2.79 (m, 1 H), 3.19–3.31 (m, 1 H), 3.58–3.88 (m, 1 H), 4.11–4.30 (m, 3 H), 7.18–7.38 (m, 5 H) ppm.

Ethyl (*S*)-2-Iodo-3-{*N*-methyl-*N*-[(*R*)-1-phenylethyl]amino}-propionate (16f): This compound was isolated with a small amount of the dehydroiodinated product. Yield 90%, colourless oil. $[\alpha]_D$ = +19 (c = 2.53, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26–1.31 (m, 3 H), 1.37 (d, J = 6.8 Hz, 3 H), 2.14 (s, 3 H), 2.75–2.86 (m, 1 H), 3.07–3.23 (m, 1 H), 3.72–3.86 (m, 1 H), 4.14–4.30 (m, 3 H), 7.22–7.38 (m, 5 H) ppm.

Ethyl (*S*)-2-Fluoro-3-{*N*-methyl-*N*-[(*R*)-1-phenylethyl]amino}-propionate (16g): Yield 71%, colourless oil. $[\alpha]_D^{25}$ = +6 (c = 1.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, J = 7.6 Hz, 3 H), 1.38 (d, J = 6.8 Hz, 3 H), 2.30 (s, 3 H), 2.98 (dd, J = 25.6, 4.4 Hz, 2 H), 3.75 (q, J = 6.8 Hz, 1 H), 4.23 (qd, J = 7.6, 5.6 Hz, 1 H), 5.03 (dt, J = 49.6, 4.8 Hz, 1 H), 7.23–7.32 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 17.4, 39.5, 39.5, 39.5, 55.2, 55.4, 61.4, 63.3, 88.4, 88.5, 90.27, 90.31, 126.9, 127.6, 128.1, 143.0, 168.8, 169.1 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}FNO_2Na$ $[M + Na]^+$ 276.1376; found 276.1377.

Ethyl (*S*)-2-Chloro-3-{*N*-methyl-*N*-[(*R*)-1-phenylethyl]amino}-propionate (16h): Yield 83%, colourless oil. $[\alpha]_D^{25}$ = +16 (c = 1.472, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 6 H), 2.19 (s, 3 H), 2.76 (dd, J = 13.0, 5.4 Hz, 1 H), 3.22 (dd, J = 13.0, 9.8 Hz, 1 H), 3.79 (q, J = 6.8 Hz, 1 H), 4.19–4.30 (m, 3 H), 7.22–7.35 (m, 5 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 16.3, 38.4, 54.1, 58.1, 61.8, 63.1, 127.0, 127.6, 128.1, 142.4, 169.4 ppm. HRMS (ESI): calcd. for $C_{14}H_{20}ClNO_2Na$ $[M + Na]^+$ 292.1080; found 292.1084.

Supporting Information (see also the footnote on the first page of this article): Cartesian coordinates, imaginary and low frequency modes (B3LYP/6-31++G** optimized) for solvent-assisted ring-opening transition states and single-point energies from MPW1B95/6-31++G** calculations (Tables S1–S6).

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