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# $S_N2$-type ring opening of substituted-*N*-tosylaziridines with zinc (II) halides: Control of racemization by quaternary ammonium salt

MANAS K GHORAI*, DEO PRAKASH TIWARI, AMIT KUMAR and KALPATARU DAS
Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208016, India
e-mail: mkghorai@iitk.ac.in

**Abstract.** Quaternary ammonium salt mediated highly regioselective ring opening of aziridines with zinc(II) halides to racemic and non-racemic $\beta$-halo amines in excellent yield and selectivity is described. The reaction proceeds via an $S_N2$-type pathway and the partial racemization of the starting substrate and the product was effectively controlled by using quaternary ammonium salts to afford the enantioenriched products (er up to 95:5).

**Keywords.** Haloamines; aziridines; enantioselective; Lewis acid; nucleophilic ring opening; quaternary ammonium salts.

## 1. Introduction

Small ring aza-heterocycles provide excellent routes for the construction of important synthetic targets via nucleophilic ring opening, cycloaddition and rearrangement reactions.[1–5] Lewis acid (LA) mediated ring opening of 2-phenyl-*N*-tosylaziridines and azetidines with several nucleophiles to afford non-racemic products in high enantiomeric excess have been reported. We demonstrated the reaction to proceed through an $S_N2$ pathway instead of a stable 1,3- or 1,4-dipolar intermediate as invoked earlier. In all the cases the enantioselectivity was reduced due to partial racemization of the starting aziridines or azetidines[5] (scheme 1).

In continuation of our earlier report for synthesis of haloamines,[5a,6] we describe here our results for the ring opening of aziridines with zinc (II) halides to afford racemic and non-racemic $\beta$-halo amines with excellent regio- and stereoselectivity in detail. Several other methods are known in the literature for synthesis of $\beta$-haloamines from ring opening of aziridines.[7] Synthesis of acyclic and cyclic $\beta$-haloamines via aziridinium ions intermediates[8b,c] and imines,[8a] have also been reported recently. Haloamination[9] and aminohalogenation[10] methods were also utilized for this purpose. Such haloamines are synthetically[11] very important and exhibit several biological activities.[12]

*For correspondence

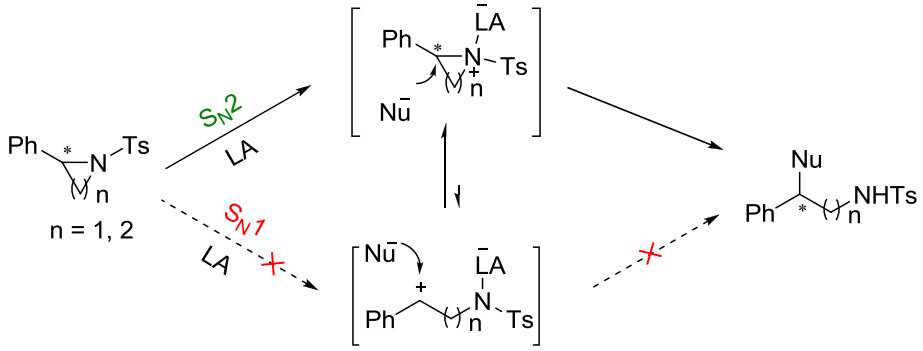
## 2. Experimental

### 2.1 *General procedure for ring-opening of aziridines with zinc dihalides*

A suspension of anhydrous zinc dihalide (0.73 mmol) in $CH_2Cl_2$ (2.0 mL) was refluxed for 5 min, then a solution of *N*-tosylaziridine **1a–d** (0.365 mmol) in anhydrous $CH_2Cl_2$ (2.0 mL) was added slowly with stirring under a nitrogen atmosphere. The resulting mixture was refluxed for the appropriate time until complete consumption of the substrate (monitored by TLC). The reaction mixture was quenched with saturated aq. $NH_4Cl$ solution (2.0 mL), and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, filtered and the solvent was removed under vacuum. The crude product was purified by the column chromatography on silica gel (using ethyl acetate in petroleum ether) to provide the corresponding $\beta$-halo amines.

### 2.2 *Procedure for ring-opening of (R)-**1a** with $ZnCl_2/ZnBr_2$ in the presence of TBAHS*

To a mixture of $ZnCl_2/ZnBr_2$ (0.1 mmol) and TBAHS (0.1 mmol), a solution of (*R*)-**1a** (0.1 mmol) in dry $CH_2Cl_2$ (0.2 mL) was added drop-wise at rt and the reaction was continued for appropriate time (table 6). After completion of the reaction (from TLC), it was quenched by adding water (1 mL). The product was extracted by $CH_2Cl_2$ (2 mL) and dried over anhyd. $Na_2SO_4$. After removal of the solvent, the crude product




**Scheme 1.** Mechanism for LA-mediated $S_N2$-type ring opening of activated aziridines and azetidines.

was purified by flash column chromatography on slilica gel (230–400 mesh) using ethyl acetate and petroleum ether as the eluents.

2.2a *2-Chloro-2-phenyl-N-tosylethanamine (**2a**)*:[5a,6] The general method 1 described above was followed when **1a** reacted with $ZnCl_2$ to afford **2a** as white solid in 86% yield; $^1$H NMR and $^{13}$C NMR data of the crude reaction mixture showed the presence of only one regioisomer; IR $\nu_{max}$ (KBr, cm$^{-1}$) 3262, 2924, 2854, 1330, 1158, 708, 551; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.37 (s, 3H, $CH_3$), 3.31–3.44 (m, 2H, $CH_2$), 4.74 (t, $J$ = 6.6 Hz, 1H, NH), 4.79 (dd, $J$ = 7.2, 2.2 Hz, 1H), 7.11–7.29 (m, 7H, Ar–H), 7.66 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 50.3, 61.6, 127.0, 127.1, 128.9, 129.1, 129.8, 136.9, 137.7, 143.5; FAB Mass: $m/z$ 311 (M$^+$+2), 310 (M$^+$+1), 289, 274, 263, 258, 234, 233, 206, 184, 178, 155, 154, 136, 120, 119, 91, 77. For (*S*)-**2a** (general procedure 2 was followed) er = 91:9, enantiomeric purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane–isopropanol, 95:5, flow rate = 1.0 mL/min; $t_R$ 1: 28.61 min (minor), $t_R$ 2: 36.08 min (major).

2.2b *2-Bromo-2-phenyl-N-tosylethanamine (**2b**)*:[5a,6] The general method 1 was followed, when **1a** reacted with $ZnBr_2$ to afford **2b** as white solid in 83% yield; $^1$H NMR and $^{13}$C NMR data of the crude reaction mixture showed the presence of only one regioisomer; IR $\nu_{max}$ (KBr, cm$^{-1}$) 3263, 2923, 2853, 1331, 1157, 696, 550; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.37 (s, 3H), 3.47–3.52 (m, 2H), 4.75 (t, $J$ = 6.4 Hz, 1H), 4.83 (t, $J$ = 6.4 Hz, 1H), 7.17–7.26 (m, 7H), 7.65 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 50.0, 52.6, 127.0, 127.6, 129.0, 129.1, 129.8, 136.9, 138.1, 143.8; FAB Mass: $m/z$ 354 (M$^+$+1). For (*S*)-**2b** (general procedure 2 was followed) er = 95:5, enantiomeric purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane–isopropanol, 95:5, flow rate = 1.0 mL/min; $t_R$ 1: 25.33 min (minor), $t_R$ 2: 31.58 min (major).

2.2c *2-Iodo-2-phenyl-N-tosylethanamine (**2c**)*:[5a,6] The general method 1 was followed, when **1a** reacted with $ZnI_2$ to afford **2c** as white solid in 88% yield; $^1$H NMR and $^{13}$C NMR data of the crude reaction mixture showed the presence of only one regioisomer; IR $\nu_{max}$ (KBr, cm$^{-1}$) 3286, 2923, 2852, 1323, 1153, 847, 697, 667, 551; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.38 (s, 3H), 3.40–3.48 (m, 1H), 3.59–3.66 (m, 1H), 4.65 (t, $J$ = 6.3 Hz, 1H), 4.94 (t, $J$ = 7.8 Hz, 1H), 7.18–7.26 (m, 7H), 7.64 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 29.8, 51.2, 127.0, 127.5, 128.7, 129.1, 129.8, 136.9, 139.8, 143.8; HRMS (ES$^+$) for (M$^+$+1) $C_{15}H_{17}INO_2S$, calcd 402.0025; found 402.0025.

2.2d *Spectral data of **2d***:[5a] The general method 1 was followed, when **1b** reacted with $ZnCl_2$ to afford **2d** as colourless liquid in 65% combined yield; It was isolated as an inseparable mixture of two diastereomers and was characterized by $^1$H NMR, $^{13}$C NMR, DEPT, 2D ($^1$H-$^1$H COSY) and mass spectral analysis. The protons of the individual diastereomer were assigned by 2D ($^1$H-$^1$H COSY) and $D_2O$ exchange experiments in $^1$H NMR to assign the NH proton. For the major diastereomer of **2d** (X = Cl): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.01 (s, 6H), 0.87 (s, 9H), 2.38 (s, 3H, $CH_3$), 3.53 (dd, $J$ = 9.5, 4.4 Hz, 1H), 3.58 (dd, $J$ = 9.8, 6.8 Hz, 1H), 3.63–3.68 (m, 1H), 4.92 (d, $J$ = 8.8 Hz, 1H, NH), 5.23 (d, $J$ = 4.6 Hz, 1H), 7.12–7.26 (m, 7H, Ar–H), 7.53 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.5, 18.1, 21.4, 25.8, 60.8, 62.1, 62.5, 126.8, 127.3, 127.8, 128.3, 129.4, 137.2, 137.8, 143.1; for the

other diastereomer of **2d** (X = Cl): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.02 (s, 6H), 0.88 (s, 9H), 2.39 (s, 3H, $CH_3$), 3.46 (dd, $J$ = 10.3, 4.4 Hz, 1H), 3.74–3.81 (m, 1H), 4.02 (dd, $J$ = 10.3, 2.7 Hz, 1H), 4.82 (d, $J$ = 9.5 Hz, 1H, NH), 4.95 (d, $J$ = 7.8 Hz, 1H), 7.12–7.26 (m, 7H, Ar–H), 7.5 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.5, 18.2, 21.4, 25.7, 60.1, 60.9, 61.7, 126.9, 127.3, 128.1, 128.4, 129.5, 137.2, 137.6, 143.2; FAB Mass: $m/z$ 455 $M^+$+2, 454 $M^+$+1, 438, 418, 396, 388, 341, 328, 286, 263, 228, 184, 155, 118, 91. HRMS ($ES^+$) for ($M^+$+1) $C_{22}H_{32}ClNO_3SSi$, calcd 454.1639; found 454.1638.

2.2e *Spectral data of **2e***:[5a] The general method 1 was followed, when **1b** reacted with $ZnBr_2$ to afford **2e** as colourless liquid in 52% combined yield; It was isolated as an inseparable mixture of two diastereomers; For the major diastereomer of **2e** (X = Br): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ −0.01 (s, 3H), 0.00 (s, 3H), 0.88 (s, 9H), 2.41 (s, 3H), 3.48 (dd, $J$ = 10.0, 3.8 Hz, 1H), 3.54 (dd, $J$ = 7.08, 4.12 Hz, 1H), 3.62–3.67 (m, 1H), 4.99 (d, $J$ = 7.8 Hz, 1H), 5.25 (d, $J$ = 5.6 Hz, 1H), 7.17–7.29 (m, 7H), 7.63 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.5. 18.1, 21.4, 25.7, 55.2, 60.6, 62.9, 126.9, 128.0, 128.4, 129.5, 137.4, 138.3, 143.3; for the other diastereomer of **2e** (X = Br): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.05 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 2.42 (s, 3H), 3.56–3.57 (m, 1H), 3.91–3.93 (m, 1H), 4.15 (dd, $J$ = 9.7, 2.2 Hz, 1H), 4.85 (d, $J$ = 9.5 Hz, 1H), 5.02 (d, $J$ = 8.3 Hz, 1H), 7.17–7.29 (m, 7H), 7.51 (d, $J$ = 8.0 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.6, 18.2, 21.4, 25.8, 52.5, 59.8, 62.5, 127.0, 128.3, 128.4, 129.5, 137.3, 138.2, 143.3. HRMS ($ES^+$) for $(M–Br)^+$ $C_{22}H_{32}BrNO_3SSi$, calcd 418.1872; found 418.1870.

2.2f *Spectral data of **2f***:[5a] The general method 1 was followed, when **1b** reacted with $ZnI_2$ to afford **2f** as colourless liquid in 56% yield as a single regioisomer. It was isolated as an inseparable mixture of two diastereomers. For the major diastereomer of **2f** (X = I): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ −0.04 (d, $J$ = 1.4 Hz, 3H), −0.01 (d, $J$ = 1.4 Hz, 3H), 0.82 (d, $J$ = 1.7 Hz, 9H), 2.33 (s, 3H), 3.54–3.58 (m, 1H), 3.78–3.83 (m, 1H), 4.08–4.12 (m, 1H), 4.71 (d, $J$ = 9.0 Hz, 1H), 5.09 (d, $J$ = 9.0 Hz, 1H), 7.06–7.21 (m, 7H), 7.42 (dd, $J$ = 8.3, 1.4 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ −5.6. 18.2, 21.4, 25.8, 31.5, 60.3, 63.8, 127.0, 127.9, 128.4, 128.5, 129.5, 137.3, 140.2, 143.3. HRMS ($ES^+$) for ($M^+$+1) $C_{22}H_{32}INO_3SSi$, calcd 546.0995; found 546.0997.

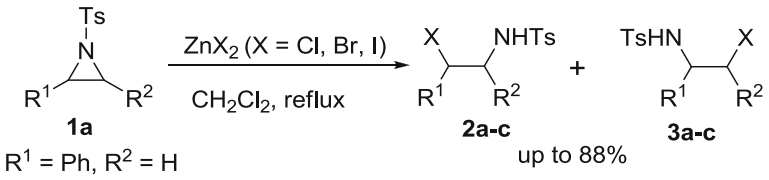
2.2g *trans-2-Chloro-N-tosylcyclohexanamine (**2g**)*:[5a,6] The general method 1 was followed, when **1c** reacted with $ZnCl_2$ to afford **2g** as white solid in 82% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.15–1.29 (m, 3H), 1.49–1.65 (m, 3H), 2.08–2.21 (m, 2H), 2.36 (s, 3H), 2.98–3.04 (m, 1H), 3.60–3.66 (m, 1H), 4.86 (d, $J$ = 5.4 Hz, 1H, NH); 7.24 (d, $J$ = 8.5 Hz, 2H), 7.68–7.72 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) 21.6, 23.4, 24.5, 32.6, 35.0, 58.8, 62.2, 127.3, 129.6, 136.9, 143.5; FAB Mass: $m/z$ 288 ($M^+$+1).

2.2h *trans-2-Bromo-N-tosylcyclohexanamine (**2h**)*:[5a] The general method 1 was followed, when **1c** reacted with $ZnBr_2$ to afford **2h** as white solid in 78% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.17–1.28 (m, 3H), 1.58–1.76 (m, 3H), 2.20–2.23 (m, 2H), 2.36 (s, 3H), 3.07–3.11 (m, 1H), 3.74–3.80 (m, 1H), 4.88 (d, $J$ = 5.1 Hz, 1H, NH), 7.24 (d, $J$ = 8.0 Hz, 2 H), 7.70 (dd, $J$ = 8.2, 1.7 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 23.4, 25.4, 35.8, 55.1, 58.7, 127.3, 129.6, 136.9, 143.5; FAB Mass: $m/z$ 332 ($M^+$+1).

2.2i *trans-2-Iodo-N-tosylcyclohexanamine (**2i**)*:[5a] The general method 1 was followed, when **1c** reacted with $ZnI_2$ to afford **2i** as white solid in 86% yield; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.18–1.34 (m, 3H), 1.44–1.59 (m, 2H), 1.84–1.97 (m, 1H), 2.15–2.30 (m, 2H), 2.36 (s, 3H), 3.16–3.19 (m, 1H), 3.90–3.92 (m, 1H), 4.92 (d, $J$ = 5.6 Hz, 1H), 7.24 (d, $J$ = 8.1 Hz, 2H), 7.72 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) 21.5, 23.6, 26.7, 33.1, 34.9, 37.9, 59.2, 127.4, 129.6, 137.1, 143.5; FAB Mass: $m/z$ 380 ($M^+$+1).

2.2j *2-Chloro-3-phenyl-N-tosylpropan-1-amine (**2j**)*:[5a,6] The general method 1 was followed, when **1d** reacted with $ZnCl_2$ to afford a mixture of **2j** and **3j** (28:72) as white solid in 87% combined yield; For regioisomer **2j**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.36 (s, 3H), 2.88–3.07 (m, 3H), 3.20–3.26 (m, 1H), 3.98–4.05 (m, 1H), 4.87 (t, $J$ = 6.8 Hz, 1H, NH), 7.05–7.07 (m, 2H), 7.16–7.24 (m, 5H), 7.62 (d, $J$ = 8.1 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 41.7, 48.3, 61.7, 127.0, 127.2, 128.6, 129.2, 129.8, 136.3, 136.6, 143.7.

2.2k *1-Chloro-3-phenyl-N-tosylpropan-2-amine (**3j**)*:[5a] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.41 (s, 3H), 2.76 (dd, $J$ = 13.7, 6.4 Hz, 1H), 2.87 (dd, $J$ = 13.6, 7.8 Hz, 1H), 3.41–3.50 (m, 2H), 3.65–3.73 (m, 1H), 4.89 (d, $J$ = 8.0 Hz, 1H, NH), 7.03–7.07 (m, 2H), 7.15–7.26 (m, 5H), 7.64 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz,




**Scheme 2.** Ring-opening of *N*-tosylaziridine with Zn(II) halides.

$CDCl_3$) $\delta$ 21.5, 38.2, 46.8, 55.0, 126.8, 126.9, 128.7, 129.1, 129.7, 136.0, 137.1, 143.5.

2.2l *2-Bromo-3-phenyl-N-tosylpropan-1-amine (**2k**)*:[5a] The general method 1 was followed, when **1d** reacted with $ZnBr_2$ to afford a mixture of **2k** and **3k** (18:82) as white solid in 73% combined yield; For regioisomer **2k**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.44 (s, 3H), 3.08–3.23 (m, 2H), 3.31–3.37 (m, 1H), 4.11–4.18 (m, 1H), 4.89 (t, $J$ = 6.1 Hz, 1H), 7.11–7.13 (m, 2H), 7.21–7.31 (m, 5H), 7.69 (dd, $J$ = 8.3, 1.9 Hz, 2H).

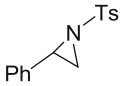
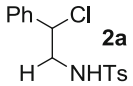
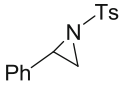
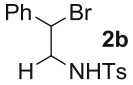
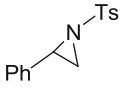
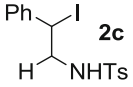
2.2m *1-Bromo-3-phenyl-N-tosylpropan-2-amine (**3k**)*: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.41 (s, 3H), 2.77 (dd, $J$ = 13.9, 6.3 Hz, 1H), 2.87 (dd, $J$ = 13.7, 7.8 Hz, 1H), 3.30–3.36 (m, 2H), 3.58–3.66 (m, 1H), 4.85 (d, $J$ = 8.5 Hz, 1H, NH), 7.03–7.08 (m, 2H), 7.18–7.25 (m, 5H), 7.64 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 21.5, 36.9, 39.2, 54.5, 126.9, 127.0, 128.8, 129.1, 129.7, 136.0, 137.2, 143.6.

2.2n *1-Iodo-3-phenyl-N-tosylpropan-2-amine (**3l**)*:[5a] The general method 1 was followed, when **1d** reacted with $ZnI_2$ to afford a mixture of **2l** and **3l** (2:98), **3l** was obtained as white solid in 78% yield; For major regioisomer **3l**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.41 (s, 3H), 2.70–2.83 (m, 2H), 3.15–3.26 (m, 3H), 4.86 (d, $J$ = 7.8 Hz, 1H, NH), 7.05–7.06 (m, 2H), 7.19–7.26 (m, 5H), 7.63 (d, $J$ = 8.3 Hz, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 13.3, 21.5, 40.9, 54.0, 126.9, 127.0, 128.7, 129.0, 129.6, 136.0, 137.1, 143.5.

## 3. Results and discussion

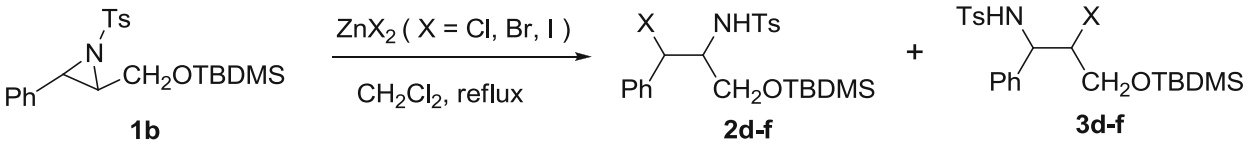
Our study began with the ring-opening of racemic 2-phenyl-*N*-tosylaziridine **1a** with one equivalent $ZnCl_2$ in $CH_2Cl_2$ as the solvent at rt to produce the corresponding $\beta$-chloro amine **2a**. However, this reaction took longer time for completion and **2a** was obtained in poor yield. When the same reaction was carried out with 2.0 equiv. $ZnCl_2$ in $CH_2Cl_2$ under refluxing condition, **2a** was formed within 1 h in 86% yield and the regioselectivity was confirmed by $^1$H NMR of the crude reaction mixture (scheme 2). Furthermore, lesser equivalent of $ZnCl_2$ was found to be insufficient and with prolonged reaction time a complex reaction mixture was obtained. Similarly, $\beta$-bromo amine derivative **2b** was obtained regioselectively in 83% yield when two equivalents $ZnBr_2$ were used as the Lewis acid. Interestingly, with $ZnI_2$ the ring opening took place at room temperature and afforded the corresponding $\beta$-iodo amine derivative **2c** as a single regioisomer within one hour (scheme 2, table 1). In contrast to the earlier report, 2-phenyl-*N*-tosylaziridine **1a** gave only one regioisomer **2a–c** (table 1) in good yield where the halide ions preferably attacked at the more electrophilic benzylic position and the other regioisomer **3** (scheme 2) did not

**Table 1.** Regioselective opening of 2-phenyl-*N*-tosylaziridine **1a** with Zn(II) halides.

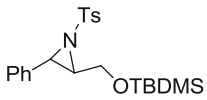
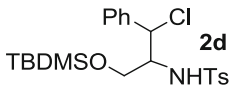
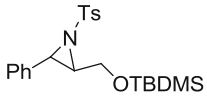
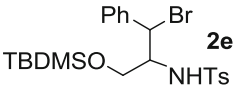
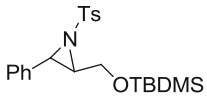
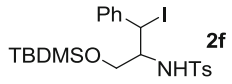
| Entry | Aziridine **1a** | $ZnX_2$ | Product **2a–c** | Time (h) | Yield[a] (%) | Ratio[b] **2:3** |
|---|---|---|---|---|---|---|
| 1 |  | $ZnCl_2$ |  **2a** | 1 | 86 | >99:1 |
| 2 |  | $ZnBr_2$ |  **2b** | 1 | 83 | >99:1 |
| 3 |  | $ZnI_2$ |  **2c** | 1 | 88 | >99:1 |

[a]Yield of isolated **2a–c** after column chromatographic purification; [b]The ratio was determined by $^1$H-NMR analysis of the crude reaction mixture

**Table 2.** Regioselective opening of *N*-tosylaziridine **1b** with Zn(II) halides.




**1b** **2d-f** **3d-f**

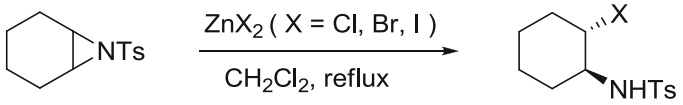
| Entry | Aziridine **1b** | $ZnX_2$ | Product **2d-f** | Time (h) | Yield[a] (%) (*trans*:*cis*) | Ratio[b] **2:3** |
|---|---|---|---|---|---|---|
| 1 |  | $ZnCl_2$ |  | 3 | 65 (42:58)[c] | 86:14 |
| 2 |  | $ZnBr_2$ |  | 2 | 52 (45:55)[c] | 82:18 |
| 3 |  | $ZnI_2$ |  | 1 | 56 (81:19)[c] | >99:1 |

[a]Yield of isolated **2d–f** after column chromatographic purification; [b]The ratio was determined by $^1$H-NMR analysis of the crude reaction mixture. [c]**2** was as obtained as a diastereomeric mixture and the diastereomeric ratio (*trans*:*cis*) is given in parentheses

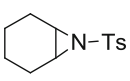
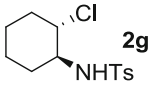
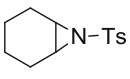
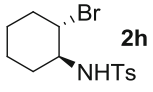
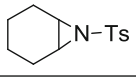
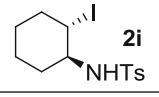
form at all. To widen the scope of our strategy, different types of *N*-tosylaziridines **1b–d** were studied under the optimized reaction conditions (two equiv. $ZnX_2$: X = Cl, Br or I, $CH_2Cl_2$, 40°C) and the results are summarized in tables 2–5.

Racemic disubstituted aziridine **1b** reacted with $ZnX_2$ under similar experimental conditions to afford the corresponding halo amines **2d–f** and **3d–f** as a mixture of regioisomers and the regioselectivity was found to be dependent on the size of the halide anions (table 2). When $ZnI_2$ was used as the Lewis acid, only one regioisomer **2f** was obtained from the attack of iodide ion at the more electrophilic benzylic position of **1b** and the corresponding **3f** was not observed in $^1$H NMR spectrum of crude reaction mixture. Furthermore, in all these cases opening of diastereomerically pure trans-**1b** produced a mixture of diastereomers and the diastereoselectivity was also found to depend on $ZnX_2$ (table 2). To find out and explain the regioselectivity of the opening of **1b** with $ZnX_2$, we have recorded the $^1$H NMR spectrum of the crude reaction mixture. The ratio of regioisomers was measured from the $^1$H NMR by comparing the integration of Me protons or ortho aromatic protons of Ts-group. However, for the reaction of **1b** with $ZnCl_2$ and $ZnBr_2$, the minor regioisomers **3d** and **3e**, respectively, could not be isolated

**Table 3.** Ring-opening of *N*-tosylaziridine **1c** with Zn(II) halides.

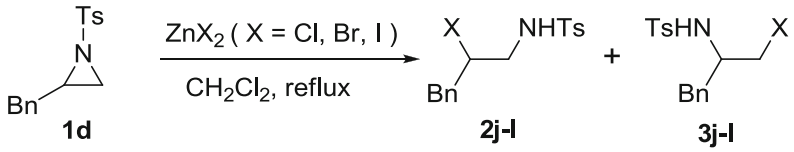


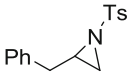
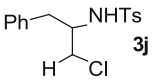
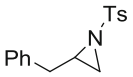
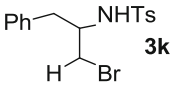
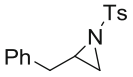
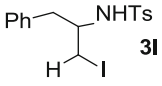

**1c** **2g-i**

| Entry | Aziridine **1c** | $ZnX_2$ | Product **2g-i** | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 |  | $ZnCl_2$ |  | 5 | 82 |
| 2 |  | $ZnBr_2$ |  | 5 | 78 |
| 3 |  | $ZnI_2$ |  | 1 | 86 |

[a]Isolated yield of **2g–i** after column chromatographic purification

**Table 4.** Regioselective opening *N*-tosylaziridine **1d** with Zn(II) halides.




| Entry | Aziridine **1d** | $ZnX_2$ | Product **3j-l**[a] | Time (h) | Yield[b] (%) | Ratio[c] **2j-l:3j-l** |
|---|---|---|---|---|---|---|
| 1 |  | $ZnCl_2$ |  **3j** | 12 | 87[d] | 28:72 |
| 2 |  | $ZnBr_2$ |  **3k** | 12 | 73[d] | 18:82 |
| 3 |  | $ZnI_2$ |  **3l** | 1 | 78 | 2:98 |

[a]Major products shown. [b]Isolated yield after column chromatographic purification. [c]The ratio was determined by $^1$H-NMR analysis of the crude reaction mixture. [d]Combined yield of isolated **2j–l** and **3j–l**

by column chromatography. The major isomers **2d** and **2e** were isolated as a mixture of diastereomers. A detail of the ratio of regio- and diastereomers of **2d–f** has been incorporated in table 2. $S_N2$ opening of the aziridine **1b** with $ZnI_2$, leads to the formation of the corresponding *trans*-**2f** as the major diastereomer. Diastereomeric ratio (*trans*:*cis*) was determined by $^1$H NMR spectroscopy and coupling constants.

Ring-opening of bicyclic *N*-tosylcyclohexene aziridine **1c**, leads to the formation of the corresponding *trans*-halo amines **2g–i** in excellent yields (table 3). In **1c** ring strain may be the driving force for the easy attack by the nucleophile. The *trans*-stereochemistry of **2g–i** was established from the coupling constants of the ring CH protons adjacent to hetero atoms.

All the *N*-tosylaziridines shown in tables 1–3 underwent nucleophilic ring opening with halide ions smoothly except for *N*-tosyl-2-benzylaziridine **1d** (table 4), which reacted slowly and afforded **3j–l** with lower yields. This can be attributed to the reduced electrophilic nature at the homobenzylic position. As a result, reversal of regioselectivity was observed with preferential attack of halides on the less substituted carbon of aziridine to produce **3j–l** as the major isomer. However, these regioisomers were easily separated by column chromatography and obtained in the pure forms.

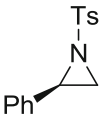
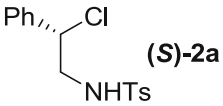
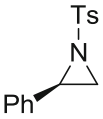
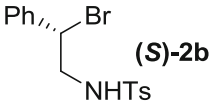
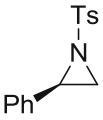
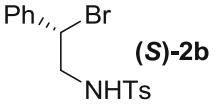
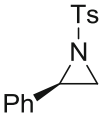
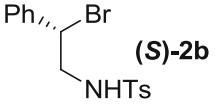
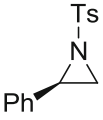
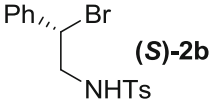
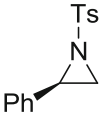
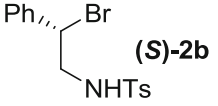
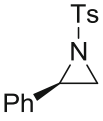
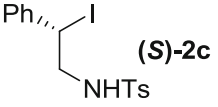
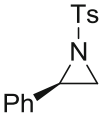
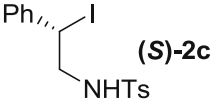
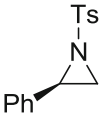
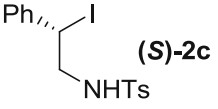
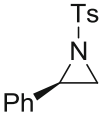
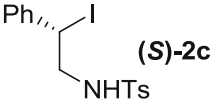
To investigate the mechanism, the same reaction was carried out with chiral (*R*)-(−)-2-phenyl-1-(toluene-4-sulfonyl) aziridine (*R*)-**1a** (ee >99%) which afforded non-racemic *β*-haloamine (*S*)-**2a–c** (scheme 3).

When (*R*)-**1a** was treated with $ZnX_2$ (X = Cl, Br and I) in $CH_2Cl_2$, non-racemic *β*-halo amines (*S*)-**2a–c** were formed with poor ee. To optimize the reaction conditions for obtaining enhanced enantioselectivity the reaction was studied in different solvents and at different temperature. The results are shown in table 5. When the reaction was performed in $CH_3CN$ as the solvent in the presence of $ZnCl_2$ as the LA at rt, the corresponding *β*-chloro amine (*R*)-**1a** was obtained with 68% ee (entry 1, table 5). Similar reaction of (*R*)-**1a** with $ZnBr_2$ and $ZnI_2$ afforded the corresponding bromo- and iodo amines in 67% and 78% ee, respectively (figures 1 and 2). Using THF as the solvent and $ZnBr_2$ as the LA ee was reduced to 46%.

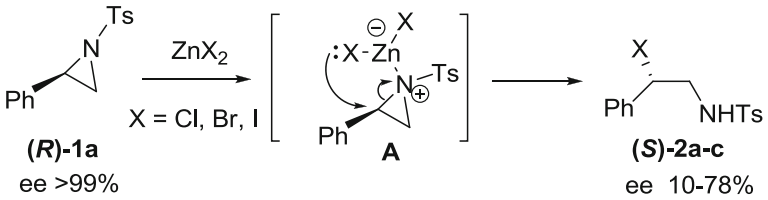
Based on the experimental results, we do believe that the ring-opening step follows an $S_N2$ type mechanism as we proposed earlier[5] (scheme 4). Zn(II) coordinates with aziridine nitrogen generating a highly reactive intermediate **A** which undergoes intramolecular $S_N2$ type ring opening by halides leading to the formation of haloamine (*S*)-**2**. The reduced ee of the products is rationalized by partial racemization of the aziridine before ring-opening via the equilibrium between the intermediates **A** and **B**.[5i,j] The coordination of Zn(II) with aziridine nitrogen polarizes the benzylic C–N bond, making it labile enough to racemize. The haloamines **2** was also found to racemize during the reaction.

According to this mechanistic proposal, it is possible to obtain haloamine (*S*)-**2** with high ee by tuning the reaction conditions to control/stop the racemization of starting aziridine (*R*)-**1a** as well as the haloamines **2**. Very recently, we have reported $S_N2$-type ring opening of aziridines and azetidines using quaternary ammonium salts with halides as the nucleophilic counter ions

**Table 5.** Nucleophilic ring-opening of (*R*)-**1a** in the presence of $ZnX_2$.

| Entry | Aziridine (*R*)-**1a** | $ZnX_2$ | Solvent | Temp (°C) | Time (h) | Product (*S*)-**2a–c** | ee[a] | Yield[b] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 |  | $ZnCl_2$ | $CH_3CN$ | 25 | 2 |  **(*S*)-2a** | 68 | 25 |
| 2 |  | $ZnBr_2$ | $CH_3CN$ | 25 | 2 |  **(*S*)-2b** | 67 | 35 |
| 3 |  | $ZnBr_2$ | $CH_3CN$ | 25 | 6 |  **(*S*)-2b** | 55 | 50 |
| 4 |  | $ZnBr_2$ | $CH_3CN$ | 60 | 0.25 |  **(*S*)-2b** | 65 | 10 |
| 5 |  | $ZnBr_2$ | THF | 25 | 12 |  **(*S*)-2b** | 46 | 30 |
| 6 |  | $ZnBr_2$ | DCM | 25 | 0.5 |  **(*S*)-2b** | 10 | 55 |
| 7 |  | $ZnI_2$ | DCM | 25 | 0.5 |  **(*S*)-2c** | 13 | 85[c] |
| 8 |  | $ZnI_2$ | $CH_3CN$ | 25 | 2 |  **(*S*)-2c** | 78 | 75 |
| 9 |  | $ZnI_2$ | $CH_3CN$ | 25 | 2 |  **(*S*)-2c** | 78 | 20[c] |
| 10 |  | $ZnI_2$ | THF | 25 | 2 |  **(*S*)-2c** | 46 | 15 |

[a]Determined by chiral hplc analysis (ADH column, Hex/IPA: 95/5) when (*R*)-**1a** was used. [b]Yield of **2** after column chromatographic purification, in most of the cases reaction was stopped before completion to check the ee. [c]One equiv. of $ZnI_2$ was used




**Scheme 3.** Ring-opening of (*R*)-**1a** by $ZnX_2$.

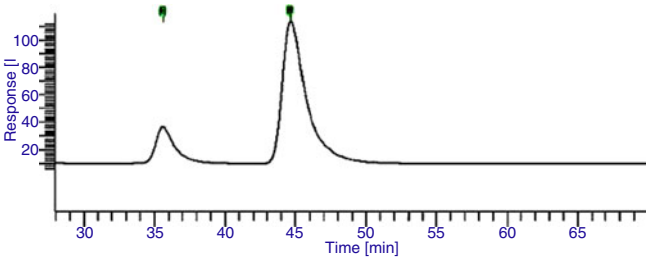



**Figure 1.** Chromatogram of bromo amine (*S*)-**2b** (67% ee).

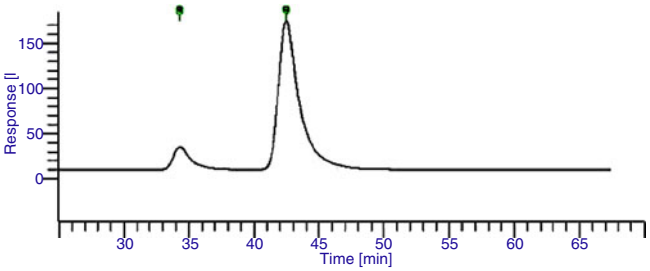
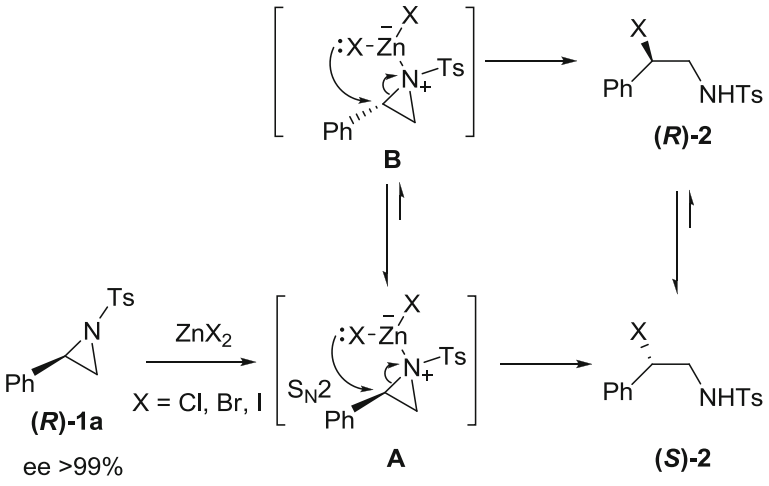



**Figure 2.** Chromatogram of iodo amine (*S*)-**2c** (78% ee).

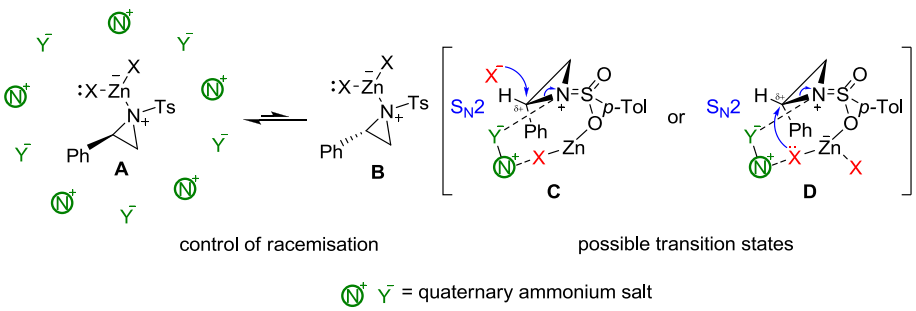
to afford haloalkylamines with excellent enantioselectivity.[6] We believe that the dipolar quaternary ammonium salt stabilizes the dipolar intermediate generated from the interaction of aziridine with the LA and the racemization of the starting aziridine was controlled affording haloalkylamines in excellent *ee* (up to 99%).

We anticipated that non-nucleophilic quaternary ammonium salts could be utilized in controlling the racemization process and it could be possible to obtain the ring opening products from aziridines with a nucleophilic Lewis acid with higher enantioselectivity (scheme 5).

Next, to control the racemization we performed the same reaction in the presence of a quaternary ammonium salt, expecting the improvement in yield, efficiency and stereoselectivity. For this purpose, tetrabutylammonium salts with non-nucleophilic counter anions viz. tetrabutylammonium hydrogensulphfate (TBAHS), tetrabutylammonium triflate (TBAT), tetrabutylammonium perchlorate (TBAPC) and tetrabutylammonium hexafluorophosphate (TBAHFP) were used. When (*R*)-**1a** was treated with $ZnCl_2$ in the

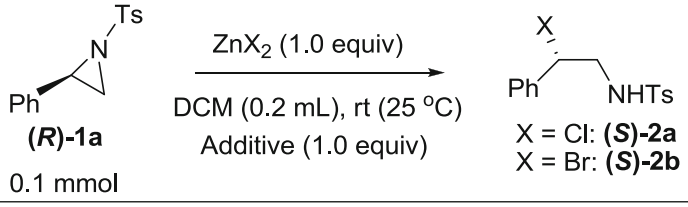



**Scheme 4.** Proposed mechanism for the ring-opening of (*R*)-**1a** by Zn(II) halides.




**Scheme 5.** Stabilization of intermediate **A** with quaternary ammonium salt.

**Table 6.** Ring-opening of (*R*)-**1a** by $ZnX_2$ in the presence of quaternary ammonium salts.




| Entry | $ZnX_2$ | Additive | X | Time | Yield (%) | er |
|---|---|---|---|---|---|---|
| 1 | $ZnCl_2$ | - | Cl | 3 h | 85 | 69:31 |
| 2 | $ZnCl_2$ | TBAHS | Cl | 20 min | 95 | 91:9 |
| 3 | $ZnBr_2$ | TBAHS | Br | 10 min | 98 | 95:5 |
| 4 | $ZnCl_2$ | TBAT | Cl | 1.5 h | 92 | 67:33 |
| 5 | $ZnCl_2$ | TBAPC | Cl | 45 min | 92 | 50:50 |
| 6 | $ZnCl_2$ | TBAHFP | Cl | 1 h | 80 | 50:50 |

**Additives:** *n*-$Bu_4N^{\oplus}$ $HSO_4^{\ominus}$ (TBAHS); *n*-$Bu_4N^{\oplus}$ $OTf^{\ominus}$ (TBAT); *n*-$Bu_4N^{\oplus}$ $ClO_4^{\ominus}$ (TBAPC); *n*-$Bu_4N^{\oplus}$ $PF_6^{\ominus}$ (TBAHFP)

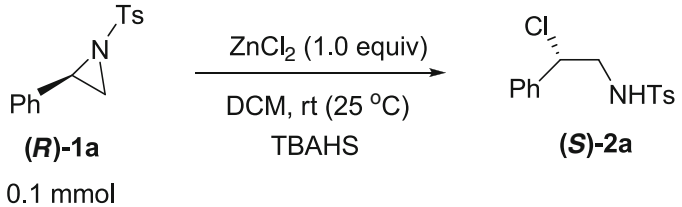
presence of TBAHS (100 mol%) in DCM medium at room temperature, to our delight, reaction was completed within 20 min affording the chloroamine (*S*)-**2a** in 95% yield and the *er* enhanced to 91:9 (entry 2, table 6). It is worth noting that similar reaction of (*R*)-**1a** with $ZnCl_2$ in the absence of TBAHS took longer time for completion (3 h) and the product (*S*)-**2a** was obtained with poor ee and lesser yield (table 6, entry 1). Best results were obtained with $ZnBr_2$ in the presence of TBAHS to afford bromoamine (*S*)-**2b** in 98% yield within 10 min with the *er* 95:5 (entry 3, table 6). Use of other quaternary ammonium salts (TBAT, TBAPC, TBAHFP) had the adverse effect on stereoselectivity, however, rate of the reaction was enhanced as compared to the non-catalyzed reactions (entries 4–6, table 6). TBAHS was found to be the best quaternary ammonium salt (table 6), in terms of controlled racemization, enhanced reactivity and selectivity.

With lesser amounts of TBAHS (<100 mol%), the stereoselectivity dropped down, although it was unchanged when 200 mol% TBAHS was used. Details of the studies related to the effect of concentration of the quaternary ammonium salt on the reaction outcome is shown in table 7.

## 4. Conclusion

In conclusion, we have developed a simple strategy for the synthesis of racemic and non-racemic $\beta$-halo amines via the ring opening of *N*-tosyl aziridines with Zn (II) halides. We have demonstrated that the ring

**Table 7.** Study on the ring-opening of (*R*)-**1a** by $ZnCl_2$ in the presence of TBAHS.




| Entry | Amount of TBAHS (mol%) | Amount of DCM (mL) | Time | Yield (%) | er |
|---|---|---|---|---|---|
| 1 | 10 | 0.2 | 2 h | 89 | 70:30 |
| 2 | 50 | 0.2 | 1.5 h | 88 | 86:14 |
| 3 | 100 | 0.2 | 20 min | 95 | 91:9 |
| 4 | 200 | 0.2 | 1.25 h | 95 | 91:9 |
| 5 | 100 | 0.5 | 35 min | 91 | 90:10 |
| 6 | 100 | 1.0 | 1.5 h | 91 | 89:11 |
| 7 | 100 | 1.5 | 2 h | 93 | 83:17 |
| 8 | 100 | 2.0 | 2.25 h | 95 | 82:18 |

opening step does proceed through an $S_N2$ type path way instead of a dipolar intermediate. To improve the enantioselectivity of the products the partial racemization of the starting aziridine and the product halo amines was controlled by employing a quaternary ammonium salt as an additive.

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