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Synthetic and Theoretical Investigation on One-Pot Halogenation of β -Amino Alcohols and Nucleophilic Ring Opening of Aziridinium Ions

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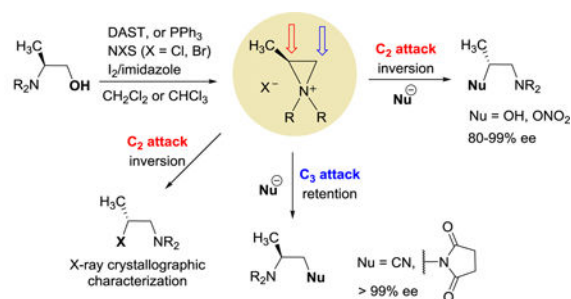
Abstract

Aziridinium ions are useful reactive intermediates for synthesis of enantiomerically enriched building blocks. However, *N,N*-dialkyl aziridinium ions are relatively underutilized in synthesis of optically active molecules as compared to other three-membered ring congeners, aziridines and epoxides. Characterization of both optically active aziridinium ions and secondary β -halo amines as precursor molecules of aziridinium ions has been scarcely reported and is often unclear. In this paper, we report for the first time preparation and experimental and theoretical characterization of optically active aziridinium ions and secondary β -halo amines. Optically active secondary *N,N*-substituted β -halo amines were efficiently synthesized from *N,N*-substituted alaniol *via* formation and ring opening at the more hindered carbon of aziridinium ions by halides. Optically active β -halo amines and aziridinium ions were characterized by NMR and computational analysis. The structure of an optically active β -chloro amine was confirmed via X-ray crystallographic analysis. The aziridinium ions derived from *N,N*-dibenzyl alaniol were attempted for X-ray crystallographic structural determination but remained stable only for several hours which was long enough for analyses of NMR and optical activity. The stereospecific ring opening of aziridinium ions by halides were computationally studied using DFT and highly-accurate DLPNO-CCSD(T) methods. Highly regioselective and stereoselective ring opening of aziridinium ions was applied to efficient one-pot conversion of β -alaniols to enantiomerically enriched β -amino alcohols, β -amino nitriles, and vicinal diamine derivatives.

Graphical Abstract

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Supporting Information. A copy of ^1H and ^{13}C NMR spectra of all new compounds and HPLC chromatograms of all chiral compounds and a Crystallographic Information Framework (CIF) file for X-ray structure of compound **5a**. This material is available free of charge *via* the Internet.



Introduction

Aziridinium ions are strained three-membered ring systems containing two electrophilic carbons and positively charged nitrogen.¹ Optically active small and complex molecules such as vicinal diamines, 1,2-amino alcohols, 1,2-amino ethers, 3,4-diamino nitriles, and α,β -diamino esters have been prepared *via* nucleophilic ring opening reactions of aziridinium ions.^{1,2} In addition, aziridinium ions are involved in anti-cancer activity of nitrogen mustards such as chlorambucil, mechlorethamine, and phosphamide derivatives.³ The biological activity of the mustards results from reaction of the aziridinium ions derived from the mustards with guanine residues in DNA to form interstrand cross-links.^{3b} Since the Leonard group reported various aziridinium ions as reactive intermediates in the 1960s,⁴ formation of aziridinium ions and their applications in the synthesis of optically active synthons have been explored.⁵ In contrast to relatively well known chemistry of other heterocyclic congeners, aziridines and epoxides, ring opening chemistry of *N,N*-dialkyl aziridinium ions remain underutilized in synthesis of enantiomerically enriched small and complex molecules.⁶

We recently reported that aziridinium ions with various structural functionality were prepared in two steps starting from primary β -amino alcohols *via* formation of secondary β -halo amines, and ring opening of aziridinium ions was applied for efficient synthesis of nitrogen-containing optically active molecules with potential biomedical applications.⁷ Although the synthetic methods to secondary β -halo amines including mesylation and halogenation of β -amino alcohols and *N*-alkylation of aziridines are known, preparation of both optically active secondary β -halo amines and aziridinium ions and their synthetic applications have been limitedly reported in literature, and characterization of the labile species is often unclear.⁸

In the present paper, we describe preparation and experimental and theoretical aspects of optically active secondary β -halo amines and aziridinium ions and their applications for nucleophilic substitution reactions (Scheme 1). Optically active β -halo amines were prepared by one-pot halogenation of β -alcohols and ring opening of aziridinium ions by halides. Optically active β -halo amines and aziridinium ions were characterized by NMR and X-ray crystallographic and computational analysis. The stereospecific ring opening of aziridinium ions by halides were computationally studied using DFT and highly-accurate DLPNO-CCSD(T) methods. Highly regioselective and stereoselective ring opening of aziridinium ions was applied to efficient one-pot conversion of β -alcohols to

enantiomerically enriched small molecules including β -amino alcohols, β -amino nitriles, and vicinal diamine derivatives.

Results and Discussion

One-pot halogenation and ring opening of aziridinium ions by halides for preparation of optically active β -halo amines.

Using *N,N*-dibenzylated β -alaniol (S)-**1a**⁹ (R = Bn) as the model system, enantiomerically enriched β -halo amines **3-8** were prepared using different halogenating agents (Table 1). *N,N*-dibenzylated β -alaniol (S)-**1a** (1 equiv) in CH₂Cl₂ at 0 °C was treated with diethylaminosulfur trifluoride (DAST, 1.2 equiv), and the resulting mixture was reacted for 4 h at 0 °C and 20 h at room temperature. Reaction of (S)-**1a** with DAST provided secondary β -fluoro amine (R)-**3a** as the major product which is formed from nucleophilic attack of fluoride counter ion at the more hindered methine carbon (C2) in aziridinium ion **2a** formed by intramolecular rearrangement (Table 1, entry 1). A small amount of primary β -fluoro amine (S)-**4a** as the minor product was formed from ring opening of aziridinium ion **2a** at the less hindered carbon (C1) by fluoride.

(S)-**1a** was studied for chlorination and bromination. (S)-**1a** (1 equiv) in CHCl₃ at 0 °C was sequentially reacted with PPh₃ (1.2 equiv) and *N*-halosuccinimide (NXS, X = Cl or Br, 1.2 equiv), and the resulting mixture was reacted for 4 h at 0 °C and 20 h at room temperature. Halogenation of **1a** with NCS/PPh₃ and NBS/PPh₃ followed by ring opening of aziridinium ions by halides afforded secondary β -chloro amine (R)-**5a**¹⁰ (Table 1, entry 2) and secondary β -bromo amine (R)-**6a**⁸ (Table 1, entry 3) as the regiospecific isomer, respectively. The structure of β -chloro amine (R)-**5a** was unambiguously confirmed *via* X-ray crystallography (Figure 1) and NMR analysis (Figure 2). The inverted stereochemistry in (R)-**5a** indicates that aziridinium ion (S)-**2a** was formed by intramolecular rearrangement of activated β -amino alcohol (S)-**1a** and subsequent stereospecific and regiospecific reaction of (S)-**2a** with the counter anion chloride at the methine carbon afforded β -chloro amine **5a**. *N,N*-dibenzyl groups in **1a** were replaced with an electron withdrawing group (**1b**) or a bulky piperazine ring (**1c**) for the study of *N*-substitution effect on formation of β -halo amines (Table 1, entries 4 and 5). Bromination of **1b** and **1c** provided the corresponding regiospecific isomers **6b** and **6c** in a slightly lower isolated yield (63% and 44%), respectively. β -Chloro amine (R)-**5a** and β -bromo amine (R)-**6a** were promptly isolated by column chromatography and remained stable at -20 °C for months.

Lastly, iodination of (S)-**1a** was conducted to understand regioselectivity in ring opening of aziridinium ion. (S)-**1a** (1 equiv) in CHCl₃ at 0 °C was sequentially reacted with PPh₃ (1.2 equiv) and imidazole (1.2 equiv), and I₂ (1.2 equiv), and the resulting mixture was reacted for 4 h at 0 °C and 20 h at room temperature. Reaction of (S)-**1a** with I₂/PPh₃ provided β -iodo amine (R)-**7a** as the major ring opening product along with a small amount of the regioisomer (S)-**8a** (Table 1, entry 6). Overall, halogenation of *N,N*-dibenzylated β -alaniol **1a** was highly regioselective and provided (R)-halo amines as the major regioisomer from attack of halide at the more substituted carbon of aziridinium ions in an S_N2 pathway.

Formation of isolable aziridinium ions.

Optically active aziridinium ions **2aa** (X = BF₄) and **2ab** (X = OTf) were directly prepared by treatment of β-chloro amine (R)-**5a** with halo-sequestering silver salts containing weakly nucleophilic counteranions, AgBF₄ and AgOTf, respectively (Scheme 2). β-chloro amine (R)-**5a** was rapidly converted to the corresponding aziridinium ion (S)-**2ab** containing triflate as a counter anion (25 min, -10 °C), while formation of aziridinium ion (S)-**2aa** containing tetrafluoroborate from (R)-**6a** took longer (1 h, -10 °C). Enantiomerically enriched aziridinium ions (S)-**2aa** and (S)-**2ab** remained stable at least for several hours at room temperature and were characterized by ¹H and ¹³C and 2D HMQC (Heteronuclear Multiple-Quantum Correlation) NMR and optical rotation. ¹H NMR spectra of aziridinium ions **2aa** or **2ab** were clearly distinguished from that of β-chloro amine **5a** (Figure 2). As expected, the methine protons in aziridinium ions **2aa** or **2ab** (δ 3.5–3.7 ppm) is more shielded than those in β-chloro amine **5a** (δ 4.1 ppm). The methylene protons in aziridinium ions **2aa** and **2ab** (δ 3.2 and 3.3 ppm) are shifted downfield compared to those in β-chloro amine **5a** (δ 2.7 and 2.8 ppm) due to the positively charged nitrogen. The diastereotopic methylene protons in β-chloro amine **5a** produce two sharp and distinctive doublets. The nonequivalent *N*-benzyl protons in aziridinium ions **2aa** and **2ab** give rise to four different resonance signals. Although a slightly different pattern in proton NMR was observed with aziridinium ions **2aa** and **2ab**, possibly due to counter ion effect, **2aa** and **2ab** produced the essentially identical ¹³C NMR signals. The methine carbon (C₂) in β-chloro amine **5a** (δ 56 ppm) and aziridinium ions **2aa** or **2ab** (δ 48 ppm) were clearly shown to resonate in different fields. The diastereotopic *N*-benzyl carbons in aziridinium ions **2aa** and **2ab** gave two different signals (δ 56 and 61 ppm) with a large difference in chemical shift. The two magnetically nonequivalent phenyl rings in aziridinium ions **2aa** and **2ab** are clearly shown in ¹³C NMR.

Nucleophilic ring opening reactions of aziridinium ions.

Nucleophilic reactions of aziridinium ions were initially studied using *N*-protected β-bromo amines (R)-**6** and cyanide as a common carbon nucleophile (Table 2). The reaction of (R)-**6a** (R = Bn) with sodium cyanide in CH₃CN provided the primary β-amino nitrile (S)-**9aa** as the major ring opening product along with a tiny amount of the secondary β-amino nitrile (R)-**10aa** (Table 2, entry 1, supporting information). Both of the regioisomeric substitution products were isolated and characterized by ¹H and ¹³C NMR, optical rotation, and chiral HPLC. The formation of the two regioisomers (**9** and **10**) clearly indicates that the reaction involved formation and ring opening of aziridinium ion **2a**. Ring opening of aziridinium ion **2a** at the less hindered methylene carbon (C-3) provided (S)-**9aa** (82.2% isolated yield, >97.4% ee), while nucleophilic attack by the cyanide ion at the more substituted methine carbon (C-2) in **2a** provided the minor regioisomer (R)-**10aa** (5.8% isolated yield, >99% ee). The nearly absolute stereoselectivity in (S)-**9aa** and (R)-**10aa** indicates that both formation and ring opening of aziridinium ions proceeded with inverted stereochemistry in a S_N2 pathway. The ring opening reaction was significantly faster in CH₃CN/H₂O (10 min) or DMSO (30 min) as compared to CH₃CN (4 days). The slow reaction observed in CH₃CN is related to poor solubility of NaCN in CH₃CN. Change of solvent to DMSO or a mixture of CH₃CN and H₂O (Table 2, entry 2) made a minimal impact on the preferential formation of

the regioisomer (S)-**9aa** over (R)-**10aa**, although both regioisomers were produced in excellent stereoselectivity (>98% ee). The effect of *N*-substitution on the ring opening reaction was investigated. Interestingly, replacement of the *N*-protecting group from benzyl to *p*-NO₂-Bn (**6b**, Table 2, entry 4) and piperazine ring (**6c**, Table 2, entry 5) as a bulky and/or electronwithdrawing group led to formation of the exclusive regioisomer **9b** and **9c** in excellent isolated yield and ee (>93%, >99% ee). Other regioisomeric ring opening products (R)-**10b** or (R)-**10c** that are expected from nucleophilic attack of the cyanide ion at the more hindered methine carbon in aziridinium ion (S)-**2** were not formed from the reaction. The exclusive regioselectivity observed in nucleophilic ring opening reactions of aziridinium ions **6b** and **6c** with cyanide can be explained by change in steric hindrance and/or electron withdrawal due to *N*-substitution. **6b** and **6c** were relatively slower in reaction with the cyanide ion than **6a**. Overall, the nucleophilic attack at the less hindered carbon to provide (S)-**9** was highly favored in ring opening of all aziridinium ions (S)-**2** by cyanide nucleophile. No clear solvent effect on the preferred formation of the major ring opening products was observed. It should be noted that nucleophilic ring opening reactions of aziridinium ions **2** with cyanide provided the regioisomeric β-amino nitriles **9** and **10** in almost absolute stereoselectivity.

With the high regioselectivity and stereospecificity observed in the ring opening of **2a** with cyanide, we extended our investigation to other nucleophiles (Table 3). Reaction of **2a** with sodium borohydride was prompt to provide a mixture of regioisomers **9ab** and **10ab** in a ratio of 2.4 to 1, with the preferred formation of the kinetic product (Table 3, entry 1). Relatively less nucleophilic azide as compared to cyanide and hydride led to the formation of **10ac** as the major product from ring opening of **2a** at the more hindered carbon (Table 3, entry 2). Both *n*-propyl amine and *n*-propane thiolate prefer to attack at the less substituted carbon (C3) of **2a** to afford the kinetic product **9ad** and **9ae**, respectively (Table 3, entries 3 and 4). Particularly, ring opening of **2a** at C3 by the strongly nucleophilic but bulky thiolate was highly favored over C2. Aziridinium ion **2a** was sluggish in reaction with the sterically hindered nucleophiles *n*-PrNH₂ or *n*-PrSNa. The formation of the major regioisomer **9ab**, **9ad**, and **9ae** is expected from the kinetically controlled reaction of **2a** at the less substituted carbon with a strong nucleophile (hydride, amine, or thiolate). Reaction of **2a** with a relatively weak oxygen nucleophile H₂O, CH₃OH, or *n*-PrOH provided the thermodynamic product **10af**, **10ag**, and **10ah** (Table 3, entries 5–7). The attack of the oxygen nucleophiles at the more hindered C2 of **2a** was highly favored over C3 to produce more stable product **10** from the reaction wherein formation and ring opening of aziridinium ion are predicted to be in equilibrium. To understand the nature of the oxygen nucleophiles better, reaction of **2a** with H₂O and CH₃OH in the presence of base (aq. NaOH) was conducted as control runs. Under the basic reaction condition, the back formation of aziridinium ions **2a** from the ring opening product **9af** and **9ag** is nearly not feasible due to the unfavorable departure of the hydroxyl and methoxy group in **9af** and **9ag** and thus regiochemistry of aziridinium opening is likely controlled by sterics. As predicted, reaction of **2a** with H₂O or CH₃OH produced the kinetic products **9af** and **9ag** as the major isomer (Table 3, entries 8 and 9).

One pot bromination and nucleophilic ring opening of aziridinium ions.

Regioselective and stereoselective ring opening of aziridinium ions with a nucleophile was applied for a convenient one-pot synthesis of enantiomerically enriched building blocks from β -amino alcohol (S)-**1a** (Table 4). (S)-**1a** was subjected to bromination followed by nucleophilic substitution reaction in the presence or the absence of a halo-sequestering agent (Ag_2CO_3 , AgNO_3 , or AgCN). When bromination of β -alaniol (S)-**1a** to provide (R)-**6a** was complete as monitored by TLC analysis, and a nucleophilic reagent (Table 4) was added to the reaction mixture. Reaction of aziridinium ion (S)-**2a** with NaCN in the presence of water and CH_3CN as a co-solvent gave β -amino nitrile (S)-**9aa** as the major product in excellent stereoselectivity (Table 4, entry 1, 74%, >99% ee, 1 h). (S)-**2a** was reacted with AgCN in a mixture of CH_3CN and H_2O to provide secondary β -amino alcohol (R)-**9af**¹¹ (Table 4, entry 2, 70%, 80% ee) from nucleophilic attack of aziridinium ion at the more hindered methine carbon. β -amino nitrile (S)-**9aa** was not formed from the substitution reaction, and this seems to reflect poor solubility of silver cyanide in CH_3CN , and a sluggish reaction (24 h) of **2a** with water instead of cyanide provided hydrolysis product (R)-**9af**. A significant loss of stereoselectivity observed in (R)-**9af** (80% ee) can be explained by possible formation of the secondary carbenium ion which is in equilibrium with aziridinium ion (S)-**2a**. Interestingly, treatment of aziridinium ion **2a** with succinimide/1M NaOH or succinimide/ Ag_2CO_3 led to the formation of β -amino succinimide (S)-**11** in excellent stereoselectivity (>99% ee) (Table 4, entries 3 and 4). This unexpected formation of **11** resulted from direct reaction of **2a** with succinimide (Su) counteranion present in the reaction mixture under basic condition. Steric hindrance seems to control the regioselectivity of the reaction which produced (S)-**11** from ring opening of **2a** at the less hindered methylene carbon. When **2a** was treated with AgNO_3 in the presence of water, β -amino nitrate (R)-**12** was obtained from ring opening of **2a** at the methine carbon by the nitrate ion (Table 4, entry 5, 67% isolated yield, >99% ee). The stereochemistry in (R)-**12** was confirmed by conversion of (R)-**12** to the known compound (R)-**9af**. The favored formation of more stable regioisomer (R)-**12** is expected from the heat promoted ring opening of aziridinium ion **2a** in equilibrium with (R)-**12** containing nitrate ion as a leaving group. Unlike (R)-**9af** formed from the reaction of **2a** with AgCN , an almost absolute stereoselectivity was observed with (R)-**12**, probably due to significantly shorter reaction time (1 h vs 24 h). It is noteworthy that the one-pot bromination and nucleophilic ring opening reactions of aziridinium ions provided the nucleophilic substitution products in excellent enantioselectivity (>99% ee, Table 4, entries 1, 3–5). The one-pot bromination and nucleophilic substitution reactions of aziridinium ions with carbon and nitrogen nucleophiles provided the kinetic products from ring opening of aziridinium ions at the less hindered carbon, while the aziridinium ions reacted with oxygen nucleophiles at the more hindered carbon as expected from the reactions controlled by thermodynamics.

To confirm regiochemistry and stereochemistry in (S)-**9aa** and (S)-**11** obtained from ring opening of aziridinium ions, syntheses of (S)-**9aa** and (S)-**11** were independently carried out as outlined in Scheme 3. Activation of *N*-Boc protected β -amino alcohol **13**¹² afforded β -amino mesylate **14**, which was reacted with sodium cyanide to provide β -amino nitrile **15**¹³. Removal of *N*-Boc group in **15** using with TFA followed by *N*-alkylation with benzyl bromide provided the authentic product (S)-**9aa**. The structure and stereochemistry of the *N*-protected vicinal diamine (S)-**11** prepared from the ring opening reaction of (S)-**2a** (Table 4)

was confirmed by preparing (S)-**11** starting from **13** by a modification of the literature procedure (Scheme 3).¹⁴ Reaction of β -amino mesylate **14** with succinimide and subsequent removal of *N*-Boc group in **16** provided **17** which was further alkylated to afford (S)-**11**. ¹H and ¹³C NMR spectra and optical rotation data of (S)-**9aa** and (S)-**11** prepared starting from **13** (Scheme 3) were essentially identical with (S)-**9aa** and (S)-**13** prepared from ring opening of aziridinium ions (S)-**2a**, respectively (Tables 2 and 3). The optical rotation data of (S)-**9aa** and (S)-**11** suggest that stereospecific rearrangement of β -bromoamine (R)-**6a** to aziridinium ions proceeds through a S_N2 pathway with inversion of the chiral center and subsequent reaction of aziridinium ions at the less hindered methylene carbon with cyanide or succinimide provided the nucleophilic substitution products.

Computational studies.

Formation and ring opening of aziridinium ions were theoretically studied by DFT (PBE0/cc-pVTZ) and DLPNO-CCSD(T) calculations. To understand the thermodynamic parameters, we initially optimized equilibrium geometries of the major ring opening products, (R)- β -halo amines (**3a**, **5a**, **6a**, and **7a**) (Table 5). Based on the X-ray crystallographic parameters of β -chloroamine **5a**, the geometrical optimization of **5a** was achieved. The bond length between the methine carbon (C2) and halide (X = Cl) in **5a** is in excellent agreement with the bond distance shown in the X-ray crystal structure of **5a** (calc: 1.814Å vs exp: 1.815Å). A small deviation in the C1-C2 distance for X-ray and computational structure **5a** was observed (calc: 1.527Å vs exp: 1.522Å). The length of the N-C1 bond in X-ray crystal structure of **5a** was slightly longer than that of DFT-optimized **5a** (calc: 1.457Å vs exp: 1.467Å). Structural optimization of other halo amines **3a**, **6a**, and **7a** was conducted by replacing the chlorine atom in the optimized structure of **5a** with other halide. As expected from electrostatic interaction and orbital overlap considerations, β -fluoro amine **3a** containing fluorine (X = F) has the shortest X-C2 bond (1.395Å), while β -iodo amine **7a** (X = I) is calculated to have the longest bond length of X-C2 (2.194Å). All (R)- β -halo amines are calculated to have a similar bond length of N-C1 (1.455~1.458Å) and C1-C2 (1.523~1.527Å). β -fluoro amine **3a** has the longest N-C2 bond (2.489Å), while no significant difference in the bond was observed with other halo amines (~2.47Å). The atomic charges were calculated within a framework of natural population analysis (NPA). In all halo amines, nitrogen (-0.57) is the most negatively charged atom in β -halo amines, and the methine carbon (C2) in β -fluoro amine **3a** (0.24) is positively charged, while C2 in other β -halo amines **5a** (-0.20), **6a** (-0.27), and **7a** (-0.35) bears a negative charge. As expected, β -fluoro amine **3a** has the largest difference in charge between C2 and X (0.64) which is reduced for **5a** (0.10), **6a** (0.23), and **7a** (0.39). The methine carbon (C2) attached to the most electronegative halogen in **3a** (X = F) is significantly more positive than C1. Similar partial charge is calculated for the less hindered carbon (C1) in all β -halo amines (-0.28 for **3a** and -0.26 for **5a**, **6a**, and **7a**). The calculations show that the optimized structures of β -halo amines have similar parameters, except high positive charge on C2 in **3a** (X = F).

Next, we optimized the geometries of aziridinium ions **3a'**, **5a'**, **6a'**, and **7a'** (Table 6). In all aziridinium ions, the more hindered carbon (C2) is more positive than the less hindered carbon (C3) regardless of the counter anions, and the N-C2 bond (average 1.53Å) is longer than the N-C3 bond (average 1.49Å) and the C2-C3 bond (average 1.47Å). As compared to

β -halo amines, the aziridinium ions have shorter C2-C3 and N-C3 bonds by average 0.06Å and 0.03Å, respectively. The counter anion halides are more closely located to C2 than C3 in the aziridinium rings (X-C2: 2.18~3.07Å vs X-C3: 2.93~3.44Å). It is noteworthy that the counter anion halide is shown to form hydrogen bonding with the proton in the more substituted carbon (C2) and one of the benzylic protons leading to construction of a six-membered ring. The hydrogen bonding interaction is predicted to further weaken N-C2 bond and build up more positive charge in C2 that can facilitate ring opening by the halide. The calculated charge on the ring carbons and length of ring bonds explains the high regioselectivity observed with the ring opening reactions of aziridinium ions by halide (Table 1).

We calculated structures of transition states for the stereospecific ring opening of aziridinium ions by the halide ion leading to the formation of (R)- β -halo amines with inverted stereochemistry at C2 (Table 6). Intrinsic reaction coordinates (IRC) calculations confirm connection of aziridinium ions and (R)- β -halo amines through transition structures. Transition states of the ring opening reactions are shown to have reactant-like structures as supported by the calculated parameters (Tables 5 and 6) and energy profiles (Table 7). The X-C2 bond (average 3.18Å) in aziridinium ions is shown to be elongated in the transition structures (average bond length 2.70Å) as expected from the partial bond between the approaching nucleophilic halide and electrophilic C2. The X-C2 bond (average 1.84Å) in β -halo amines is significantly shorter than the X-C2 bond in the transition structures. The N-C2 bond in aziridinium ions is partially dissociated in transition state (average bond length from 1.52Å to 1.74Å), while the distance of the N-C3 bond remains almost unchanged along the pathway (average distance: 1.49 Å vs 1.48Å). In all transition structures, the methine carbon (C2) is more positively charged than C3, and the N-C2 bond (average 1.74Å) is much longer than the N-C3 bond (1.48Å). The change in bond length between atoms along the intrinsic reaction coordinates (IRC) is well reflected on progressive development of charges on the atoms. More positive charge is built on C2 in transition states relative to aziridinium ion, and no substantial change in charge on C3 and nitrogen is observed with conversion of aziridinium ions to transition structures.

Relative energies of aziridinium ions, transition states (TS), and (R)- β -halo amines involved in the ring opening reaction of aziridinium ions (Az⁺) with halides via a S_N2 pathway were calculated (Table 7). While using PBE0 functional for all geometric manipulations and electronic structure analysis, the energetics were evaluated at with help of DLPNO-CCSD(T) method¹⁵ (using DFT-optimized geometries) as providing more reliable estimations. The ring opening of aziridinium ions at the more substituted carbon (C2) for the formation of the major β -halo amines is calculated to be thermodynamically favored (Table 8). The activation barrier (24 kcal/mol) was highest for the ring opening of aziridinium ion **3a'** by fluoride being the least efficient nucleophile. The formation of β -fluoro amine **3a** (-49.7 kcal/mol) was significantly more exothermic than that of other halo amines **5a** (-33.3 kcal/mol), **6a** (-29.0 kcal/mol), and **7a** (-24.9 kcal/mol). Given the extremely high activation barrier (74 kcal/mol), the back reaction of fluoro amine **3a** to aziridinium ion **3a'** traversing the highly labile transition state is shown to be nearly impossible. The calculation predicts that the reaction is kinetically controlled to produce the major regioisomer **3a** which

is estimated to be more stable than the minor regioisomer **4a** (Table 8). The ring opening reactions of other aziridinium ions **5a'**, **6a'**, and **7a'** has smaller activation barrier (11~13 kcal/mol) as compared to that of **3a'** (X = F). The barrier in the back reaction of the ring opening products **5a**, **6a**, and **7a** to aziridinium ions **5a'**, **6a'**, and **7a'** is not too large to overcome. The energy released in the formation of the ring opening products might be also used to surmount the kinetic barrier required for the back reaction. The ring opening reaction of **5a'**, **6a'**, and **7a'** is predicted to be dominantly controlled by stability of the products to favor formation of the thermodynamic products **5a**, **6a**, and **7a**.

The major ring opening products (R)- β -halo amines **3a**, **5a**, **6a**, and **7a** are more stable than the regioisomeric minor products by 6.31, 4.94, 4.50, 3.81 kcal/mol, respectively (Table 8). Difference in relative energies between the fluorine-containing isomers was largest ($E = 6.31$ kcal/mol). It seems that the difference in energies between the regioisomeric β -halo amine parallels with efficiency of leaving group. While the reaction of chloride and bromide with the aziridinium ion provided more stable (R)-**5a** and (R)-**6a** as the exclusive regioisomer, a small amount of less stable regioisomers (S)-**4a** (X = F) and (S)-**8a** (X = I) were formed from attack of fluoride and iodide at the less hindered carbon (C3) of the aziridinium ions. The minor ring opening product (S)-**8a** (X = I) is less stable than the major regioisomer (R)-**7a** by 3.81 kcal/mol. This relatively small difference in energy between the regioisomers containing iodide as an efficient and bulky leaving group is expected to dilute the regiocontrol dominated by stability of product, leading to formation of less stable regioisomer (S)-**8a**. The formation of the minor product **4a** (X = F) may be ascribed to the unusually large positive charge on C2 in **3a** (Table 5) that can facilitate direct isomerization of (R)-**3a** to (S)-**4a** through back formation of aziridinium ion.

The regioisomeric products that can be obtained in nucleophilic reactions of aziridinium ions as outlined in Table 3 and 4 were compared for relative energies (Table 8). For all ring opening products, the (S)-isomers produced from nucleophilic attack at C2 of aziridinium ions are estimated to be more stable than the (R)-isomers by ($E = 1.5\sim 5.7$ kcal/mol). A smaller difference in energies between two isomers was calculated for ring opening products containing hydride ($E = 1.52$ kcal/mol), succinimide ($E = 1.67$ kcal/mol), and cyanide ($E = 2.03$ kcal/mol). Given the small difference in stability of the isomers, sterics involving interaction of aziridinium ion and the relatively stronger nucleophiles in the presence of bromide counter anion is predicted to be a major factor in controlling regiochemistry in ring opening of aziridinium ion leading to the preferred formation of (S)-**9aa**, (S)-**9ab**, and (S)-**11** from the respective nucleophilic attack at the less hindered carbon of cyanide, hydride, and succinimide. (R)-isomers formed from reaction of **2a** with the nitrogen nucleophiles azide and n-propyl amine were calculated to be more stable than (S)-isomers by ~ 5 kcal/mol. A smaller difference in relative energies between the regioisomers was calculated with the ring opening product containing a thio propyl group ((S)-**9ae**/(R)-**10ae**, $E = 3.41$ kcal/mol) as compared to an amino propyl group ((S)-**9ad**/(R)-**10ad**, $E = 5.28$ kcal/mol). The highly preferred formation of (S)-**9ae** as experimentally observed appeared to be outcome of a kinetically controlled reaction due to a negatively charged but sterically hindered thiolate. The formation of (R)-**9af**, (R)-**9ag**, (R)-**9ah** and (R)-**12** over the regioisomeric counterparts from ring opening at the more hindered carbon by oxygen nucleophiles is

thermodynamically favored ($\Delta E = 5.65, 3.96, 2.56,$ and 4.70 kcal/mol, respectively). Indeed, the reaction of **2a** with all oxygen nucleophiles provided more stable regioisomers as the major products. This can be explained by formation and ring opening of aziridinium ions in thermodynamic equilibrium that is achieved by a weak or neutral oxygen nucleophile. With the oxygen nucleophile in steric demand, the back reaction of less stable (S)-ring opening product for the formation of aziridinium ion is less feasible, and thus regiochemistry of ring opening is controlled by activation barrier. The steric effect of oxygen nucleophiles on regiochemistry is well reflected in both the experimental and theoretical results. Under basic reaction condition, the ring opening reaction of aziridinium ion with oxygen nucleophiles produced the less stable but kinetically favorable (R)-isomer as the major product. This experimental finding demonstrates that the steric factor is more significant in controlling ring opening of aziridinium ions with oxygen nucleophiles as the activation barrier for the back formation of aziridinium ions from the less stable ring opening product containing a poor leaving group becomes too high to overcome.

Conclusion

Optically active β -halo amines and aziridinium ions were prepared starting from β -alaniols and characterized and experimentally and theoretically studied for the nucleophilic substitution reactions. Ring opening of aziridinium ions by halides was highly regioselective and occurred preferably at the more hindered carbon to provide more stable β -halo amines. The high regioselectivity experimentally observed in the ring opening reactions in an S_N2 pathway was rationalized by optimized geometries and relative stability of aziridinium ions, transition states, and the ring opening products using DFT and DLPNO-CCSD(T) methods. Ring opening at the less hindered carbon of aziridinium ions by cyanide, hydride, thiolate, amine and succinimide as relatively stronger nucleophiles was shown to be kinetically more favorable and provided less stable ring opening products as the major regioisomers. Azide and oxygen nucleophiles reacted at the more hindered carbon of aziridinium ions leading to the formation of thermodynamically favored β -amino azide, β -amino alcohol, β -amino ether, and β -amino nitrate analogues as the major ring opening products. One-pot halogenation of primary β -amino alcohol and nucleophilic ring opening of aziridinium ions was demonstrated to provide β -amino nitrile, β -amino alcohol, and vicinal diamine derivatives in excellent stereoselectivity (>99% ee).

Experimental Section

General Information.

^1H and ^{13}C NMR spectra were obtained using a Bruker 300 instrument and chemical shifts are reported in ppm on the δ scale relative to TMS or solvent. Electrospray ionization (ESI) high resolution mass spectra (HRMS) were obtained on JEOL double sector JMS-AX505HA mass spectrometer (University of Notre Dame, IN). Structure determination of compound **5a** was conducted using SMART V5.054 (Bruker Analytical X-ray Systems, Madison, WI) at the X-Ray Crystallographic Laboratory (Department of Chemistry, University of Minnesota). Analytical chiral HPLC was performed on an Agilent 1200 (Agilent, Santa Clara, CA) equipped with a diode array detector and a column (Chiralpak®

AD-H, 4.6 × 150 mm, 80Å). Enantiomeric excess of optically active compounds (20 µL, 1 mg of sample in 1 mL of hexanes) was determined by chiral HPLC (isocratic, 230 nm) using the following chromatographic conditions: method A (1/99 = *i*-PrOH/Hexanes at a flow rate of 0.5 mL/min, 30 min); method B (1/99 = *i*-PrOH/Hexanes at a flow rate of 1 mL/min, 15 min); method C (10/90 = *i*-PrOH/Hexanes at a flow rate of 0.5 mL/min, 60 min); method D (8/92 = *i*-PrOH/Hexanes at a flow rate of 0.5 mL/min, 160 min); method E (0.2/99.8 = *i*-PrOH/Hexanes at a flow rate of 0.5 mL/min, 15 min); method F (3/97 = *i*-PrOH/Hexanes at a flow rate of 1 mL/min, 15 min). Optical rotation was determined using JASCO P-2000 polarimeter.

(2S)-2-{bis[(4-nitrophenyl)methyl]amino}propan-1-ol ((S)-1b).

To a stirred solution of (S)-alaninol (100 mg, 1.33 mmol) in CH₃CN (2 mL) was added K₂CO₃ (405 mg, 2.93 mmol) at 0 °C. To the resulting mixture was added dropwise a solution of 4-nitrobenzyl bromide (605 mg, 2.80 mmol) in CH₃CN (1 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 24 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–230 mesh) eluted with 30% ethyl acetate in hexanes to afford pure (S)-**1b** (254 mg, 55%) as a yellow waxy solid. $[\alpha]_D^{25} = -25.0^\circ$ ($c = 1.0$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.05 (d, $J = 6.6$ Hz, 3H), 2.48 (s, br, 1H), 2.87–3.02 (m, 1H), 3.45 (dd, $J = 10.5, 4.2$ Hz, 1H), 3.54–3.63 (m, 3H), 3.85 (d, $J = 14.1$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 4H), 8.13 (d, $J = 8.1$ Hz, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 9.6 (q), 53.1 (t), 55.5 (d), 63.4 (t), 123.8 (d), 129.5 (d), 147.0 (s), 147.2 (s). HRMS (Positive ion ESI) Calcd for C₁₇H₂₀N₃O₅ [M + H]⁺ m/z 346.1397. Found: [M + H]⁺ m/z 346.1399.

2-{bis[(4-nitrophenyl)methyl]amino}propan-1-ol ((rac)-1b).

To a stirred solution of (rac)-alaninol (300 mg, 3.99 mmol) in CH₃CN (5 mL) was added K₂CO₃ (1.21 g, 8.79 mmol) at 0 °C. To the mixture was added dropwise a solution of 4-nitrobenzyl bromide (1.90 g, 8.79 mmol) in CH₃CN (10 mL) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 24 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–230 mesh) eluted with 40% ethyl acetate in hexanes to afford pure (rac)-**1b** (900 mg, 65.3%) as a yellow waxy solid.

(2S)-2-{4-[(4-methylbenzene)sulfonyl]piperazin-1-yl}propan-1-ol ((S)-1c).

To a stirred solution of (S)-alaninol (108 mg, 1.44 mmol) in CH₃CN (8 mL) was added Na₂CO₃ (1.52 g, 14.4 mmol) at 0 °C. To the mixture was added dropwise a solution of tritosyldiethanolamine¹⁵ (817 mg, 1.44 mmol) in CH₃CN (6.5 mL) at 0 °C. The reaction mixture was refluxed for 26 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–230 mesh) eluted with 2% CH₃OH in CH₂Cl₂ to afford pure (S)-**1c** (259 mg, 60%) as a white waxy solid. $[\alpha]_D^{25} = -15.6^\circ$ ($c = 1.0$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (d, $J = 6.6$ Hz, 3H), 1.60 (s, br, 1H), 2.40–2.54 (m, 5H), 2.70–2.89 (m, 3H), 2.90–3.10 (m, 4H), 3.28 (dd, $J = 10.2, 10.2$ Hz, 1H), 3.38 (dd, $J = 11.1, 5.4$ Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.64 (d, $J = 8.1$ Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 9.7 (q), 21.5 (q), 46.4 (t), 47.0 (t),

60.2 (d), 62.1 (t), 127.8 (d), 129.7 (d), 132.2 (s), 143.8 (s). HRMS (Positive ion ESI) Calcd for $C_{14}H_{23}N_2O_3S$ $[M + H]^+$ m/z 299.1424. Found: $[M + H]^+$ m/z 299.1433.

2-{4-[(4-methylbenzene)sulfonyl]piperazin-1-yl}propan-1-ol ((rac)-1c).

To a stirred solution of (rac)-alaninol (200 mg, 2.66 mmol) in CH_3CN (3 mL) was added Na_2CO_3 (2.82 g, 26.6 mmol) at 0 °C. To the resulting mixture was added dropwise a solution of tritosyldiethanolamine (1.66 g, 2.93 mmol) in CH_3CN (5 mL) at 0 °C. The reaction mixture was refluxed for 22 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–230 mesh) eluted with 2% CH_3OH in CH_2Cl_2 to afford pure (rac)-1c (250 mg, 31.5%) as a white waxy solid. 1H and ^{13}C NMR data were essentially identical to those of (R)-1c as described above.

Dibenzyl[(2R)-2-fluoropropyl]amine ((R)-3a).

To a solution of (S)-1a⁹ (50 mg, 0.196 mmol) in CH_2Cl_2 (3 mL) in an ice-bath maintained at 0 °C was added dropwise (diethylamino)sulfur trifluoride (DAST, 37.9 mg, 0.235 mmol) in CH_2Cl_2 (2 mL) over 10 min. The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 20 h. Then the reaction mixture was treated with 10% Na_2CO_3 aqueous solution (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL) to provide crude mixture (49 mg), which was sequentially purified by silica gel column chromatography eluted with 3% ethyl acetate in hexanes to afford (R)-3a in an inseparable mixture with (S)-4a (35.6 mg, 71%, 3a/4a = 5:1, as determined by 1H NMR) as a yellow oil. 1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (dd, J = 24.0, 6.3 Hz, 3H), 2.51–2.78 (m, 2H), 3.72 (s, 4H), 4.83 (dm, J = 49.2, 1H), 7.23–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.3 (dq, J = 22.5 Hz), 58.5 (dt, J = 22.5 Hz), 59.1 (t), 89.9 (dd, J = 165.0 Hz), 127.0 (d), 128.2 (d), 128.8 (d), 139.5 (s). HRMS (ESI) Calcd for $C_{17}H_{21}FN$: $[M + H]^+$ m/z 258.1653. Found: $[M + H]^+$ m/z 258.1642.

Dibenzyl[(2R)-2-chloropropyl]amine ((R)-5a)¹⁰

To a solution of (S)-1a⁹ (50 mg, 0.196 mmol) and PPh_3 (61.7 mg, 0.235 mmol) in $CHCl_3$ (5 mL) maintained at 0 °C was added NCS (31.4 mg, 0.235 mmol). The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 20 h before evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 5% ethyl acetate in hexanes to afford (R)-5a (38 mg, 70%) as a white solid. M.P. 37.1–40.1 °C. $[\alpha]_D^{26} = +16.5^\circ$ (c = 1.0, $CHCl_3$). [Lit.¹⁰ $[\alpha]_D^{22} = +19.3^\circ$ (c = 0.8, $CHCl_3$)]. 1H NMR ($CDCl_3$, 300 MHz) δ 1.44 (d, J = 6.6 Hz, 3H), 2.66 (dd, J = 13.2, 7.8 Hz, 1H), 2.82 (dd, J = 6.3, 3.0 Hz, 1H), 3.59 (d, J = 13.5 Hz, 2H), 3.71 (d, J = 13.5 Hz, 2H), 4.00–4.06 (m, 1H), 7.24–7.40 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1 (q), 55.5 (d), 59.2 (t), 62.1 (t), 127.1 (d), 128.3 (d), 128.9 (d), 139.1 (s). 1H and ^{13}C NMR data were essentially identical to those of (R)-5a previously reported.¹⁰

Dibenzyl[(2R)-2-bromopropyl]amine ((R)-6a).⁸

To a solution of (S)-1a (50 mg, 0.196 mmol) and PPh_3 (61.6 mg, 0.235 mmol) in $CHCl_3$ (5 mL) maintained at 0 °C was added NBS (45.3 mg, 0.235 mmol). The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to

room temperature and stirred for 20 h before evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 5% ethyl acetate in hexanes to afford (R)-**6a** (54 mg, 86%) as a white solid. M.P. 37.3–38.3 °C $[\alpha]_D^{26} = +15.1^\circ$ ($c = 1.0$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.67 (d, $J = 6.6$ Hz, 3H), 2.75 (dd, $J = 13.2, 8.1$ Hz, 1H), 2.94 (dd, $J = 13.2, 6.0$ Hz, 1H), 3.61 (d, $J = 13.5$ Hz, 2H), 3.72 (d, $J = 13.5$ Hz, 2H), 4.09–4.16 (m, 1H), 7.30–7.44 (m, 10H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 24.0 (q), 47.9 (d), 59.1 (t), 62.7 (t), 127.2 (d), 128.3 (d), 129.0 (d), 139.1 (s). ^1H and $^{13}\text{C NMR}$ data were essentially identical to those of (R)-**6a** previously reported.⁸

Dibenzyl[(2R)-2-iodopropyl]amine ((R)-7a).

To a solution of (S)-**1a**⁹ (50 mg, 0.196 mmol) and PPh_3 (61.6 mg, 0.235 mmol) in CHCl_3 (6 mL) maintained at 0 °C was added imidazole (16 mg, 0.235 mmol) and I_2 (59.6 mg, 0.235 mmol). The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed and the reaction mixture was warmed to room temperature and stirred for 20 h before evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 5% ethyl acetate in hexanes to afford (R)-**7a** as an inseparable mixture with (S)-**8a** (52 mg, 72.6%, **7a/8a** = 6.3:1, as determined by $^1\text{H NMR}$) as a light yellow oil. $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.85 (d, $J = 7.2$ Hz, 3H), 2.59 (dd, $J = 13.5, 8.1$ Hz, 1H), 2.94 (dd, $J = 13.2, 6.9$ Hz, 1H), 3.50–3.74 (m, 4H), 4.11–4.18 (m, 1H), 7.25–7.45 (m, 10H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 25.9 (q), 26.7 (d), 58.8 (t), 64.3 (t), 127.2 (d), 128.3 (d), 129.1 (d), 139.0 (s). HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{22}\text{NO}$: $[\text{M} - \text{I} + \text{H}_2\text{O}]^+ m/z$ 256.1696. Found: $[\text{M} - \text{I} + \text{H}_2\text{O}]^+ m/z$ 256.1682.

[(2R)-2-bromopropyl]bis[(4-nitrophenyl)methyl]amine ((R)-6b).

To a solution of (S)-**1b** (500 mg, 1.23 mmol) and PPh_3 (386 mg, 1.47 mmol) in CHCl_3 (10 mL) maintained at 0 °C was added NBS (262 mg, 1.47 mmol). The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 20 h and evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 15% ethyl acetate in hexanes to afford (R)-**6b** (314 mg, 63%) as a yellow solid. M.P. 125.1–127.8 °C. $[\alpha]_D^{26} = -9.1^\circ$ ($c = 1.0$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.64 (d, $J = 6.9$ Hz, 3H), 2.69 (dd, $J = 13.8, 6.0$ Hz, 1H), 2.86 (dd, $J = 13.8, 8.1$ Hz, 1H), 3.69 (d, $J = 14.4$ Hz, 2H), 3.78 (d, $J = 14.4$ Hz, 2H), 4.11–4.18 (m, 1H), 7.58 (d, $J = 8.7$ Hz, 2H), 8.20 (d, $J = 8.7$ Hz, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 23.9 (q), 46.8 (d), 58.4 (t), 62.8 (t), 123.7 (d), 129.5 (d), 146.2 (s), 147.4 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_3\text{O}_5$: $[\text{M} - \text{Br} + \text{H}_2\text{O}]^+ m/z$ 346.1397. Found: $[\text{M} - \text{Br} + \text{H}_2\text{O}]^+ m/z$ 346.1375.

(2-bromopropyl)bis[(4-nitrophenyl)methyl]amine ((rac)-6b).

To a solution of (rac)-**1b** (400 mg, 1.158 mmol) and PPh_3 (455.6 mg, 1.737 mmol) in CHCl_3 (6 mL) maintained at 0 °C was added NBS (309.3 mg, 1.737 mmol). The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 20 h and evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 15% ethyl acetate in hexanes to afford (rac)-**6b** (360 mg, 76.7%) as a yellow solid. ^1H and $^{13}\text{C NMR}$ data were essentially identical to those of (R)-**6b** as described above.

1-[(2R)-2-bromopropyl]-4-[(4-methylbenzene)sulfonyl]piperazine ((R)-6c).

To a solution of (S)-**1c** (180 mg, 0.603 mmol) and PPh₃ (189.9 mg, 0.724 mmol) in CHCl₃ (5 mL) at 0 °C was added NBS (139.6 mg, 0.784 mmol) and stirred for 4 h while being maintained at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 20 h and evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate in hexanes to afford (R)-**6c** (106 mg, 44%) as a light yellow solid. M.P. 102.0–104.3 °C. $[\alpha]_D^{26} = -26.8^\circ$ ($c = 1.0$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.64 (d, $J = 6.3$ Hz, 3H), 2.44 (s, 3H), 2.59 (s, 4H), 2.74 (dd, $J = 13.2, 7.2$ Hz, 2H), 3.03 (s, 4H), 4.04–4.06 (m, 1H), 7.33 (d, $J = 7.8$ Hz, 2H), 7.63 (d, $J = 8.1$ Hz, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ 21.5 (q), 24.0 (q), 46.0 (t), 46.3 (d), 52.5 (t), 66.3 (t), 127.8 (d), 129.7 (d), 132.6 (s), 143.7 (s). HRMS (ESI) Calcd for C₁₄H₂₃N₂O₃S [M + H]⁺ m/z 299.1424. Found: [M + H]⁺ m/z 299.1428.

1-(2-bromopropyl)-4-[(4-methylbenzene)sulfonyl]piperazine ((rac)-6c).

To a solution of (rac)-**1c** (200 mg, 0.650 mmol) and PPh₃ (255.7 mg, 0.975 mmol) in CHCl₃ (3 mL) at 0 °C was added NBS (173.6 mg, 0.975 mmol) and stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 20 h and evaporated to dryness. The residue was purified by silica gel column chromatography eluted with 20% ethyl acetate in hexanes to afford (rac)-**6c** (140 mg, 59.6%) as a light yellow solid. ¹H and ¹³C NMR data were essentially identical to those of (R)-**6c** previously reported.

General synthesis of isolable aziridinium ions.

To a solution of β -halo amine in CDCl₃ (0.8 mL) at –10 °C was added silver tetrafluoroborate (1 equiv) or silver triflate (5 equiv). The resulting mixture was continuously stirred at –10 °C, while the reaction progress was monitored using TLC. After completing of the reaction, silver halide was filtered, and the resulting solution was immediately characterized by ¹H and ¹³C NMR and HMQC.

(2S)-1,1-dibenzyl-2-methylaziridin-1-ium tetrafluoroboranuide ((S)-2aa).

The general procedure was followed for the reaction of (R)-**5a** (40 mg, 0.15 mmol) and AgBF₄ (28.4 mg, 0.15 mmol) in CDCl₃ (0.8 mL) for 1 h. After completion of the reaction, silver chloride was filtered, and the filtrate was immediately characterized by NMR and optical rotation. $[\alpha]_D^{26} = +22.8^\circ$ ($c = 1.0$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.77 (d, $J = 6.3$ Hz, 3H), 3.17 (dd, $J = 8.4, 3.9$ Hz, 1H), 3.27 (dd, $J = 7.2, 3.9$ Hz, 1H), 3.51–3.58 (m, 1H), 4.12 (d, $J = 13.5$ Hz, 1H), 4.19 (d, $J = 14.4$ Hz, 1H), 4.33 (d, $J = 9.9$ Hz, 1H), 4.38 (d, $J = 10.8$ Hz, 1H), 7.21 (d, $J = 6.3$ Hz, 2H), 7.30–7.47 (m, 8H); ¹³C NMR (CDCl₃, 75 MHz) δ 11.6 (q), 42.9 (t), 47.8 (d), 56.1 (t), 61.0 (t), 128.3 (s), 129.2 (s), 129.6 (d), 129.7 (d), 130.0 (d), 130.1 (d), 130.6 (d), 131.0 (d).

(2S)-1,1-dibenzyl-2-methylaziridin-1-ium trifluoromethanesulfonate ((S)-2ab).

The general procedure was followed for the reaction of (R)-**5a** (40 mg, 0.15 mmol) and AgOTf (187.8 mg, 0.75 mmol) in CDCl₃ (0.8 mL) for 25 min. After completion of the reaction, silver chloride was filtered, and the filtrate was immediately characterized by

NMR. $[\alpha]_D^{26} = +16.0^\circ$ ($c = 1.0$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.77 (d, $J = 6.0$ Hz, 3H), 3.25–3.38 (m, 2H), 3.61–3.72 (m, 1H), 4.14 (d, $J = 14.1$ Hz, 1H), 4.19 (d, $J = 14.1$ Hz, 1H), 4.30 (d, $J = 5.7$ Hz, 1H), 4.35 (d, $J = 5.1$ Hz, 1H), 7.22 (d, $J = 6.6$ Hz, 2H), 7.30–7.48 (m, 8H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 11.8 (q), 43.4 (t), 48.4 (d), 55.8 (t), 61.2 (t), 120.5 (q, $J = 322.5$ Hz), 128.5 (s), 129.2 (s), 129.4 (d), 129.9 (d), 130.3 (d), 130.8 (d).

General Procedure for nucleophilic reaction of **6** with NaCN.

To a stirred solution of (R)-**6** (0.1 mmol) in solvent was added NaCN (0.12 mmol). The reaction mixture was stirred at room temperature. The resulting mixture was evaporated and dissolved in CH_2Cl_2 and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluted with 2–4% ethyl acetate in hexanes to afford (S)-**9** and (R)-**10**.

(S)-3-(dibenzylamino)butanenitrile ((S)-**9aa**) and (R)-3-(dibenzylamino)-2-methylpropanenitrile ((R)-**10aa**).

From reaction of 6a in CH_3CN .—To the stirred solution of (R)-**6a** (60 mg, 0.188 mmol) in CH_3CN (1.5 mL) was added NaCN (18.4 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 4 d. The resulting mixture was evaporated and dissolved in CH_2Cl_2 and filtered. The filtrate was concentrated and dried *in vacuo*. A mixture of (S)-**9aa** and (R)-**10aa** (49.7 mg, 100%) was obtained. The regioisomeric mixture was separated by preparative thin layer column chromatography (Prep-TLC, SiO_2) eluted with 2–4% ethyl acetate in hexanes to provide (S)-**9aa** (40.8 mg, 82.2%) as a white solid and (R)-**10aa** (2.9 mg, 5.8%) as a colorless oil.

(S)-9aa: M.P. 95.6–98.5 °C. $[\alpha]_D^{26} = +4.0^\circ$ ($c = 1.0$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.21 (d, $J = 6.9$ Hz, 3H), 2.36 (dd, $J = 16.5$, 6.6 Hz, 1H), 2.56 (dd, $J = 16.8$, 8.1 Hz, 1H), 3.22–3.28 (m, 1H), 3.55 (d, $J = 13.8$ Hz, 2H), 3.70 (d, $J = 13.8$ Hz, 2H), 7.26–7.45 (m, 10H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 14.0 (q), 21.9 (t), 50.4 (d), 53.4 (t), 118.8 (s), 127.2 (d), 128.4 (d), 128.6 (d), 139.1 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2$ $[\text{M} + \text{H}]^+$ m/z 265.1699. Found: $[\text{M} + \text{H}]^+$ m/z 265.1707. Chiral HPLC (method A): $t_R = 15.4$ min (S, major), $t_R = 16.8$ min (R, minor), 97.4% e.e.

(R)-10aa: $[\alpha]_D^{25} = -17.2^\circ$ ($c = 0.15$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.19 (d, $J = 6.6$ Hz, 3H), 2.52 (dd, $J = 12.0$, 5.7 Hz, 1H), 2.63–2.84 (m, 2H), 3.59 (d, $J = 13.5$ Hz, 2H), 3.69 (d, $J = 13.5$ Hz, 2H), 7.26–7.41 (m, 10H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 15.8 (q), 25.0 (t), 56.9 (d), 59.0 (d), 127.3 (d), 128.4 (d), 128.9 (d), 138.6 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_2$ $[\text{M} + \text{H}]^+$ m/z 265.1699. Found: $[\text{M} + \text{H}]^+$ m/z 265.1728. Chiral HPLC (method B): $t_R = 4.6$ min (R, major), $t_R = 5.9$ min (S, minor), >99% e.e.

From reaction of (R)-6a in DMSO.

To a solution of (R)-**6a** (60 mg, 0.188 mmol) in DMSO (2 mL) was added NaCN (18.4 mg, 0.38 mmol). The reaction mixture was continuously stirred at room temperature for 30 min. The resulting mixture was treated with H_2O (25 mL) and extracted with diethyl ether (3×25 mL). The combined organic layer was treated with MgSO_4 and concentrated *in vacuo*. A mixture of (S)-**9aa** and (R)-**10aa** (49 mg, 98.8%) was obtained. The regioisomeric mixture

was separated by Prep-TLC (SiO₂) eluted with 2–4% ethyl acetate in hexanes to provide (S)-**9aa** (37.8 mg, 76.2 %) as a white solid and (R)-**10aa** (3.5 mg, 7.1%) as a colorless oil.

(S)-9aa: $[\alpha]_D^{26} = +3.5^\circ$ ($c = 1.0$, CHCl₃). ¹H and ¹³C NMR data of (S)-**9aa** was identical to those of (S)-**9aa** obtained from the reaction described above. Chiral HPLC (method A): $t_R = 15.2$ min (S, major), $t_R = 16.9$ min (R, minor), 97.5% e.e.

(R)-10aa: $[\alpha]_D^{26} = -13.2^\circ$ ($c = 0.18$, CHCl₃). ¹H and ¹³C NMR data of (S)-**10aa** was identical to those of (S)-**10aa** obtained from the reaction described above. Chiral HPLC (method B): $t_R = 4.6$ min (R, major), $t_R = 5.9$ min (S, minor), 97.9% e.e.

From reaction of (R)-**6a** in CH₃CN/H₂O.

To a stirred solution of (R)-**6a** (60 mg, 0.188 mmol) in CH₃CN/H₂O (1.25 mL/0.25 mL) was added NaCN (18.4 mg, 0.38 mmol). The reaction mixture was stirred at room temperature for 10 min. The resulting mixture was evaporated and dissolved in CH₂Cl₂ and filtered. The filtrate was concentrated and dried *in vacuo*. A mixture of (S)-**9aa** and (R)-**10aa** (49.3 mg, 99.3%) was obtained. The regioisomeric mixture was separated by Prep-TLC (SiO₂) eluted with 2–4% ethyl acetate in hexanes to provide (S)-**9aa** (39.6 mg, 79.8%) as a white solid and (R)-**10aa** (3.5 mg, 7.1%) as a colorless oil.

(S)-9aa: $[\alpha]_D^{26} = +3.0^\circ$ ($c = 1.0$, CHCl₃). Chiral HPLC (method A): $t_R = 15.2$ min (S, major), $t_R = 17.0$ min (R, minor), 97.9% e.e. ¹H and ¹³C NMR data of (S)-**9aa** was identical to the one of (S)-**9aa** obtained from the above reaction.

(R)-10aa: $[\alpha]_D^{26} = -15.1^\circ$ ($c = 0.18$, CHCl₃). Chiral HPLC (method B): $t_R = 4.7$ min (R, major), $t_R = 6.0$ min (S, minor), 98.6% e.e. ¹H and ¹³C NMR data of (S)-**10aa** was identical to those of (S)-**10aa** obtained from the reaction described above.

3-(dibenzylamino)butanenitrile ((rac)-**9aa**)¹⁶ and 3-(dibenzylamino)-2-methylpropanenitrile ((rac)-**10aa**).

To a solution of (rac)-**6a** (150 mg, 0.471 mmol) in CH₃CN/H₂O (2.5 mL/0.5 mL) was added NaCN (46 mg, 0.95 mmol). The reaction mixture was continuously stirred at room temperature for 10 min. The resulting mixture was evaporated and dissolved in CH₂Cl₂ and filtered. The filtrate was concentrated and dried *in vacuo*. A mixture of (rac)-**9aa** and (rac)-**10aa** (123.0 mg, 98%) was obtained. The regioisomeric mixture was separated by Prep-TLC (SiO₂) eluted with 2–4% ethyl acetate in hexanes to provide (rac)-**9aa** (93.4 mg, 75.3%) as a white solid and (rac)-**10aa** (9.6 mg, 7.7%) as a colorless oil. ¹H and ¹³C NMR of (rac)-**9aa** and (rac)-**10aa** were identical to those of (S)-**9aa** and (S)-**10aa** obtained from the reaction described above. Chiral HPLC: $t_R = 15.4$ min (S) and 16.8 min (R) (method A) for **9a** and $t_R = 4.6$ min (R) and 5.9 min (S) (method B) for **10aa**.

(3S)-3-{bis[(4-nitrophenyl)methyl]amino}butanenitrile ((S)-**9b**).

To a solution of (R)-**6b** (30 mg, 0.074 mmol) in DMSO (1.5 mL) was added NaCN (7.2 mg, 0.15 mmol). The reaction mixture was continuously stirred at room temperature for 4 h. The resulting mixture was treated with H₂O (25 mL) and extracted with diethyl ether (3 × 25

mL). The combined organic layer was dried over MgSO_4 and concentrated *in vacuo* to provide (S)-**9b** which was purified by column chromatography eluting 25% ethyl acetate in hexane to afford pure **9b** (24.3 mg, 92.8%) as a colorless oil. $[\alpha]_D^{26} = -40.2^\circ$ ($c = 1.0$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.23 (d, $J = 6.6$ Hz, 3H), 2.45 (dd, $J = 16.8$, 5.4 Hz, 1H), 2.61 (dd, $J = 17.1$, 9.3 Hz, 1H), 3.14–3.19 (m, 1H), 3.65 (d, $J = 14.7$ Hz, 2H), 3.81 (d, $J = 14.7$ Hz, 2H), 7.61 (d, $J = 8.7$ Hz, 2H), 8.20 (d, $J = 8.6$ Hz, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 13.8 (q), 22.5 (t), 51.2 (d), 53.1 (t), 118.1 (s), 123.9 (d), 129.3 (d), 146.1 (s), 147.5 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 355.1401. Found: $[\text{M} + \text{H}]^+$ m/z 355.1401. Chiral HPLC (method C): $t_R = 49.0$ min (R, minor) and 51.2 min (S, major), >99% ee.

3-{bis[(4-nitrophenyl)methyl]amino}butanenitrile ((rac)-**9b**).

To a solution of (rac)-**6b** (50 mg, 0.122 mmol) in $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1.25 mL/0.25 mL) was added NaCN (12 mg, 0.245 mmol). The reaction mixture was continuously stirred at room temperature for 8 h. The resulting mixture was treated with H_2O (25 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was treated with MgSO_4 and concentrated *in vacuo* to provide (rac)-**9b** (41 mg, 92.5 %) as a colorless oil. ^1H and $^{13}\text{C NMR}$ of (rac)-**9b** was identical to (S)-**9b**. Chiral HPLC (method C): $t_R = 49.0$ min (R) and 51.7 min (S)

(3S)-3-{4-[(4-methylbenzene)sulfonyl]piperazin-1-yl}butanenitrile ((S)-**9c**).

To a solution of (R)-**6c** (30 mg, 0.083 mmol) in CH_3CN (1.25 mL) and H_2O (0.25 mL) was added NaCN (8.1 mg, 0.17 mmol). The reaction mixture was continuously stirred at room temperature for 30 min. The resulting mixture was evaporated to dryness and the residue was treated with H_2O (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was treated with MgSO_4 and concentrated under vacuum to provide (S)-**9c** which was purified by column chromatography eluting 10% ethyl acetate in hexane to afford pure (S)-**9c** (25.1 mg, 98.5%) as a white solid. M.P. 101.4–103.9 °C. $[\alpha]_D^{26} = +3.32^\circ$ ($c = 1.0$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz) δ 1.13 (d, $J = 6.6$ Hz, 3H), 2.31–2.43 (m, 5H), 2.60–2.62 (m, 4H), 2.91–3.09 (m, 4H), 7.32 (d, $J = 8.1$ Hz, 2H), 7.62 (d, $J = 8.1$ Hz, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz) δ 15.0 (q), 21.5 (d), 21.7 (t), 46.2 (t), 47.6 (t), 56.0 (d), 118.3 (s), 127.8 (d), 129.7 (d), 132.3 (s), 143.8 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{15}\text{H}_{22}\text{N}_3\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ m/z 308.1427. Found: $[\text{M} + \text{H}]^+$ m/z 308.1424. Chiral HPLC (method D): $t_R = 85.7$ min (R, minor) and 89.4 min (S, major), >99% ee.

3-{4-[(4-methylbenzene)sulfonyl]piperazin-1-yl}butanenitrile ((rac)-**9c**).

To a solution of (rac)-**6c** (25 mg, 0.069 mmol) in CH_3CN (1.25 mL) and H_2O (0.25 mL) was added NaCN (6.8 mg, 0.138 mmol). The reaction mixture was continuously stirred at room temperature for 2 h. The resulting mixture was evaporated to dryness and the residue was treated with H_2O (15 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic layer was treated with MgSO_4 and concentrated under vacuum to afford (rac)-**9c** (21 mg, 98.6%) a white solid. ^1H and $^{13}\text{C NMR}$ of (rac)-**9c** was identical to (S)-**9c**. Chiral HPLC (method D): $t_R = 85.7$ min (R) and 90.1 min (S).

(S)-3-(dibenzylamino)butanenitrile ((S)-9aa)

From one-pot reaction of (S)-1a with NaCN (Table 4, entry 1).—To a solution of (S)-1a (100 mg, 0.392 mmol) and PPh₃ (123.3 mg, 0.470 mmol) in CH₃CN (5 mL) at 0 °C was added NBS (83.6 mg, 0.470 mmol) over 5 min. The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h. NaCN (23 mg, 0.470 mmol) was added to the reaction mixture followed by the addition of H₂O (0.5 mL). The reaction mixture was stirred for 1 h at room temperature. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 5% ethyl acetate in hexanes to afford (S)-9aa (76.2 mg, 73.6%) as a white solid. $[\alpha]_D^{26} = +3.13^\circ$ ($c = 1.0$, CHCl₃). ¹H and ¹³C NMR data were essentially identical to those described above. Chiral HPLC (method A): $t_R = 15.0$ min (S, major) and 16.8 min (R, minor), >99% ee.

From synthesis of authentic sample for structural determination (Scheme 3).

To a solution of **18** (60 mg, 0.33 mmol) in CH₃Cl (3 mL) at 0 °C was added dropwise trifluoroacetic acid (3 mL). The resulting mixture was stirred for 3 h at room temperature. The reaction mixture was concentrated to dryness to provide (3S)-3-aminobutanenitrile as a waxy yellowish solid. The compound was directly used for the next step without purification. To a solution of (3S)-3-aminobutanenitrile (38 mg, 0.24 mmol) and K₂CO₃ (220.8 mg, 1.6 mmol) in CH₃CN (1 mL) was added benzyl bromide (107.8 mg, 0.63 mmol). The resulting mixture was stirred at 60 °C for 24 h. The resulting mixture was filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 3–5% ethyl acetate in hexanes to afford (S)-9aa (53.1 mg, 83.8%) as a white solid. $[\alpha]_D^{26} = +4.6^\circ$ ($c = 1.0$, CHCl₃). ¹H and ¹³C NMR data were essentially identical to those described above. Chiral HPLC (method A): $t_R = 7.8$ min (S, major) and 8.6 min (R, minor), >99% ee.

dibenzyl(propan-2-yl)amine (9ab)²⁴ and dibenzyl(propyl)amine (10ab)²⁵.

To the stirred solution of (R)-6a (60 mg, 0.188 mmol) in CH₃CN (1.25 mL) was added NaBH₄ (14.3 mg, 0.377 mmol), and the reaction mixture was stirred at room temperature for 15 min. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of **9ab** and **10ab** (43.5 mg, 96.5%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% ethyl acetate in hexane to provide an inseparable mixture of **9ab** and **10ab** (41.8 mg, 92.7%, **9ab/10ab** = 2.4/1, as determined by ¹H NMR) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 0.89 (t, $J = 7.2$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 6H), 1.53–1.60 (m, 2H), 2.41 (t, $J = 7.2$ Hz, 2H), 2.91–3.00 (m, 1H), 3.59 (s, 8H), 7.21–7.43 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 11.8 (q), 17.6 (q), 20.2 (t), 48.2 (d), 53.2 (t), 55.4 (t), 58.3 (t), 126.6 (d), 126.7 (d), 128.1 (d), 128.3 (d), 128.5 (d), 128.8 (d), 140.1 (s), 141.0 (s).

[(2S)-1-azidopropan-2-yl]dibenzylamine ((S)-9ac) and [(2R)-2-azidopropyl]dibenzylamine ((R)-10ac).

To the stirred solution of (R)-6a (60 mg, 0.188 mmol) in CH₃CN (1.25 mL) was added the solution of NaN₃ (24.5 mg, 0.377 mmol) in H₂O (0.25 mL), and the reaction mixture was stirred at room temperature for 10 min. The resulting mixture was evaporated and dissolved in CH₂Cl₂ and filtered. The filtrate was concentrated and dried *in vacuo* to provide a regioisomeric mixture of (S)-9ac and (R)-10ac (52.3 mg, 98.9%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% ethyl acetate in hexane to provide a mixture of (S)-9ac and (R)-10ac (50.7 mg, 95.8%, 9ac/10ac = 1/2, as determined by ¹H NMR). ¹H NMR showed the ratio of (S)-9ac to (R)-10ac is 1/2. ¹H NMR (CDCl₃, 300 MHz) δ 1.10–1.15 (m, 6H), 2.47 (dd, *J* = 13.2, 5.1 Hz, 1H), 2.64 (dd, *J* = 13.2, 7.8 Hz, 1H), 3.05–3.17 (m, 2H), 3.44 (dd, *J* = 12.3, 7.2 Hz, 1H), 3.52–3.62 (m, 5H), 3.71 (d, *J* = 13.5 Hz, 2H), 3.79 (d, *J* = 13.8 Hz, 2H), 7.24–7.46 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 11.8 (q), 18.0 (q), 53.0 (d), 53.8 (t), 54.2 (t), 56.1 (d), 59.2 (t), 59.7 (t), 127.0 (d), 127.1 (d), 128.3 (d), 128.7 (d), 128.9 (d), 139.0 (s), 139.8 (s). HRMS (ESI) Calcd for C₁₇H₂₁N₄ [M + H]⁺ *m/z* 281.1761. Found: [M + H]⁺ *m/z* 281.1757.

[(2S)-2-(dibenzylamino)propyl](propyl)amine ((S)-9ad) and [(2R)-1-(dibenzylamino)propan-2-yl](propyl)amine ((R)-10ad).

To the stirred solution of (R)-6a (60 mg, 0.188 mmol) in CH₃CN (0.75 mL) was added propan-1-amine (0.75 mL), and the reaction mixture was stirred at room temperature for 4 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-9ad and (R)-10ad (55.3 mg, 99.2%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% methanol in DCM to 30% methanol in DCM containing 1% Et₃N to provide a mixture of (S)-9ad and (R)-10ad (53.6 mg, 96.2%, 9ad/10ad = 2.1/1, as determined by ¹H NMR) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 0.82 (t, *J* = 7.5 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H), 1.04–1.08 (m, 6H), 1.44–1.56 (m, 4H), 2.15–2.24 (m, 3H), 2.39–2.44 (m, 1H), 2.49–2.57 (m, 2H), 2.66–2.80 (m, 3H), 3.07–3.16 (m, 1H), 3.40 (d, *J* = 13.2 Hz, 2H), 3.54 (d, *J* = 13.5 Hz, 2H), 3.66 (d, *J* = 13.5 Hz, 2H), 3.75 (d, *J* = 13.5 Hz, 2H), 5.92 (s, br, 2H), 7.22–7.34 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 10.6 (q), 11.4 (q), 11.6 (q), 16.8 (q), 21.8 (t), 22.1 (t), 47.7 (t), 50.0 (t), 51.1 (d), 51.3 (d), 51.5 (t), 53.5 (t), 59.4 (t), 59.7 (t), 127.2 (d), 128.1 (d), 128.5 (d), 129.0 (d), 139.0 (s), 139.7 (s). HRMS (Positive ion ESI) Calcd for C₂₀H₂₉N₂ [M + H]⁺ *m/z* 297.2331. Found: [M + H]⁺ *m/z* 297.2333.

dibenzyl[(2S)-1-(propylsulfanyl)propan-2-yl]amine ((S)-9ae) and dibenzyl[(2R)-2-(propylsulfanyl)propyl]amine ((R)-10ae).

To the stirred solution of (R)-6a (60 mg, 0.188 mmol) in CH₃CN (0.75 mL) was added propane-1-thiol (0.75 mL), and the reaction mixture was stirred at room temperature for 10 min. After which, 1M NaOH aqueous solution (0.38 mL) was added and the resulting mixture was stirred at room temperature for 4 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then

extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-**9ae** and (R)-**10ae** (56.2 mg, 95.1%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 4% ethyl acetate in hexane to provide the mixture of (S)-**9ae** and (R)-**10ae** (53.4 mg, 90.4%, **9ae/10ae** = 5.7/1, as determined by ¹H NMR) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 0.93–1.01 (m, 6H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.49–1.60 (m, 4H), 2.31–2.48 (m, 6H), 2.85–3.00 (m, 4H), 3.47–3.55 (m, 4H), 3.72 (d, *J* = 14.1 Hz, 4H), 7.22–7.47 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 13.4 (q), 13.5 (q), 13.7 (q), 19.7 (q), 22.9 (t), 23.3 (t), 32.4 (t), 34.5 (t), 36.3 (t), 38.1 (d), 52.7 (d), 53.4 (t), 59.1 (t), 60.4 (t), 126.8 (d), 127.0 (d), 128.2 (d), 128.7 (d), 129.0 (d), 139.5 (s), 140.3 (s). HRMS (Positive ion ESI) Calcd for C₂₀H₂₈NS [M + H]⁺ *m/z* 314.1942. Found: [M + H]⁺ *m/z* 314.1937.

(2S)-2-(dibenzylamino)propan-1-ol ((S)-9af**)¹¹ and (2R)-1-(dibenzylamino)propan-2-ol ((R)-**10af**)^{7b}.**

From reaction of (R)-6a** and H₂O with NaOH.**—To the stirred solution of (R)-**6a** (60 mg, 0.188 mmol) in CH₃CN (0.75 mL) was added H₂O (0.75 mL), and the reaction mixture was stirred at room temperature for 10 min. After which, 1M NaOH aqueous solution (0.38 mL) was added and the resulting mixture was stirred at room temperature for 3 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-**9af** and (R)-**10af** (47.3 mg, 98.3%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 8% ethyl acetate in hexane to provide the mixture of (S)-**9af** and (R)-**10af** (44.4 mg, 92.3%, **9af/10af** = 1.2/1, as determined by ¹H NMR). ¹H NMR (CDCl₃, 300 MHz) δ 1.00 (d, *J* = 6.6 Hz, 3H), 1.08 (d, *J* = 6.0 Hz, 3H), 2.43 (d, *J* = 6.6 Hz, 2H), 2.98–3.05 (m, 1H), 3.30 (s, 1H), 3.35–3.44 (m, 7H), 3.85–3.91 (m, 5H), 7.26–7.38 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 8.7 (q), 20.0 (q), 53.0 (t), 54.3 (d), 58.5 (t), 61.5 (t), 62.8 (t), 63.2 (d), 127.2 (d), 127.3 (d), 128.5 (d), 128.6 (d), 129.0 (d), 129.1 (d), 138.6 (s), 139.3 (s).

From reaction of (R)-6a** and H₂O without NaOH.**—To the stirred solution of (R)-**6a** (60 mg, 0.188 mmol) in CH₃CN (0.75 mL) was added H₂O (0.75 mL), and the reaction mixture was stirred at room temperature for 5 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-**9af** and (R)-**10af** (45.1 mg, 93.8%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% ethyl acetate in hexane to provide a mixture of (S)-**9af** and (R)-**10af** (43.6 mg, 90.6%, **9af/10af** = 1/8.6, as determined by ¹H NMR) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 1.00 (d, *J* = 6.3 Hz, 3H), 1.08 (d, *J* = 6.0 Hz, 3H), 2.43 (d, *J* = 6.3 Hz, 2H), 2.98–3.05 (m, 1H), 3.26–3.52 (m, 8H), 3.82–3.89 (m, 5H), 7.27–7.33 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 8.7 (q), 19.9 (q), 52.9 (t), 54.2 (d), 58.5 (t), 61.4 (t), 62.7 (t), 63.1 (d), 127.2 (d), 127.3 (d), 128.5 (d), 128.6 (d), 129.0 (d), 129.1 (d), 138.6 (s), 139.3 (s).

dibenzyl[(2S)-1methoxypropan-2-yl]amine ((S)-9ag) and dibenzyl[(2R)-2-methoxypropyl]amine ((R)-10ag).

From reaction of (R)-6a and MeOH with NaOH.—To the stirred solution of (R)-6a (60 mg, 0.188 mmol) in CH₃CN (0.75 mL) was added MeOH (0.75 mL), and the reaction mixture was stirred at room temperature for 10 min. After which, 1M NaOH aqueous solution (0.38 mL) was added and the resulting mixture was stirred at room temperature for 1.5 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-9ag and (R)-10ag (49.8 mg, 98.4%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% ethyl acetate in hexane to provide the mixture of (S)-9ag and (R)-10ag (49.0 mg, 96.8%, 9ag/10ag = 1.6/1, as determined by ¹H NMR) as a colorless oil. For preparation of analytical samples, the regioisomeric mixture was separated by Prep-TLC (SiO₂) eluted with 1–2% ethyl acetate in hexanes.

(S)-9ag.—[α]_D²⁵ = − 4.9° (*c* = 0.5, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.08 (d, *J* = 6.6 Hz, 3H), 3.02 (q, *J* = 6.6 Hz, 1H), 3.30 (s, 3H), 3.33–3.36 (m, 1H), 3.54–3.62 (m, 3H), 3.72 (d, *J* = 13.8 Hz, 2H), 7.19–7.32 (m, 6H), 7.40 (d, *J* = 7.2 Hz, 4H); ¹³C NMR (CDCl₃, 75 MHz) δ 12.1 (q), 52.1 (q), 54.1 (t), 58.8 (d), 75.8 (t), 126.7 (d), 128.1 (d), 128.5 (d), 140.7 (s). HRMS (Positive ion ESI) Calcd for C₁₈H₂₄NO [M + H]⁺ *m/z* 270.1858. Found: [M + H]⁺ *m/z* 270.1867.

(R)-10ag.—[α]_D²⁵ = + 13.0° (*c* = 0.5, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.10 (d, *J* = 6.0 Hz, 3H), 2.41 (dd, *J* = 12.9, 6.0 Hz, 1H), 2.58 (dd, *J* = 13.2, 5.7 Hz, 1H), 3.31 (s, 3H), 3.45 (q, *J* = 14.7 Hz, 1H), 3.54 (d, *J* = 13.5 Hz, 2H), 3.69 (d, *J* = 13.8 Hz, 2H), 7.21–7.39 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ 17.9 (q), 56.3 (q), 58.9 (t), 59.3 (t), 75.9 (d), 126.8 (d), 128.1 (d), 128.9 (d), 139.7 (s). HRMS (Positive ion ESI) Calcd for C₁₈H₂₄NO [M + H]⁺ *m/z* 270.1858. Found: [M + H]⁺ *m/z* 270.1865.

From reaction of (R)-6a and MeOH without NaOH.—(R)-6a (60 mg, 0.188 mmol) was dissolved in MeOH (1.5 mL), and the reaction mixture was refluxed for 1 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-9ag and (R)-10ag (49.6 mg, 98.0%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% ethyl acetate in hexane to provide the mixture of (S)-9ag and (R)-10ag (48.8 mg, 96.4%, 9ag/10ag = 1/6.3, as determined by ¹H NMR) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 1.09–1.13 (m, 6H), 2.44 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.60 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.01–3.10 (m, 1H), 3.32–3.36 (m, 7H), 3.38–3.77 (m, 10H), 7.23–7.41 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 12.1 (q), 17.9 (q), 52.1 (q), 54.1 (t), 56.4 (q), 58.9 (t), 59.3 (t), 75.8 (t), 75.9 (d), 126.7 (d), 126.9 (d), 128.2 (d), 128.6 (d), 128.9 (d), 139.8 (s), 140.7 (s).

dibenzyl[(2S)-1-propoxypropan-2-yl]amine ((S)-9ah) and dibenzyl[(2R)-2-propoxypropyl]amine ((R)-10ah).

To the stirred solution of (R)-6a (60 mg, 0.188 mmol) in CH₃CN (0.75 mL) was added propan-1-ol (0.75 mL), and the reaction mixture was refluxed for 3 h. The resulting mixture was evaporated to dryness. The residue was treated with buffer (Et₃N/AcOH, 0.05M, pH 6, 15 mL) and then extracted with DCM (3 × 15 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo* to provide a regioisomeric mixture of (S)-9ah and (R)-10ah (51.8 mg, 92.3%) as colorless oil which was further purified by column chromatography on silica gel (60–220 mesh) eluting with 5% ethyl acetate in hexane to provide the mixture of (S)-9ah and (R)-10ah (50.6 mg, 90.2%, 9ah/10ah = 1/5.9, as determined by ¹H NMR) as a colorless oil. ¹H NMR (CDCl₃, 300 MHz) δ 0.89–0.97 (m, 6H), 1.08–1.12 (m, 6H), 1.53–1.63 (m, 4H), 2.43 (dd, *J* = 12.9, 6.0 Hz, 1H), 3.40 (dd, *J* = 12.9, 5.7 Hz, 1H), 3.01–3.07 (m, 1H), 3.32–3.47 (m, 4H), 3.53–3.73 (m, 11H), 7.21–7.42 (m, 20H); ¹³C NMR (CDCl₃, 75 MHz) δ 10.7 (q), 12.4 (q), 18.5 (q), 23.0 (t), 23.4 (t), 52.3 (d), 54.1 (t), 59.2 (t), 59.3 (t), 70.6 (t), 72.8 (t), 73.7 (t), 74.3 (d), 126.6 (d), 126.8 (d), 128.1 (d), 128.6 (d), 128.9 (d), 139.9 (s), 140.9 (s). HRMS (Positive ion ESI) Calcd for C₂₀H₂₈NO [M + H]⁺ *m/z* 298.2171. Found: [M + H]⁺ *m/z* 298.2176.

(2R)-1-(dibenzylamino)propan-2-ol ((R)-9af).¹¹

From one-pot reaction using AgCN/H₂O (Table 4, entry 2).—To a solution of (S)-1a (100 mg, 0.392 mmol) and PPh₃ (123.3 mg, 0.470 mmol) in CH₃CN (5 mL) at 0 °C was added NBS (83.6 mg, 0.470 mmol) over 5 min. The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h. Then AgCN (62.9 mg, 0.470 mmol) was added to the reaction mixture followed by the addition of H₂O (0.5 mL). The reaction mixture was allowed to stir at room temperature for 24 h and evaporated to dryness. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 10% ethyl acetate in hexanes to afford (R)-9af (70 mg, 70%) as a colorless oil. [α]_D²⁵ = –75.1° (*c* = 1.0, CHCl₃). [Lit.¹¹ [α]_D²⁰ = –92.2° (*c* = 1.0, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.10 (d, *J* = 6.3 Hz, 3H), 2.45 (d, *J* = 6.9 Hz, 2H), 3.29 (s, 1H), 3.43 (d, *J* = 13.5 Hz, 2H), 3.88 (d, *J* = 13.5 Hz, 2H), 7.26–7.40 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ 20.0 (q), 58.5 (t), 61.4 (t), 63.2 (d), 127.3 (d), 128.5 (d), 129.1 (d), 138.6 (s). ¹H and ¹³C NMR data were essentially identical to those previously reported.¹¹ Chiral HPLC (method E): *t*_R = 6.6 min (S, minor) and 8.0 min (R, major), 90% ee.

From acidification of (R)-12 (Table 4).—(R)-12 (30 mg, 0.010 mmol) was treated dropwise with 4M HCl in 1,4-dioxane (5 mL) at 0 °C. The reaction mixture was heated to 50 °C and stirred for 2 d. H₂O (20 mL) and 2M NaOH (aq) (10 mL) were added to the reaction mixture. The resulting mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated to the dryness *in vacuo*. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 10% ethyl acetate in hexanes to afford (R)-9af (16 mg, 61%) as a colorless oil. [α]_D²⁵ = –65.6° (*c* = 0.8, CHCl₃). Chiral HPLC (method E): *t*_R = 6.7 min (S) and 8.3 min (R). Chiral HPLC (method E): *t*_R = 6.6 min (S, minor) and 8.0 min (R, major), 81% ee. ¹H and ¹³C NMR data of (R)-9af were essentially identical to those described above.

1-[(2S)-2-(dibenzylamino)propyl]pyrrolidine-2,5-dione ((S)-11).

From one-pot reaction using 1M NaOH (Table 4, entry 3).—To a solution of (S)-**1a** (100 mg, 0.392 mmol) and PPh₃ (123.3 mg, 0.470 mmol) in CH₃CN (5 mL) at 0 °C was added NBS (83.6 mg, 0.470 mmol) over 5 min. The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h. 1M NaOH (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 15% ethyl acetate in hexanes to afford (S)-**11** (77 mg, 58%) as a colorless oil. $[\alpha]_D^{26} = +99.3^\circ$ ($c = 1.0$, CHCl₃). ¹H and ¹³C NMR data were essentially identical to those described above Chiral HPLC (method F): $t_R = 10.4$ min (S, major) and 9.4 min (R, minor), >99% ee.

From one-pot reaction using Ag₂CO₃ (Table 4, entry 4).—To a solution of (S)-**1a** (100 mg, 0.392 mmol) and PPh₃ (123.3 mg, 0.470 mmol) in CH₃CN (5 mL) at 0 °C was added NBS (83.6 mg, 0.470 mmol) over 5 min. The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h. Ag₂CO₃ (129.6 mg, 0.470 mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at room temperature for 24 h. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 15% ethyl acetate in hexanes to afford (S)-**11** (69 mg, 52%) as a colorless oil. $[\alpha]_D^{26} = +89.7^\circ$ ($c = 1.0$, CHCl₃). ¹H NMR (CDCl₃, 300 MHz) δ 1.12 (d, $J = 6.6$ Hz, 3H), 2.44–2.59 (m, 4H), 3.12–3.16 (m, 2H), 3.29 (d, $J = 13.2$ Hz, 2H), 3.72–3.91 (m, 3H), 7.22–7.38 (m, 10H); ¹³C NMR (CDCl₃, 75 MHz) δ 11.1 (q), 28.0 (t), 41.3 (t), 51.1 (d), 53.0 (t), 126.9 (d), 128.1 (d), 129.1 (d), 140.1 (s), 177.0 (s). HRMS (Positive ion ESI) Calcd for C₂₁H₂₅N₂O₂ [M + H]⁺ m/z 337.1911. Found: [M + H]⁺ m/z 337.1911. Chiral HPLC (method F): $t_R = 10.4$ min (S, major) and 9.4 min (R, minor), >99% ee.

For structural determination prepared as the authentic sample (Scheme 3).—To a solution of **17** (30 mg, 0.19 mmol) and K₂CO₃ (131.1 mg, 0.95 mmol) in CH₃CN (3 mL) was added benzyl bromide (65.7 mg, 0.38 mmol). The resulting mixture was warmed to 60 °C and continuously stirred for 40 h. The resulting mixture was concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 15% ethyl acetate in hexanes to afford (S)-**11** (43.4 mg, 68%) as a colorless oil. $[\alpha]_D^{26} = +83.2^\circ$ ($c = 1.0$, CHCl₃). ¹H and ¹³C NMR spectra of the compound were essentially identical to (S)-**13** reported above. Chiral HPLC (method F): $t_R = 10.4$ min (S, major) and 9.4 min (R, minor), >99% ee.

1-[2-(dibenzylamino)propyl]pyrrolidine-2,5-dione((rac)-11).—To a solution of (rac)-**1a** (100 mg, 0.392 mmol) and PPh₃ (123.3 mg, 0.470 mmol) in CH₃CN (5 mL) at 0 °C was added NBS (83.6 mg, 0.470 mmol) over 5 min. The resulting mixture was stirred for 4 h at 0 °C. The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h. Then 1M NaOH (0.5 mL) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 h. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 15% ethyl acetate in

hexanes to afford (rac)-**11** (50 mg, 37.7%) as a colorless oil. ^1H and ^{13}C NMR of (rac)-**11** was identical to (S)-**11**. Chiral HPLC (method F): $t_{\text{R}} = 9.4$ (R) and 10.6 min (S).

(2R)-1-(dibenzylamino)propan-2-yl nitrate ((R)-12).—To a solution of (S)-**1a** (100 mg, 0.392 mmol) and PPh_3 (123.3 mg, 0.470 mmol) in CH_3CN (5 mL) at 0°C was added NBS (83.6 mg, 0.470 mmol) over 5 min. The resulting mixture was stirred for 4 h at 0°C . The ice bath was removed, and the reaction mixture was warmed to room temperature and stirred for 1 h. Then AgNO_3 (80 mg, 0.470 mmol) was added to the reaction mixture followed by the addition of H_2O (0.5 mL). The reaction mixture was allowed to stir at room temperature for 1 h. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 3% ethyl acetate in hexanes to afford (R)-**12** (80 mg, 67%) as a colorless oil.

$[\alpha]_{\text{D}}^{26} = +25.1^\circ$ ($c = 1.0$, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz) δ 1.27 (d, $J = 6.6$ Hz, 3H), 2.58 (dd, $J = 13.8$, 5.4 Hz, 1H), 2.78 (dd, $J = 13.8$, 7.2 Hz, 1H), 3.64 (d, $J = 13.8$ Hz, 2H), 3.71 (d, $J = 13.5$ Hz, 2H), 5.23–5.25 (m, 1H), 7.28–7.38 (m, 10H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 16.8 (q), 56.8 (t), 59.3 (t), 78.9 (d), 127.3 (d), 128.4 (d), 128.9 (d), 138.8 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ m/z 301.1547. Found: $[\text{M} + \text{H}]^+$ m/z 301.1562. Chiral HPLC (method E): $t_{\text{R}} = 8.7$ min (S, minor) and 9.2 min (R, major), >99% ee.

1-(dibenzylamino)propan-2-yl nitrate ((rac)-12).—To a solution of (rac)-**6a** (50 mg, 0.106 mmol) in CH_3CN (1 mL) was added AgNO_3 (32.7 mg, 0.192 mmol) followed by the addition of H_2O (0.1 mL). The reaction mixture was stirred at room temperature overnight. The residue was purified by column chromatography on silica gel (60–230 mesh) eluting with 5% ethyl acetate in hexanes to afford (rac)-**12** (30 mg, 59%) as a colorless oil. ^1H and ^{13}C NMR of (rac)-**12** was identical to (S)-**12**. Chiral HPLC (method E): $t_{\text{R}} = 8.7$ min (S) and 9.3 min (R).

tert-Butyl N-[(2S)-1-(methanesulfonyloxy)propan-2-yl]carbamate (14).¹⁴—To a solution of **13**¹² (300 mg, 1.71 mmol) and triethylamine (207.1 mg, 2.05 mmol) in CH_2Cl_2 (10 mL) at 0°C was added methanesulfonyl chloride (216.4 mg, 1.89 mmol) over 5 min. The resulting mixture was stirred for 3 h at 0°C . The reaction mixture was concentrated to dryness, treated with H_2O (30 mL), and extracted with CH_2Cl_2 (3×20 mL). The organic layers were combined, dried over MgSO_4 , filtered, and evaporated. The residue was purified by column chromatography on silica gel (60–220 mesh) eluting 5% ethyl acetate in hexanes to provide (S)-**14** (406 mg, 93.8%) as a waxy solid. $[\alpha]_{\text{D}}^{26} = -26.4^\circ$ ($c = 1.0$, CHCl_3). ^1H NMR (CDCl_3 , 300 MHz) δ 1.14 (d, $J = 6.9$ Hz, 3H), 1.35 (s, 9H), 2.96 (s, 3H), 3.80–3.95 (m, 1H), 4.07–4.09 (m, 2H), 4.84 (d, $J = 6.9$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 17.0 (q), 28.2 (q), 37.2 (d), 45.4 (t), 72.1 (t), 79.6 (s), 155.1 (s). The compound was not very stable and directly used for the next step without further purification.

tert-butyl N-[(2S)-1-cyanopropan-2-yl]carbamate (15).¹³—To a solution of (S)-**14** (150 mg, 0.59 mmol) in DMF (1.5 mL) was added NaCN (43.6 mg, 0.89 mmol) at room temperature. The reaction mixture was stirred at 90°C for 1 h. The resulting mixture was washed by H_2O (50 mL) and extracted with ethyl acetate (3×20 mL). The organic layers

were combined, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–220 mesh) eluting 10% ethyl acetate in hexanes to provide (S)-**15** (93.6 mg, 86%) as a white solid. $[\alpha]_D^{26} = -81.6^\circ$ ($c = 1.0$, CHCl_3). [Lit.¹³ $[\alpha]_D^{20} = -89.3^\circ$ ($c = 0.96$, CHCl_3)]. ^1H NMR (CDCl_3 , 300 MHz) δ 1.28 (d, $J = 6.9$ Hz, 3H), 1.40 (s, 9H), 2.50 (dd, $J = 16.8, 4.2$ Hz, 1H), 2.71 (dd, $J = 16.5, 4.8$ Hz, 1H), 3.85–3.98 (m, 1H), 4.81 (d, $J = 5.4$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 19.4 (q), 25.1 (t), 28.3 (q), 43.2 (d), 80.0 (s), 117.4 (s), 154.8 (s). ^1H and ^{13}C NMR data of (S)-**15** were essentially identical to those previously reported.¹³

tert-butyl N-[(2S)-1-(2,5-dioxopyrrolidin-1-yl)propan-2-yl]carbamate (16).¹⁴—To a solution of (S)-**14** (150 mg, 0.59 mmol) in DMF (3 mL) was added K_2CO_3 (162.8 mg, 1.18 mmol) and succinimide (58.5 mg, 0.59 mmol) at room temperature. The reaction mixture was stirred at 90 °C for 1 h. The resulting mixture was washed by H_2O (50 ml) and extracted with ethyl acetate (3×20 mL). The organic layers were combined, dried over MgSO_4 , filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–220 mesh) eluting 15% ethyl acetate in hexanes to provide (S)-**16** (90.7 mg, 60%) as a white solid. $[\alpha]_D^{26} = +19.1^\circ$ ($c = 1.0$, CHCl_3). $[\alpha]_D^{26} = +18.3^\circ$ ($c = 0.9$, CHCl_3). M.P. 117.2–120.5 °C. ^1H NMR (CDCl_3 , 300 MHz) δ 1.11 (d, $J = 6.6$ Hz, 3H), 1.34 (s, 9H), 2.64–2.70 (m, 4H), 3.39–3.50 (m, 2H), 3.90–4.05 (m, 1H), 4.65 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 18.5 (q), 28.3 (q), 44.5 (d), 44.9 (t), 79.1 (s), 155.6 (s), 177.6 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_4\text{Na}$ $[\text{M} + \text{H}]^+$ m/z 279.1315. Found: $[\text{M} + \text{H}]^+$ m/z 279.1326.

1-[(2S)-2-aminopropyl]pyrrolidine-2,5-dione (17).—To a flask containing **16** (60 mg, 0.23 mmol) was added 4 M HCl in 1,4-dioxane (2 mL) at 0 °C. The resulting mixture was stirred at room temperature for 18 h. Ethyl ether (20 mL) was added to the mixture, and the resulting mixture was stirred for 15 min. The resulting mixture was filtered, and the slurry on the filter funnel was immediately treated with H_2O (30 mL). The aqueous solution was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60–220 mesh) eluting 5% ethyl acetate in hexanes to provide product (S)-**17** (37.8 mg, 84.1%) as a white solid. $[\alpha]_D^{26} = +16.4$. M.P. 226.3–228.9 °C. ^1H NMR (D_2O , 300 MHz) δ 1.15 (d, $J = 5.7$ Hz, 3H), 2.68 (s, 4H), 3.45–3.70 (m, 3H); ^{13}C NMR (D_2O , 75 MHz) δ 15.6 (t), 28.1 (q), 41.4 (d), 46.6 (t), 181.4 (s). HRMS (Positive ion ESI) Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ m/z 157.1000. Found: $[\text{M} + \text{H}]^+$ m/z 157.0972.

Calculation details.

Geometry optimizations were performed at the Density Functional Theory (DFT) level of theory using Perdew-Burke-Erzenhof parameter-free exchange-correlation functional (PBE0).¹⁸ All atoms were described by correlation-consistent basis sets of triple- ζ quality (cc-pVTZ). Basis set for heavy iodine was augmented by effective core potential (so-called cc-pVTZ-pp). In all cases, no symmetry restrictions were applied. All calculated structures were found to be minima on PES (no negative elements of the Hessian matrix and, consequently, no imaginary frequencies) unless otherwise noted. Transition states were found to possess only one imaginary frequency, corresponding to the transition between reactants and products intended. The nature of transition states was probed through IRC

(intrinsic reaction coordinate) technique that led directly to target products or reactants. All computations were performed by Firefly 8.1.0 program package.¹⁹

In the next step, optimized geometries were used to get insight into the electronic structure of our target systems in terms of natural bond orbitals (NBO).²⁰ Bond orders quoted are those from the Wiberg formulation²¹ (so-called Wiberg bond indexes) incorporated in the NBO analysis. All computations were performed with NBO 6.0 program,²² using the converged wavefunctions generated by Firefly program.

In order to get more reliable evaluation on reaction energetics, single-point calculations (for DFT-optimized geometries) were performed for all minimum structures and transition states with help of highly-accurate single-reference correlated method DLPNO-CCSD(T)¹⁵ (domain-based local pair natural orbitals coupled-cluster with single, double and perturbative triple corrections) with the same basis sets. This method was recently proposed by the group Neese and found to be very accurate, providing accuracy comparable with that of CCSD(T), which has reputation of serving as benchmarking method. To accelerate these calculations, the resolution-of-identity (RI) algorithm was applied using the chain-of-sphere approach (RIJCOSX).²³ All these high-level calculations were carried out by using ORCA program suite (version 3.1.0).

X-ray Crystal Determination of (R)-5a.

Crystals for structure determination were obtained by slow evaporation of **5a** from a mixture of CH₂Cl₂/hexanes. The structure was solved using SIR-92 and refined using Bruker SHELXTL. Crystallographic data for **5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication NO. CCDC 999697. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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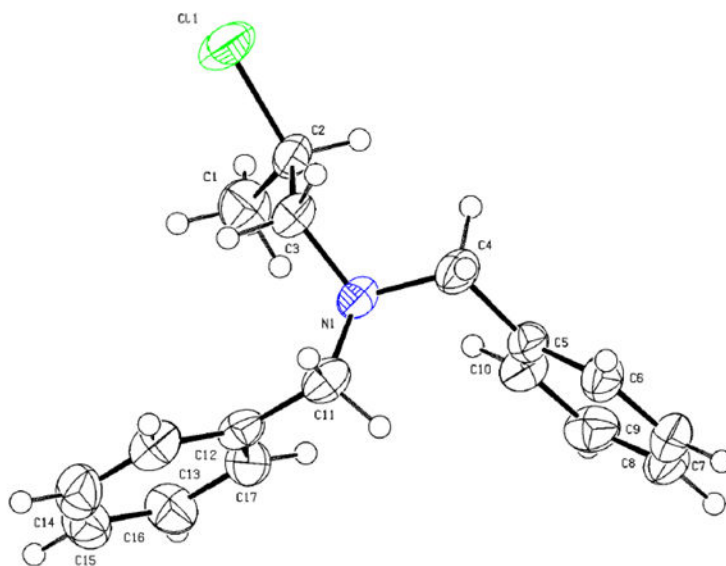


Figure 1.
X-ray crystallographic structure of β -chloroamine (R)-5a.

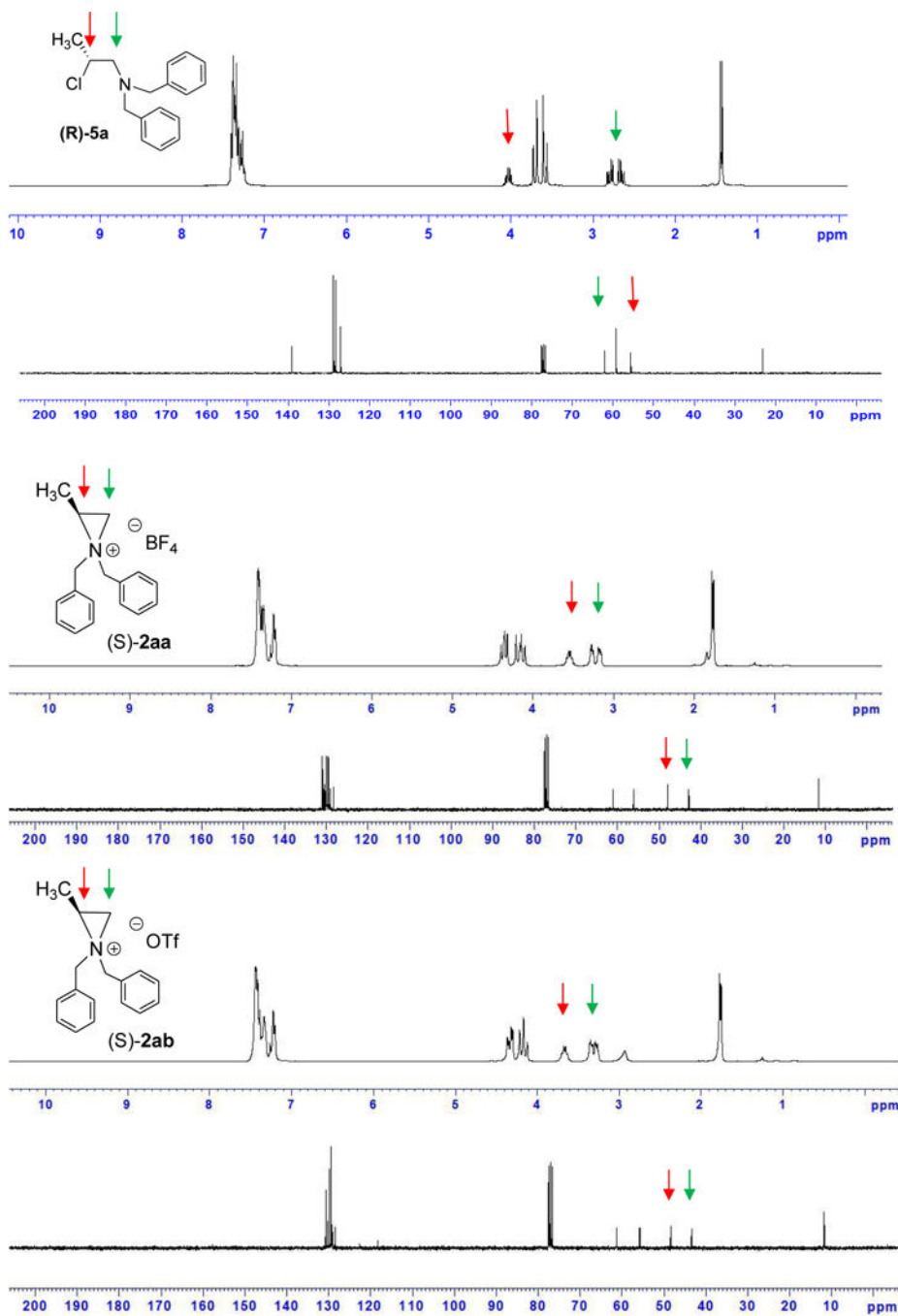
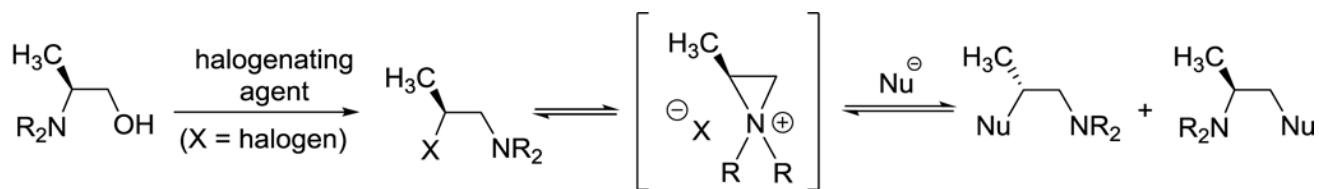
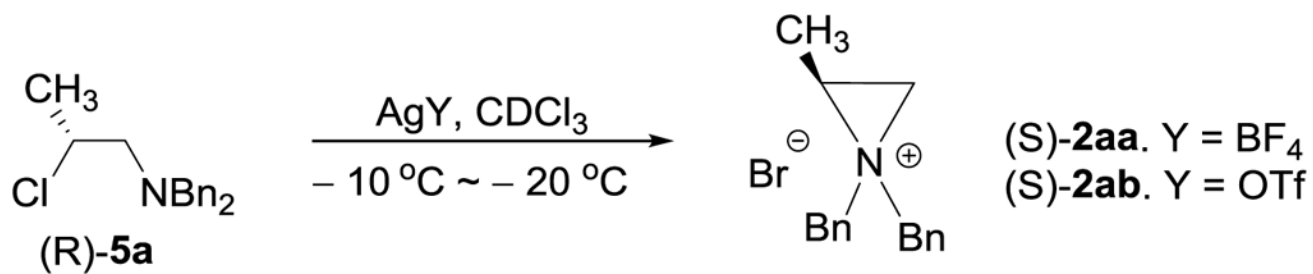
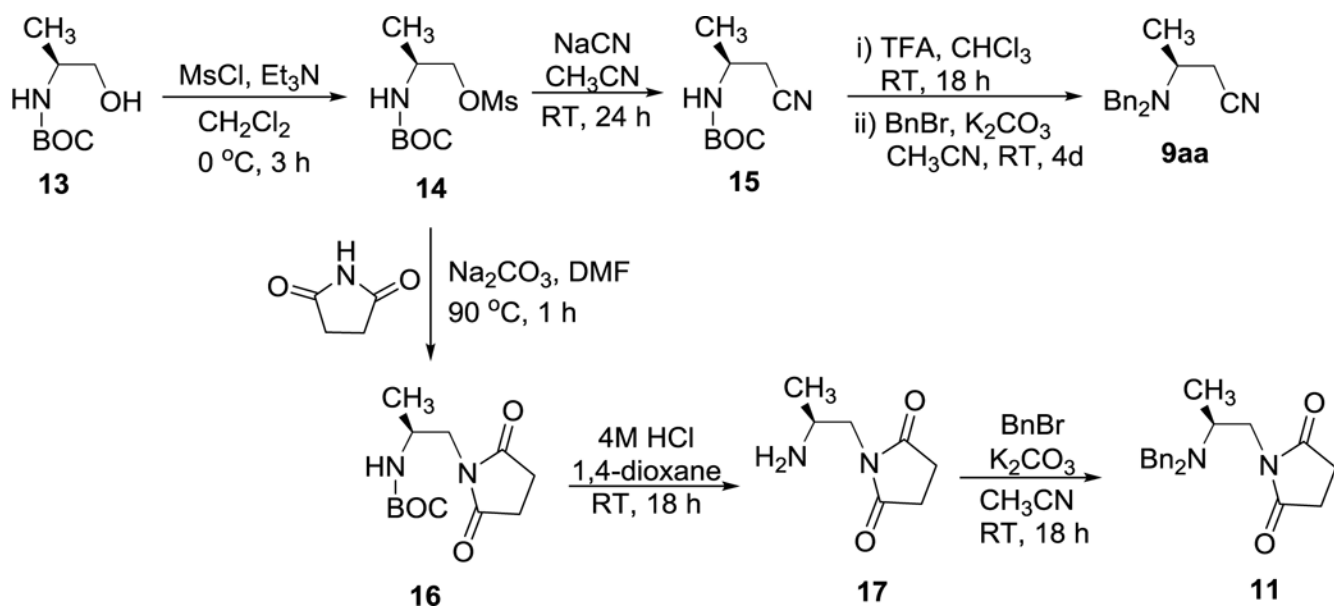


Figure 2.
 ^1H and ^{13}C NMR spectra of β -chloroamine and aziridinium ions.

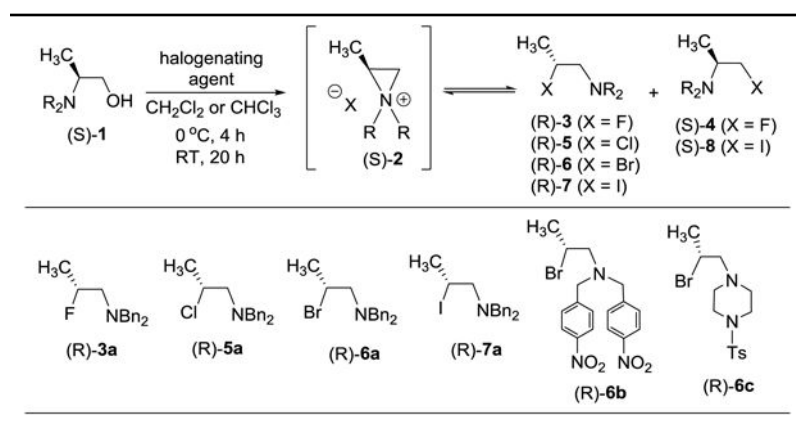
**Scheme 1.**Formation and reactions of β -haloamines and aziridinium ions derived from β -alaniol



Scheme 2.
Synthesis of enantiomerically enriched aziridinium ions

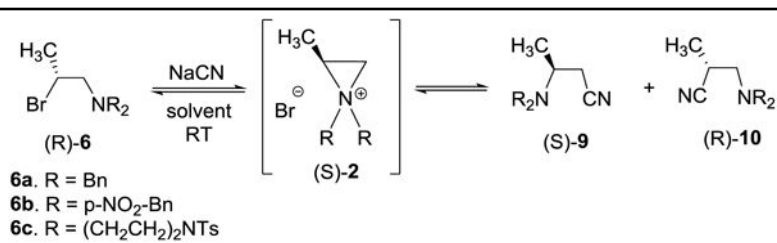


Scheme 3.
Structural determination of **9aa** and **11**

Table 1.Formation and ring opening of aziridinium ions: synthesis of optically active β -haloamines

entry	substrate	halogenating agent	product	# ratio of isomers	yield (%)
1	1a	⁺ DAST	3a/4a	5:1	71
2	1a	NCS/PPh ₃	5a		70
3	1a	NBS/PPh ₃	6a		86
4	1b	NBS/PPh ₃	6b		63
5	1c	NBS/PPh ₃	6c		44
6	1a	I ₂ /PPh ₃ /imidazole	7a/8a	6:1	73

#Determined by ¹H NMR;⁺ diethylaminosulfur trifluoride (DAST)

Table 2.Ring opening of aziridiniums: Synthesis of optically active β -aminonitriles

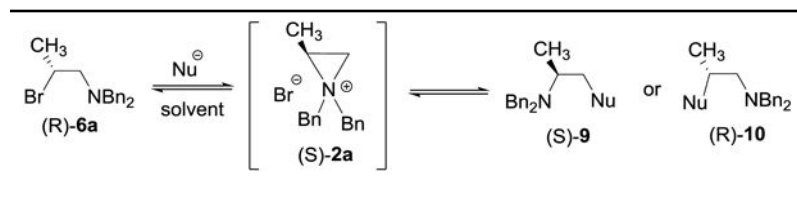
entry	substrate	Nu	solvent	reaction time	product (yield%)	*ratio of (S)-9/(R)-10	⁺ ee (%) of (S)-9/(R)-10
1	6a	CN	CH ₃ CN	4 d	9aa/10aa (82/6)	14:1	97.4/ >99
2	6a	CN	DMSO	30 min	9aa/10aa (76/7)	11:1	97.5/ >97.9
3	6a	CN	CH ₃ CN/H ₂ O	10 min	9aa/10aa (80/7)	11:1	97.9/ 98.6
4	6b	CN	DMSO	4 h	9b (92.8)		>99
5	6c	CN	CH ₃ CN/H ₂ O	30 min	9c (98.5)		>99

* determined by isolated yield of the regioisomers by prep-TLC or flash LC.

⁺ determined by chiral HPLC.

Table 3.

Ring opening of aziridinium ions: Synthesis of optically active molecules



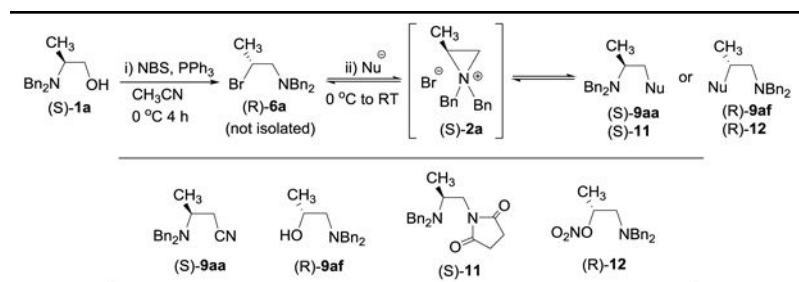
entry	Reagent (Nu)	solvent	Additive*	time	temp	⁺ product (yield%)	*ratio of (S)-9/(R)-10
1	NaBH ₄	CH ₃ CN		15 min	RT	9ab/10ab (93)	2.4/1
2	NaN ₃	CH ₃ CN/H ₂ O		10 min	RT	9ac/10ac (96)	1/2
3	n-PrNH ₂	CH ₃ CN		4 h	RT	9ad/10ad (96)	2/1
4	n-PrSH	CH ₃ CN	1M NaOH	4 h	RT	9ae/10ae (90)	5.7/1
5	H ₂ O	CH ₃ CN/H ₂ O		5 h	RT	9af/10af (91)	1/8.6
6	CH ₃ OH	CH ₃ OH		1 h	reflux	9ag/10ag (96)	1/6.4
7	n-PrOH	CH ₃ CN/n-PrOH		3 h	reflux	9ah/10h (90)	1/5.9
8	H ₂ O	CH ₃ CN/H ₂ O	1M NaOH	3 h	RT	9af/10af (92)	1.2/1
9	CH ₃ OH	CH ₃ CN/CH ₃ OH	1M NaOH	1.5 h	RT	9ag/10ag (97)	1.6/1

⁺ a mixture of the regioisomeric products was isolated via flash column chromatography;

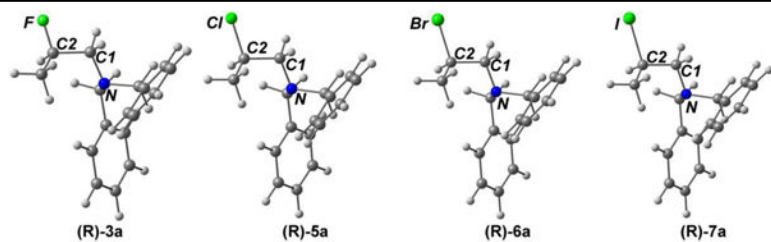
* determined by ¹H NMR.

Table 4.

One-pot synthesis of *N*-protected β -amino nitriie, β -amino alcohol, and vicinal diamine from primary β -amino alcohol (S)-1a



entry	Nu/reagent	time	product	ee (%)
1	NaCN/H ₂ O	1 h	(S)-9aa (74%)	>99
2	AgCN/H ₂ O	24 h	(R)-9af (70%)	80
3	1M NaOH	2 h	(S)-11 (58%)	>99
4	Ag ₂ CO ₃	24 h	(S)-11 (52%)	>99
5	AgNO ₃ /H ₂ O	1 h	(R)-12 (67%)	>99

Table 5.Selected geometrical parameters of (R)- β -halo amines **3a**, **5a**, **6a**, and **7a**. (PBE0/cc-pVTZ).

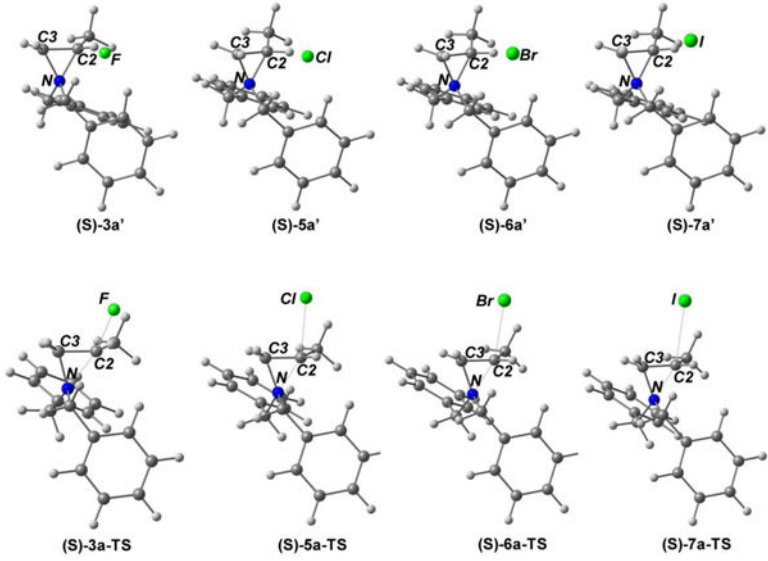
Parameter	(R)- 3a (X = F)	(R)- 5a (X = Cl)	(R)- 5a (X = Cl, X-ray)	(R)- 6a (X = Br)	(R)- 7a (X = I)
X-C1 [*]	2.338	2.702		2.837	3.031
X-C2 [*]	1.395	1.814	1.815	1.974	2.194
N-C1 [*]	1.455	1.457	1.467	1.458	1.458
N-C2 [*]	2.489	2.474		2.470	2.467
C1-C2 [*]	1.523	1.527	1.522	1.526	1.526
X [#]	-0.40	-0.10	-	-0.04	0.04
N [#]	-0.57	-0.57	-	-0.57	-0.57
C1 [#]	-0.28	-0.26	-	-0.26	-0.26
C2 [#]	0.24	-0.20	-	-0.27	-0.35

^{*} All bond lengths are in Angstrom.

[#] Atomic charges are calculated within the NPA framework.

Table 6.

Optimized geometries and selected parameters of (S)-aziridinium ions **3a'**, **5a'**, **6a'**, and **7a'** and transition states (TS) for formation of (R)- β -halo amines **3a**, **5a**, **6a**, and **7a** from ring opening reaction of aziridinium ion (Az⁺) with halide via a S_N2 pathway (PBE0/cc-pVTZ).



parameter	(S)-3a' (X = F)	(S)-3a-TS (X = F)	(S)-5a' (X = Cl)	(S)-5a-TS (X = Cl)	(S)-6a' (X = Br)	(S)-6a-TS (X = Br)	(S)-7a' (X = I)	(S)-7a-TS (X = I)
X-C2 [*]	2.610	2.184	3.184	2.705	3.351	2.846	3.591	3.068
X-C3 [*]	3.228	2.931	3.434	3.086	3.564	3.217	3.779	3.445
N-C2 [*]	1.527	1.813	1.517	1.693	1.516	1.715	1.515	1.749
N-C3 [*]	1.487	1.474	1.494	1.485	1.494	1.482	1.494	1.477
C2-C3 [*]	1.473	1.460	1.469	1.453	1.469	1.454	1.469	1.457
X [#]	-0.75	-0.68	-0.82	-0.82	-0.82	-0.80	-0.84	-0.79
N [#]	-0.38	-0.46	-0.38	-0.43	-0.38	-0.43	-0.38	-0.43
C2 [#]	-0.06	-0.05	-0.04	0.00	-0.04	0.00	-0.03	0.00
C3 [#]	-0.21	-0.23	-0.20	-0.21	-0.20	-0.22	-0.20	-0.22

^{*} All bond lengths are in Angstrom.

[#] Atomic charges are calculated within the NPA framework.

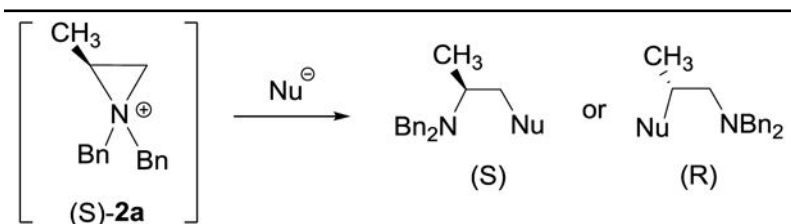
Table 7.

Relative energies of aziridinium ions, transition states (TS), and (R)- β -halo amines involved in ring opening reactions of aziridinium ions with halides in a S_N2 pathway (DLPNO-CCSD(T)/cc-pVTZ).

X	energies (kcal/mol)		
	aziridinium ion	transition state	(R)- β -halo amine
F	(S)- 3a'	3a-TS	(R)- 3a
	0.0	24.0	-49.7
Cl	(S)- 5a'	5a-TS	(R)- 5a
	0.0	13.3	-33.3
Br	(S)- 6a'	6a-TS	(R)- 6a
	0.0	12.1	-29.0
I	(S)- 7a'	7a-TS	(R)- 7a
	0.0	11.1	-24.9

Table 8.

Difference in electronic energies (kcal/mol) between regioisomeric ring opening products (R or S isomer) from reaction of (S)-**2a** with nucleophile (DLPNO-CCSD(T)/cc-pVTZ).



Nu	Major isomer ⁺	Minor isomer ⁺	E = E _(S) -E _(R) (kcal/mol)
F	(R)- 3a	(S)- 4a	6.31
Cl	(R)- 5a		4.94
Br	(R)- 6a		4.50
I	(R)- 7a	(S)- 8a	3.81
CN	(S)- 9aa	(R)- 10aa	2.03
H	(S)- 9ab	(R)- 10ab	1.52
N ₃	(R)- 9ac	(S)- 10ac	5.04
n-PrNH	(S)- 9ad	(R)- 10ad	5.28
n-PrS	(S)- 9ae	(S)- 10ae	3.41
OH	(R)- 9af	(S)- 10af	5.65
CH ₃ O	(R)- 9ag	(S)- 10ag	3.96
n-PrO	(R)- 9ah	(S)- 10ah	2.56
Su [*]	(S)- 11		1.67
ONO ₂	(R)- 12		4.70

* succinimidyl;

⁺ isolated