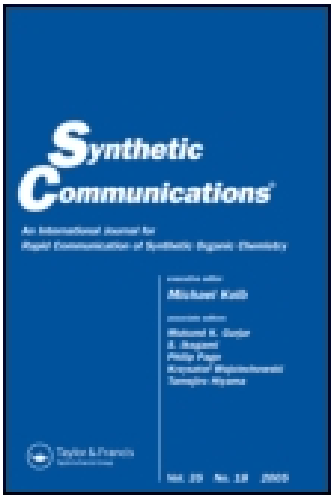


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

$ZrCl_4$-Catalyzed Synthesis of β-Aminosulfides from Aziridines and Thiols

Barahman Movassagh [a] & Amir Rakhshani [a]

[a] Department of Chemistry , K. N. Toosi University of Technology , Tehran , Iran

Accepted author version posted online: 27 Oct 2011.Published online: 26 Mar 2012.

To cite this article: Barahman Movassagh & Amir Rakhshani (2012) $ZrCl_4$-Catalyzed Synthesis of β-Aminosulfides from Aziridines and Thiols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 42:14, 2121-2130, DOI: 10.1080/00397911.2011.553698

To link to this article: http://dx.doi.org/10.1080/00397911.2011.553698

Synthetic Communications®, 42: 2121–2130, 2012

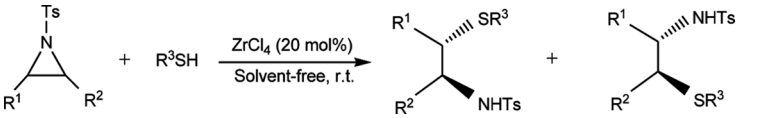
ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.553698

Taylor & Francis
Taylor & Francis Group

$ZrCl_4$-CATALYZED SYNTHESIS OF β-AMINOSULFIDES FROM AZIRIDINES AND THIOLS

Barahman Movassagh and Amir Rakhshani
Department of Chemistry, K. N. Toosi University of Technology, Tehran, Iran

GRAPHICAL ABSTRACT



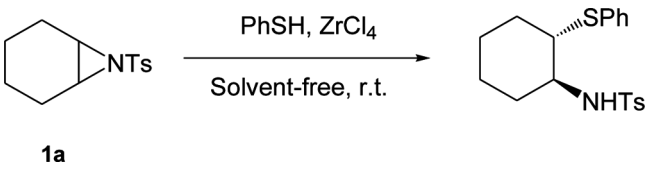
Abstract *A simple and efficient synthesis of* β*-aminosulfides has been introduced by ring opening of aziridine rings with aromatic thiols in the presence of zirconium(IV) chloride under solvent-free conditions at room temperature.*

Keywords β-Aminosulfides; aziridines; thiols; zirconium(IV) chloride

INTRODUCTION

Aziridines are versatile precursors for the synthesis of various nitrogen-containing bioactive molecules, such as amino acids,[1] alkaloids,[2] heterocycles,[3] aza sugars,[1b,4] and natural products.[1b] Because of their ring strain and high reactivity, reactions of aziridines with various nucleophiles lead to highly regio- and stereoselective ring-opened products. Therefore, there is significant current interest in the ring-opening reactions of aziridines. In particular, the cleavage of aziridines with thiols is interesting because the resultant β-aminosulfides are important building blocks for the synthesis of many bioactive molecules.[5] These compounds have been prepared previously by ring opening of aziridines with thiols, Lewis acids, bases, and catalysts.[6] However, many of these procedures involve the use of strongly acidic or basic conditions, harsh conditions, the use of stoichiometric amounts of catalysts, and an excess amount of thiols and anhydrous conditions. Thus, the development of an efficient and mild catalytic process for the synthesis of β-aminosulfides is in demand.

Received November 19, 2010.
Address correspondence to Barahman Movassagh, Department of Chemistry, K. N. Toosi University of Technology, P.O. Box 16315-1618, Tehran, Iran. E-mail: bmovass1178@yahoo.com



Scheme 1. $ZrCl_4$-catalyzed reaction of *N*-tosyl aziridine and thiophenol.

RESULTS AND DISCUSSION

Recently, zirconium(IV) chloride has been used as a safe, stable, inexpensive, environmentally friendly, and efficient Lewis acid in many organic transformations.[7] Therefore, we investigated a simple, mild, and efficient method for $ZrCl_4$-catalyzed ring opening of *N*-substituted aziridines under solvent-free conditions. To the best of our knowledge, this is the first report on the use of zirconium(IV) chloride as a catalyst for the synthesis of β-aminosulfides.

Initially, a model reaction of *N*-tosyl aziridine **1a** (1.0 mmol) and thiophenol (1.2 mmol) in the presence of $ZrCl_4$ under dry air and solvent-free conditions at room temperature was planned (Scheme 1); various solvents such as $PhCH_3$, CH_2Cl_2, tetrahydrofuran (THF), CH_3CN, and $CHCl_3$ were also screened for this reaction. The best results were observed under solvent-free conditions.

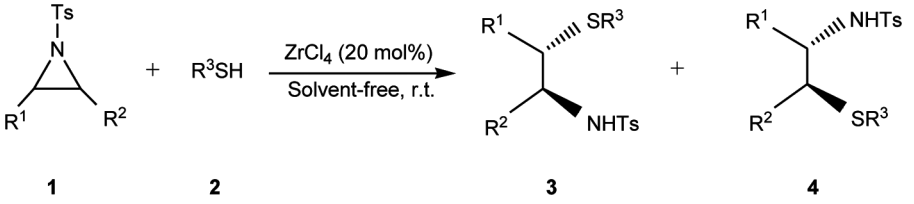
Furthermore, to study the catalyst loading in our model reaction, the procedure was optimized using different molar concentrations of zirconium tetrachloride under solvent-free conditions at room temperature (Table 1). A good yield of the product was observed using 20 mol% of the catalyst. Increased concentration of the catalyst did not improve the result to any greater extent. In one case (Table 1, entry 5), after completion of the reaction, the catalyst was recovered by diluting the reaction mixture with CH_2Cl_2 (6 mL) and reused in subsequent reactions; a gradual decrease in activity was observed, affording 90% and 81% yields over two more cycles.

To probe the generality and scope of this method, a variety of *N*-tosyl aziridines were treated with different thiols in the presence of 20 mol% of $ZrCl_4$ under solvent-free conditions at room temperature (Scheme 2). The reaction conditions are mild, and no side products or decomposition of the products were observed. The results are shown in Table 2. As can be seen from Table 2, while treatment of aromatic thiols with various *N*-tosyl aziridines in general are fast (25–85 min) and

Table 1. Effect of catalyst loading on the model reaction of **1** and thiophenol[a]

Entry	$ZrCl_4$ (mol %)	Yield of **2a** (%)
1	—	38[b]
2	5	35
3	10	39
4	15	51
5	20	95
6	25	92
7	30	90

[a]Reaction conditions: **1** (1 mmol), thiophenol (1.2 mmol), reaction time 60 min, rt.
[b]Reaction time = 6 h.



Scheme 2. $ZrCl_4$-promoted synthesis of *β*-aminosulfides.

give the corresponding β-aminosulfides in good to excellent yields, aliphatic thiols give the corresponding products in trace amounts under the same conditions (Table 2, entries 5 and 6). All the reactions with bicyclic aziridines (Table 2, entries 1–6) gave products with *anti*-stereochemistry, which were confirmed by the coupling constants ($J = 9.9$ Hz) of the two cyclic methine hydrogens at the *trans* positions ($\delta = 3.01$). The reactions of styrene- and 4-methylstyrene *N*-tosyl aziridines with thiols were completely regioselective with the attack of thiols on the more hindered (benzylic) position (Table 2, entries 7–13); this is due to stabilization of developing positive charge at the benzylic position of aziridine. In the cleavage of *N*-tosyl-2-alkyl aziridines (Table 2, entries 14–17), minor (4–8%) preferential cleavage at low hindered (terminal) aziridine-ring carbon was observed. A proposed mechanism is depicted in Scheme 3.

In conclusion, $ZrCl_4$ is found to be a useful and efficient alternative to other conventional Lewis acids for the ring-opening reactions of aziridines with aromatic thiols, leading to the synthesis of β-aminosulfides in good to excellent yields. The specific advantages of this methodology are that the reactions are performed under mild and solvent-free conditions within short times. The lack of appreciable toxicity [LD_{50} ($ZrCl_4$, oral rat) $= 1688\ mg \cdot Kg^{-1}$][8] and low cost of $ZrCl_4$ are consistent with increasing environmental concerns.

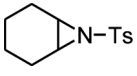
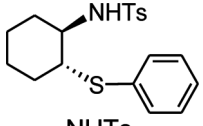
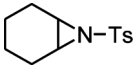
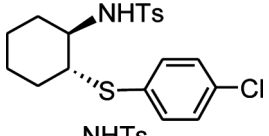
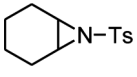
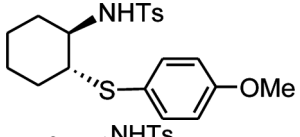
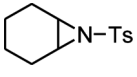
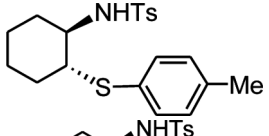
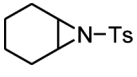
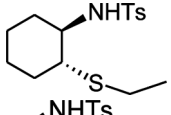
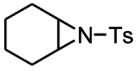
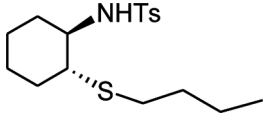
EXPERIMENTAL

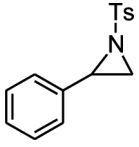
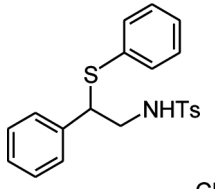
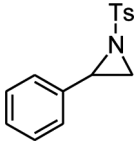
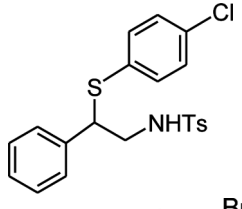
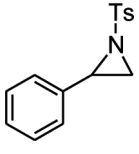
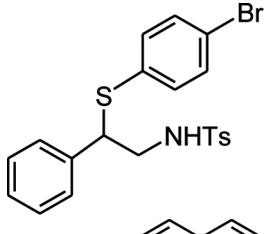
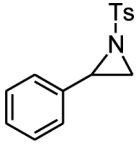
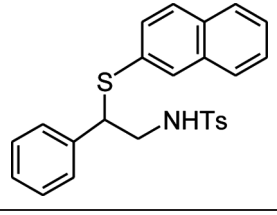
Chemicals were purchased from Merck. Preparative thin-layer chromatography (TLC) was used for purification of β-aminosulfides using silica gel $60\ PF_{254+366}$ coated on 20×20-cm glass plates. Melting points were recorded on a Buchi B-540 apparatus and are uncorrected. Infrared (IR) spectra were recorded on an ABB FTLA 2000 instrument. NMR spectra were recorded with either a Bruker AQS-300 or Bruker DRX-500 spectrometer with nominal frequencies of 300 and 500 MHz for proton or 75 and 125 MHz for carbon, respectively, in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard.

Typical Procedure: Preparation of 2-(4-Methoxyphenylthio)-2-*p*-tolyl-*N*-tosylethanamine (Table 2, Entry 13)

N-(*p*-Toluenesulfonyl)-2-*p*-tolyl aziridine (287 mg, 1.0 mmol) and 4-methoxybenzenethiol (168 mg, 1.2 mmol) were mixed together, and anhydrous $ZrCl_4$ (47 mg, 20 mol%) was added. The solution was stirred at room temperature under a dry air atmosphere for 40 min. After the completion of the reaction, monitored

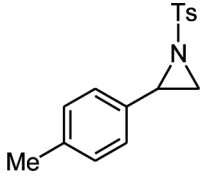
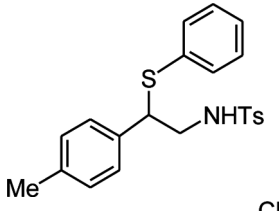
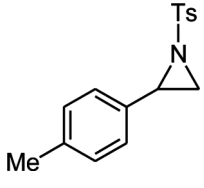
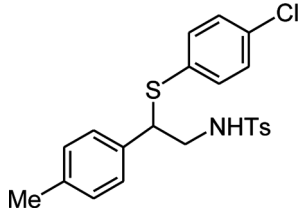
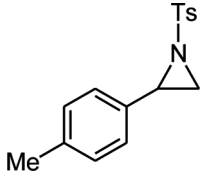
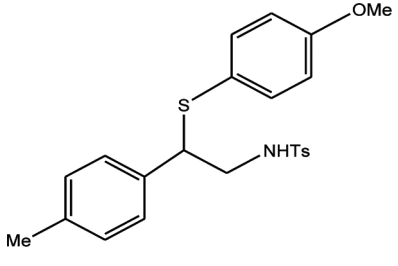
Table 2. Synthesis of β-aminosulfides catalyzed by $ZrCl_4$ under solvent-free conditions

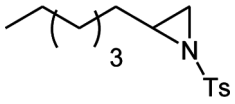
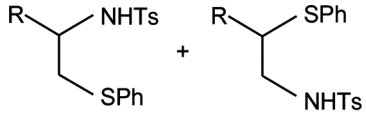
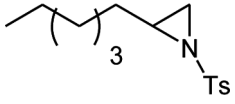
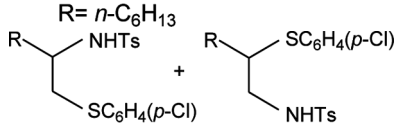
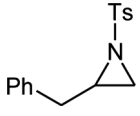
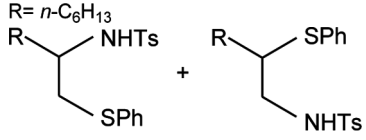
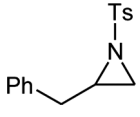
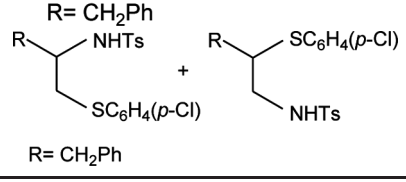
Entry	Aziridine	Thiol	Product	Time (min)	Yield (%)[a,b]
1		PhSH		25	95[6g]
2		4-ClC_6H_4SH		50	92[6h]
3		4-$MeOC_6H_4SH$		85	99[6g]
4		4-MeC_6H_4SH		45	97[6i]
5		CH_3CH_2SH		360	Trace
6		$CH_3(CH_2)_3SH$		360	Trace

7		PhSH		30	95[6g]
8		4-ClC_6H_4SH		35	91[6h]
9		4-BrC_6H_4SH		50	88[6j]
10		Naphthalene-2-thiol		60	90[6g]

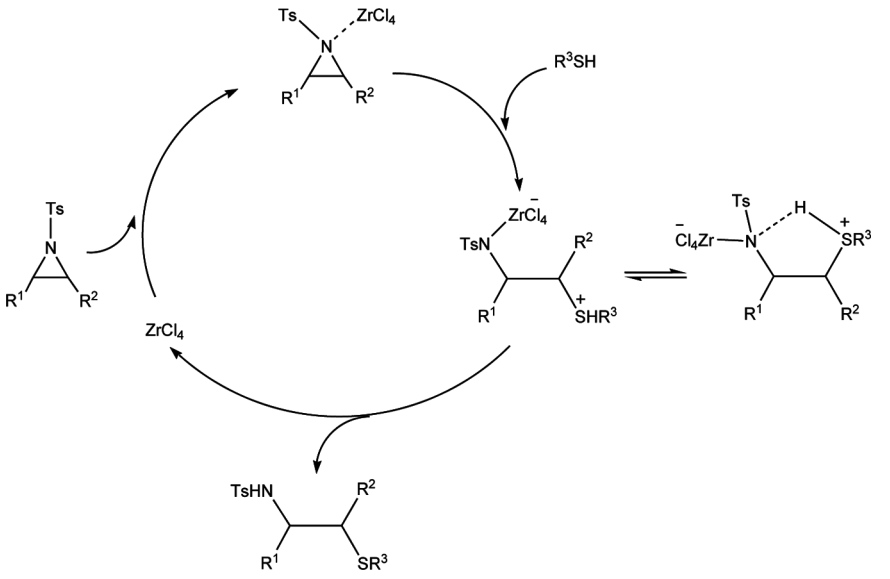
(*Continued*)

Table 2. Continued

Entry	Aziridine	Thiol	Product	Time (min)	Yield (%)[a,b]
11		PhSH		30	95[6h]
12		4-ClC_6H_4SH		35	93[6j]
13		4-$MeOC_6H_4SH$		40	96[6g]

14		PhSH		35	95[6h]
15		4-ClC_6H_4SH		40	89[6g]
16		PhSH		50	90[6k]
17		4-ClC_6H_4SH		65	85[9]

[a]Isolated yields.
[b]References given for known compounds.



Scheme 3. Plausible mechanism for the $Zrcl_4$-catalyzed synthesis of β-aminosulfides.

by TLC, the reaction mixture was subjected to preparative TLC (silica gel, eluent *n*-hexane/EtOAc = 3:1) to obtain the pure product (412 mg, 96%) as colorless crystals, mp 99–101 °C; IR (KBr): $\nu_{max} = 3291$, 3019, 2927, 1591, 1494 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H), 2.45 (s, 3H), 3.33 (t, $J = 7.5$ Hz, 2H), 3.79 (s, 3H), 3.92 (t, $J = 7.5$ Hz, 1H), 4.74 (t, $J = 6.1$ Hz, 1H), 6.73 (d, $J = 8.6$ Hz, 2H), 6.93 (d, $J = 8.1$ Hz, 2H), 7.06 (d, $J = 7.9$ Hz, 2H), 7.14 (d, $J = 8.6$ Hz, 2H), 7.27 (d, $J = 7.9$ Hz, 2H), 7.63 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.1$, 21.6, 46.7, 53.0, 55.3, 114.5, 122.9, 127.1, 127.7, 129.4, 135.2, 136.0, 136.9, 137.7, 143.5, 159.9.

Supplementary Data

2-(Phenylthio)-*N*-tosylcyclohexanamine (Table 2, Entry 1)

White crystals; mp 130–131 °C; IR (KBr): $\nu_{max} = 3276\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.18$–1.43 (m, 4H), 1.55–1.61 (m, 2H), 1.99–2.04 (m, 1H), 2.12–2.41 (m, 1H), 2.42 (s, 3H), 2.91–3.04 (m, 2H), 5.46 (d, $J = 4.4$ Hz, 1H), 7.22–7.37 (m, 7H), 7.76 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.6$, 23.2, 24.4, 31.5, 32.1, 51.2, 55.2, 127.3, 127.6, 128.9, 129.6, 129.7, 132.9, 137.3, 143.3.

2-Phenyl-2-(phenylthio)-*N*-tosylethanamine (Table 2, Entry 7)

Light yellow oil; IR (neat): $\nu_{max} = 3291\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H), 3.40 (t, $J = 7.6$ Hz, 2H), 4.16 (t, $J = 7.6$ Hz, 1H), 4.86 (t, $J = 6.7$ Hz, 1H), 7.12-7.33 (m, 12H), 7.64 (d, $J = 9.8$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.6$, 47.1, 52.5, 127.1, 127.8, 127.9, 128.1, 128.9, 129.0, 129.8, 132.6, 133.1, 136.9, 138.3, 143.6.

2-(4-Chlorophenylthio)-2-phenyl-*N*-tosylethanamine (Table 2, Entry 8)

Light yellow oil; IR (neat): $\nu_{max} = 3291\,cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.47$ (s, 3H), 3.39–3.44 (m, 2H), 4.17 (t, $J = 7.5$ Hz, 1H), 4.71 (t, $J = 6.3$ Hz, 1H), 7.15–7.33 (m, 11H), 7.67 (d, $J = 8.2$ Hz, 2H).

2-(Phenylthio)-2-*p*-tolyl-*N*-tosylethanamine (Table 2, Entry 11)

Yellow oil; IR (neat): $\nu_{max} = 3289\,cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H), 2.44 (s, 3H), 3.29–3.44 (m, 2H), 4.13 (t, $J = 7.7$ Hz, 1H), 4.80 (t, $J = 6.3$ Hz, 1H), 7.03 (d, $J = 8.2$ Hz, 2H), 7.09 (d, $J = 8.2$ Hz, 2H), 7.23–7.28 (m, 7H), 7.64 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.1, 21.6, 47.2, 52.1, 127.1, 127.7, 127.8, 129.0, 129.6, 129.8, 132.4, 133.3, 135.1, 136.9, 137.9, 143.5.

2-(4-Chlorophenylthio)-2-*p*-tolyl-*N*-tosylethanamine (Table 2, Entry 12)

Yellow oil; IR (neat): $\nu_{max} = 3294\,cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.31$ (s, 3H), 2.40 (s, 3H), 3.27 (t, $J = 7.1$ Hz, 2H), 4.09 (t, $J = 7.1$ Hz, 1H), 4.58 (t, $J = 7.1$ Hz, 1H), 6.96–7.18 (m, 8H), 7.27 (d, $J = 8.2$ Hz, 2H), 7.59 (d, $J = 8.2$ Hz, 2H).

1-(4-Chlorophenylthio)-*N*-tosyloctan-2-amine (Table 2, Entry 15)

Yellow oil; IR (neat): $\nu_{max} = 3280\,cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (t, $J = 7.1$ Hz, 3H), 1.12–1.33 (m, 8H), 1.37–1.62 (m, 2H), 2.43 (s, 3H), 2.61 (dd, $J = 10.4$, 7.0 Hz, 1H), 3.05 (dd, $J = 10.3$, 4.2 Hz, 1H), 3.22–3.35 (m, 1H), 4.71 (d, $J = 4.5$ Hz, 1H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.26 (d, $J = 8.2$ Hz, 2H), 7.39 (d, $J = 8.2$ Hz, 2H), 7.68 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.3$, 21.6, 22.7, 25.4, 28.6, 31.9, 33.6, 39.8, 52.8, 114.4, 122.8 127.0, 129.7, 132.3, 137.8, 144.4, 159.9.

ACKNOWLEDGMENT

We thank the K. N. Toosi University of Technology Research Council for financial support of this work.

REFERENCES

1. (a) McCoull, W.; Davis, F. A. Recent synthetic applications of chiral aziridines. *Synthesis* **2000**, 1347–1365; (b) Tanner, D. Chiral aziridines—Their synthesis and use in stereoselective transformations. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.
2. Hudlicky, T.; Luna, H.; Price, J. D.; Rulin, F. Microbial oxidation of chloroaromatics in the enantiodivergent synthesis of pyrrolizidine alkaloids—Trihydroxyheliotridanes. *J. Org. Chem.* **1990**, *55*, 4683–4687.
3. (a) Tanner, D.; He, H. M. Enantioselective routes toward 1-β-methylcarbapenems from chiral aziridines. *Tetrahedron* **1992**, *48*, 6079–6086; (b) Dureault, A.; Tranchepain, I.; Depezay, J. C. Nucleophilic opening of chiral bis(aziridines): A route to enantiomerically pure α-amino aldehydes or acids and polysubstituted piperidines. *J. Org. Chem.* **1989**, *54*, 5324–5330.

4. (a) Chakraborty, T. K.; Jaiprakash, S. Synthesis of 1,7-diamino-1,2,6,7-tetradeoxy-2,6-imino-D-glycero-D-ido-heptitol by intramolecular amination of aziridine ring. *Tetrahedron Lett.* **1997**, *38*, 8899–8902; (b) Joly, G. J.; Peeters, K.; Mao, H.; Brossette, T.; Hoornaert, G. J.; Compernolle, F. Use of the N-tosyl-activated aziridine 1,2-dideoxy-1,2-iminomannitol as a synthon for 1-deoxymannojirimycin analogues. *Tetrahedron Lett.* **2000**, *41*, 2223–2226.
5. (a) Ingenitio, R.; Bianchi, E.; Fattori, D.; Pessi, A. Solid-phase synthesis of peptide C-terminal thioesters by Fmoc/t-Bu chemistry. *J. Am. Chem. Soc.* **1999**, *121*, 11369–11374; (b) Bae, J. H.; Shin, S. H.; Park, C. S.; Lee, W. K. Preparation of cysteinol derivatives by highly regioselective ring opening of nonactivated chiral aziridines by thiols. *Tetrahedron* **1999**, *55*, 10041–10046; (c) Adams, B.; Beresford, K. J. M.; Whyte, S. M.; Young, D. W. Stereochemistry of the reaction of the inhibitor β-chloroalanine with mercaptoethanol, a β-substitution reaction catalysed by an aminotransferase. *J. Chem. Soc., Chem. Commun.* **2000**, 619–620.
6. (a) Fan, R.-H.; Hou, X.-L. Efficient ring-opening reaction of epoxides and aziridines promoted by tributylphosphine in water. *J. Org. Chem.* **2003**, *68*, 726–730; (b) Katagiri, T.; Takahashi, M.; Fujiwara, Y.; Ihara, H.; Uneyama, K. General syntheses of optically active α-trifluoromethylated amines via ring-opening reactions of N-benzyl-2-trifluoromethylaziridine. *J. Org. Chem.* **1999**, *64*, 7323–7329; (c) Carreaux, F.; Dureault, A.; Depezay, J. C. Tartaric acid–derived aziridines as chiral precursors of 3-amino-3-deoxy and 2-amino-2-deoxy tetroses—An efficient approach towards mugineic acid. *Synlett.* **1992**, 527–529; (d) Wu, J.; Hou, X.-L.; Dai, L. X. An efficient procedure for cleavage of aziridines with various thiols promoted by $ZnCl_2$. *J. Chem. Soc., Perkin Trans. 1/I* **2001**, 1314–1317; (e) Wang, Z.; Sun, X.; Ye, S.; Wang, W.; Wang, B.; Wu, J. Quinine-catalyzed enantioselective desymmetrization of *meso*-aziridines with benzenethiols. *Tetrahedron Asymmetry* **2008**, *19*, 964–969; (f) Somi Reddy, M.; Narender, M.; Rao, K. R. Regioselective ring opening of aziridines with thiophenol in the presence of β-cyclodextrin in water. *Synlett.* **2005**, 489–490; (g) Kamal, A.; Rajasekhar Reddy, D.; Rajendar. Polyethylene glycol (PEG) as an efficient recyclable medium for the synthesis of β-amino sulfides. *Tetrahedron Lett.* **2006**, *47*, 2261–2264; (h) Das, B.; Ramu, R.; Ravikanth, B.; Reddy, K. R. Regioselective ring opening of aziridines with potassium thiocyanate and thiols using sulfated zirconia as a heterogeneous recyclable catalyst. *Tetrahedron Lett.* **2006**, *47*, 779–782; (i) Luo, Z.-B.; Hou, X.-L.; Dai, L.-X. Enantioselective desymmetrization of meso-N-sulfonylaziridines with thiols. *Tetrahedron: Asymmetry* **2007**, *18*, 443–446; (j) Yadav, J. S.; Reddy, P. V. S.; Baishya, G.; Reddy, P. V.; Harshavardhan, S. J. Bismuth triflate as novel and efficient catalyst for the synthesis of β-aminosulfides. *Synthesis* **2004**, 1854–1858; (k) Wu, J.; Sun, X.; Li, Y. DABCO: An efficient organocatalyst in the ring-opening reactions of aziridines with amines or thiols. *Eur. J. Org. Chem.* **2005**, 4271–4275.
7. (a) Smitha, G.; Reddy, S. C. $ZrCl_4$-catalyzed aza-Michael addition of carbamates to enones: Synthesis of Cbz-protected β-amino ketones. *Catal. Commun.* **2007**, *8*, 434–436; (b) Kumar, V.; Kaur, S.; Kumar, S. $ZrCl_4$-catalyzed highly selective and efficient Michael addition of heterocyclic enamines with α, β-unsaturated olefins. *Tetrahedron Lett.* **2006**, *47*, 7001–7005; (c) Chakraborti, A. K.; Kondaskar, A. $ZrCl_4$ as a new and efficient catalyst for the opening of epoxide rings by amines. *Tetrahdron Lett.* **2003**, *44*, 8315–8319; (d) Smitha, G.; Chandrasekhar, C.; Reddy, S. Applications of zirconium (IV) chloride in organic synthesis. *Synthesis* **2008**, 829–855.
8. (a) Lewis, R. J. S. R. *Dangerous Properties of Industrial Materials*, 8th ed.; vol. 3; Van Nostrand Reinhold: New York, 1989, (b) Emsley, J. *The Elements*; 3rd ed., Clarendon: Oxford, 1988.
9. Ganesh, V.; Chandrasekaran, S. One-pot synthesis of β-amino/β-hydroxy selenides and sulfides from aziridines and epoxides. *Synthesis* **2009**, 3267–3278.