SPECIAL FOCUS ON NONRACEMIC AZIRIDINES AND OXAZOLINES

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Aziridines and Oxazolines: Valuable Intermediates in the Synthesis of Unusual Amino Acids

Highlights of the Chemistry of Enantiomerically Pure Aziridine-2-carboxylates

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*Won Koo Lee**
Department of Chemistry
Sogang University
Seoul 121-742, Korea
Email: wonkoo@sogang.ac.kr

*Hyun-Joon Ha**
Department of Chemistry
Hankuk University of Foreign Studies
Yongin, Kyunggi-Do 449-791, Korea
Email: hjha@hufs.ac.kr

Outline

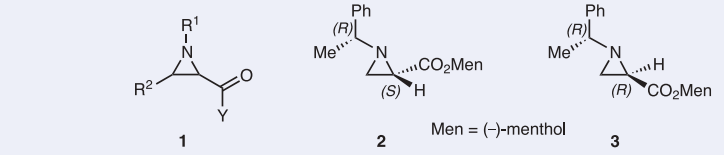
1. Introduction

The chemistry of enantiomerically pure substituted aziridines has been the subject of extensive research, because of their versatility in the synthesis of various nitrogen-containing molecules. Owing to the ring strain in aziridines, regio- and stereoselective ring-opening reactions with various nucleophiles, including carbon and heteroatoms, proceed smoothly and allow access to various nitrogen-containing compounds with predictable stereochemistry. In particular, the ring-opening reactions of enantiomerically pure aziridine-2-carboxylates provide either α- or β-amino esters and their derivatives. Many of these are biologically active and can serve as precursors for the synthesis of other biologically important compounds. Most such ring-opening reactions have focused on N-activated aziridines possessing a functional group that conjugatively stabilizes the lone-pair electrons on the nitrogen. There have been few reports on the ring-opening reactions of *N*-alkylaziridines.

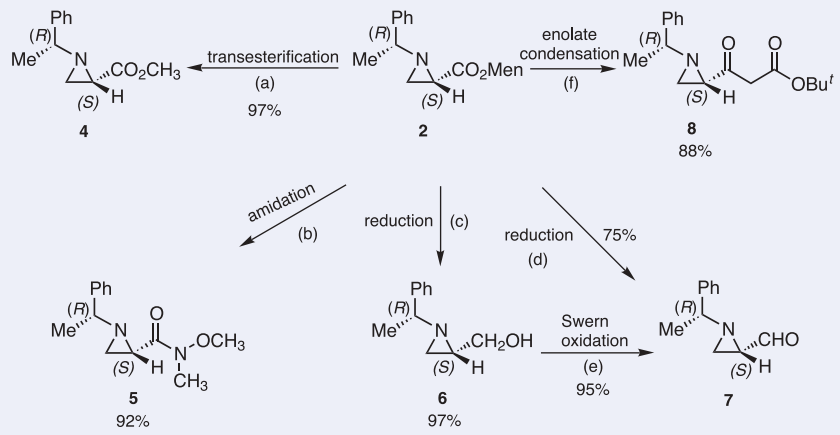
A number of surveys of the chemistry of chiral aziridines have been published.[1] Aziridines **1** in which R^2 is an alkyl or aryl group can be easily prepared, mainly as the trans isomers, from the corresponding imines and olefins. This is not the case for simple aziridine-2-carboxylates in which R^2 = H. The conformational stability and reactivity of the aziridine ring toward nucleophiles are dependent on the nature of R^1.[1e] When R^1 is an electron-withdrawing group such as carboxamide or sulfonamide, the aziridine becomes quite reactive, which is consistent with conformational destabilization of the aziridine ring. However, if R^1 is an electron-donating group, especially alkyl, the opposite is observed: the aziridine ring conformation is more stable and less reactive toward nucleophiles. This review focuses on the preparation and utilization of *N*-(*R*)-α-methylbenzylaziridine-2-carboxylates **2** and **3** and their derivatives.

2. Preparation of Enantiomerically Pure Aziridine-2-carboxylates

Enantiomerically pure aziridine-2-carboxylates can be prepared from suitably protected chiral serine.[2] Asymmetric synthesis can be achieved by either the

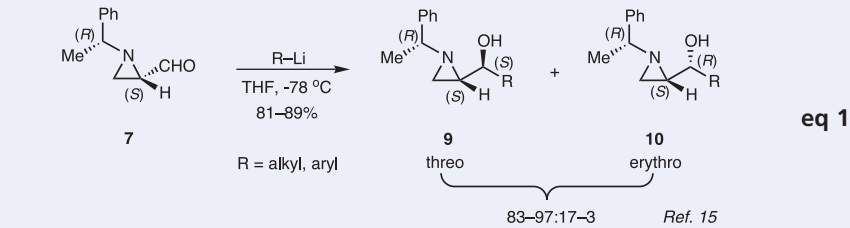


1 2 3



Representative reaction conditions: (a) Mg, CH_3OH, reflux, 2 h; (b) *N,O*-dimethylhydroxylamine hydrochloride, $AlMe_3$, CH_2Cl_2, -10 °C, 2 h; (c) $LiAlH_4$, Et_2O, 0 °C, 1 h; (d) DIBAL-H, toluene, -78 °C, 2 h; (e) DMSO, oxalyl chloride, CH_2Cl_2, NEt_3, -78 °C, 1.5 h; (f) LiHMDS, $CH_3CO_2Bu^t$, THF, -78 °C, 30 min.

Scheme 1. Elaboration of the C-2 Carboxylate Group.



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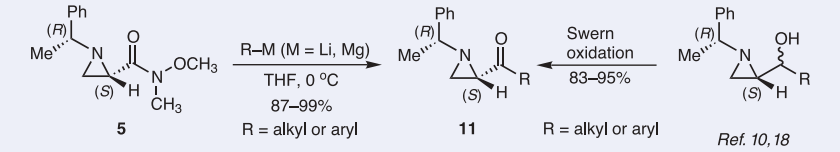
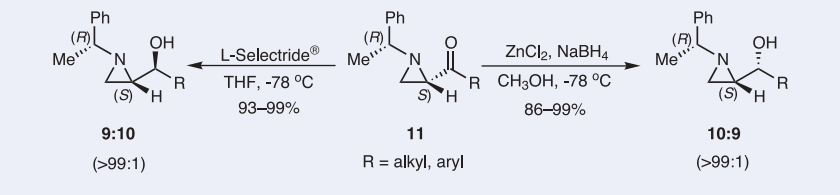


Scheme 2. Syntheses of Enantiomerically Pure α-Amino Ketone **11**.



Scheme 3. Improved Diastereoselectivities in the Preparation of α-Amino Alcohols **9** and **10**.

Gabriel–Cromwell reaction of camphorsultam[3] or imidazolidin-2-one[4], or by nitrene addition to α,β-unsaturated acid derivatives bearing a chiral auxiliary.[5] The aza-Darzens reaction of *N*-bromoacetylcamphorsultam has also been used and gives high stereoselectivities.[6] A chiral phase-transfer catalyst mediated the reaction between *N*-arylhydroxamic acids and *tert*-butyl acrylates to give *N*-arylaziridine-2-carboxylates in 16–61% ee's.[7] Chromatographic separation or fast ester cleavage with a strong base[8] can be used to resolve a diastereomeric mixture of aziridine-2-carboxylates bearing a chiral group on the nitrogen. Lipase-mediated stereoselective transesterification[9] or ammonolysis[10] of aziridine-2-carboxylates have also been developed. However, none of the preceding methods is suitable for the multikilogram-scale preparation of aziridine-2-carboxylates, since most are not stereoselective and/or require a chiral auxiliary or chromatographic separation. Recently, we have achieved the selective crystallization and isolation of each diastereomer of 1-(1'-α-methylbenzyl)-aziridine-2-carboxylic acid menthol esters.[11] The *N*-α-methylbenzyl group differentiates the stereoisomers at the C-2 position of the aziridine and controls the reactivity in ring-opening reactions. Furthermore, it serves as a good nitrogen protecting group, which tolerates various chemical transformations and is easy to remove either by hydrogenolysis, metal–ammonia reduction, or treatment at the carbamate stage with methanesulfonic acid and anisole.

3. Elaboration of the C-2 Carboxylate Group

The C-2 menthol ester group of chiral aziridine **2** can be transesterified into the methyl, **4**, or ethyl ester upon treatment with 1.0 equivalent of Mg in methanol or ethanol (**Scheme 1**). The reaction of **2** with Weinreb's amine hydrochloride and $AlMe_3$ in CH_2Cl_2 provides the corresponding Weinreb amide **5** in high yield.[12] We have obtained the primary alcohol **6** in almost quantitative yield by reduction of **2** with $LiAlH_4$ or $NaBH_4$. We have also prepared the α-amino aldehyde **7** in high yield by careful reduction of **2** with DIBAL-H at -78 °C or by Swern oxidation of primary alcohol **6**. α-Amino aldehydes usually have a low configurational stability; however, the presence of the three-membered ring at the α position of **7** makes the C-2 proton nonenolizable and allows the purification of **7** using silica gel chromatography. We have found that enantiomerically pure aziridine-2-carbox-

aldehyde **7** can be stored in the refrigerator for months without losing its stereochemical integrity. We believe that **7** is the most configurationally stable α-amino aldehyde reported to date. The reaction of aziridine-2-carboxylate **2** with enolates provides β-keto esters **8** in high yields.[13]

Vicinal amino alcohol units are found in many important natural products and biologically active compounds including ephedra alkaloids and sphingolipids bearing a distinctive sphingoid backbone.[14] The reaction of amino aldehyde **7** with various organometallic reagents is expected to yield a diastereomeric mixture of two aziridine-2-methanols, **9** and **10** (**eq 1**). Alkyl- or aryllithium reagents provide better stereoselectivity in the addition reactions than Grignard reagents, and increasing the steric requirement around the nucleophilic center results in better stereoselectivity.[15] The diastereoselectivity of the addition reaction of organolithium reagents to enantiomerically pure **7** varies from 1:1 to 32:1 in favor of **9**, depending on the reaction conditions (source of the organometallic reagent, solvent, and the presence of additional lithium salt).

We found, however, a better way to increase the diastereomeric ratio of the secondary alcohols by stereoselectively reducing the corresponding α-amino ketones, **11**, with a suitable hydride reducing agent. In this regard, enantiomerically pure **11** can be precursors for various 1,2-amino alcohols. Ketones **11** are easily prepared by addition of organometallics[12,16] to Weinreb amide **5**,[10] or by oxidation[17] of secondary alcohols of type **9** or **10** (**Scheme 2**).[18]

The reduction of ketones **11** with L-Selectride® in THF provides predominantly the threo isomers **9** through a "Felkin-Anh" transition state. Most of the substrates exhibit high stereoselectivities, except for the 1-hexynyl ketone, which does not have adequate steric requirements due to the geometry of the triple bond at the α position of the ketone.[18] We have recently found that the chelation-controlled reduction of (2*S*)-2-acylaziridines **11** in the presence of the bidentate Lewis acid $ZnCl_2$ and $NaBH_4$ predominantly gives the erythro isomers **10** in high chemical yields (**Scheme 3**).[19]

The excellent stereochemical control of the reaction using $ZnCl_2$ and $NaBH_4$ can be explained by hydride delivery to the chelated intermediate (**Figure 1**). Ab initio calculations showed this intermediate to be the most stable form, lying at least 30 kcal/mol below the other local minimum structures. This chelated structure appears to be stabilized by strong interactions of the empty *d* orbitals of Zn^{2+} with the lone pairs of the nitrogen and oxygen atoms as well as with the aromatic π electrons in the benzene ring.[19]

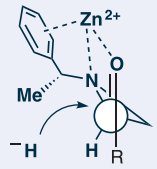
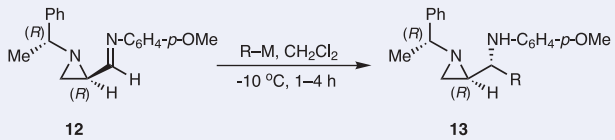
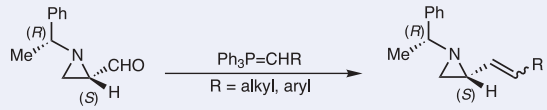


Figure 1. Most Stable Structure of the Chelated Intermediate in the $ZnCl_2$–$NaBH_4$ Reduction of **11**.



eq 2



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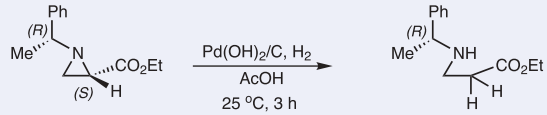
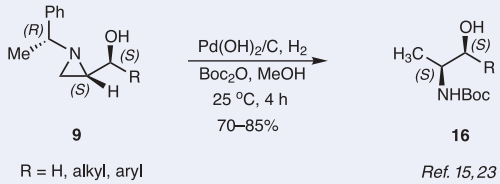


eq 4



eq 5

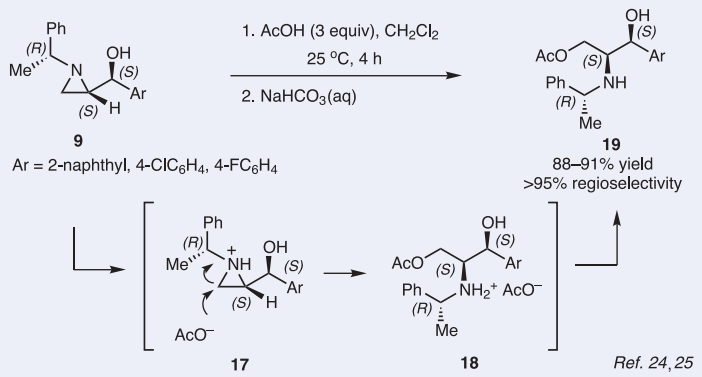
Aziridinylaldimine **12**, formed by the condensation of aldehyde (*R*,*R*)-**7** and *p*-anisidine, readily reacts with organometallics to give the corresponding amines in high yields. In most cases, addition of alkyl or aryl Grignards in the presence of BF_3•OEt_2 yields the chelation-controlled products, **13**, as the major isomers with >95% de's (**eq 2**).[20,21]

The aldehyde group of aziridine-2-carboxaldehyde **7** can be transformed into an olefin by Wittig reaction with suitable ylides (**eq 3**). This reaction efficiently provides various chain-extended 2-vinylaziridines, **14**. The reaction usually gives a mixture of trans and cis olefins, but the Horner–Emmons–Wadsworth conditions lead exclusively to the trans olefin.[22]

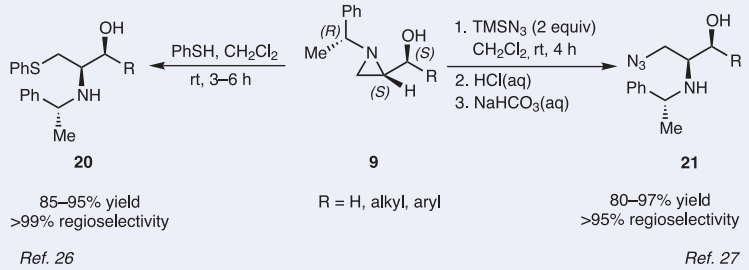
4. Aziridine Ring Opening

4.1. Regioselective Reductive Ring Opening

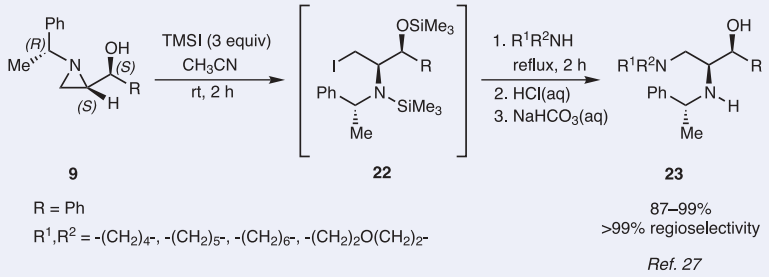
We have found that the regioselectivity of the catalytic hydrogenation of 2-substituted aziridines is controlled by the electronic character of the substituent. With an electron-withdrawing substituent at C-2, the ring-opening reduction takes place at the C(2)–N bond, with a resulting loss of the stereochemistry at C-2, and leads to the β-amino carbonyl derivative **15** highly regioselectively (**eq 4**).[23] However, when the



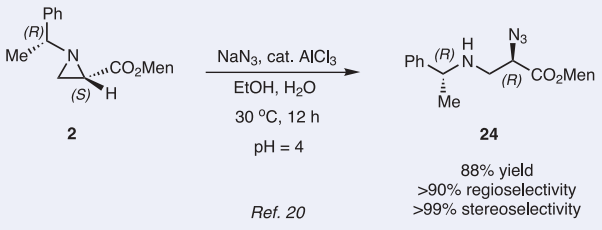
Scheme 4. Regioselective Ring Opening of Nonactivated Aziridines **9**.



Scheme 5. Regioselective Ring Opening with Nitrogen and Sulfur Nucleophiles.



Scheme 6. Regioselective Ring Opening with Iodide.



eq 6

carbonyl group is first reduced to the corresponding alcohol, thus removing the electron-withdrawing character at C-2, ring-opening reduction occurs at the C(3)–N bond and yields β-amino alcohol **16** (**eq 5**).[15,23] The presence of Boc_2O in the reaction medium facilitates cleavage of the α-methylbenzyl group from the nitrogen after ring reduction.[23] Since we can stereoselectively prepare the secondary alcohols **9** and **10** by reduction of ketones **11** (see Scheme 3), both (*S*,*S*)- and (*R*,*S*)-β-amino alcohols (**16** and their diastereomers) can readily be obtained from **11** via aziridinols **9** and **10**.

4.2. Regioselective Ring Opening with Heteroatom Nucleophiles

The regioselective introduction of a heteroatom nucleophile into enantiomerically pure 2-substituted aziridines makes it possible to synthesize polyfunctionalized chiral compounds. The ring strain present in aziridines is responsible for the facile ring-opening reactions of N-activated aziridines that have been cited in the literature.[1] To our knowledge, there has been less extensive reporting on the reactions of nonactivated aziridines. 2-Alkyl-*N*-(α-methylbenzyl)aziridines have an electron-rich nitrogen, and their reactions with strong organometallic nucleophiles do not provide any ring-opened product. However, the addition of Brønsted or Lewis acids facilitates their ring-opening reactions, an example of which is the efficient, room-temperature conversion of *N*-(*R*)-(α-methylbenzyl-2-methanol derivatives **9** into (1*S*,2*S*)-2-amino-1,3-propanediols **19** (**Scheme 4**). The ring-opening reaction is accelerated by protonation of the nitrogen atom with AcOH to form aziridinium salts **17**. The nucleophile, AcO^-, then attacks the aziridine ring at the less sterically hindered C-3 position to form ammonium salts **18**. Subsequent treatment with saturated aqueous $NaHCO_3$ solution affords the ring-opened products **19** in high yields and excellent regioselectivities.[24,25]

Sulfur[26] and azide nucleophiles[27] react similarly (**Scheme 5**). The aziridine ring-opening reaction with thiols usually requires Lewis acid activation even for activated aziridines. However, the nitrogen of nonactivated aziridine **9** is basic enough to pick up a proton from thiols. This proton transfer produces an aziridinium intermediate, which is attacked by the thiolate ion at the less sterically hindered C-3 position to provide the ring-opened product **20** exclusively and in high yield. We hypothesized that the rate-determining step of the ring-opening reaction was proton transfer from the thiol to the ring nitrogen to form the aziridinium intermediate, and that the reaction rate could be influenced by the acidity of the thiol. A kinetic study of the ring-opening reaction showed a good correlation between the acidity of thiols and the reaction rate.[26]

Sodium azide has traditionally been used as a nitrogen nucleophile in most of the ring-opening reactions of activated aziridines. However, the presence of the *N*-(α-methylbenzyl substituent in the nonactivated aziridine **9** requires activation of the basic

nitrogen prior to ring opening. Azidotrimethylsilane serves a dual function: it activates the basic ring nitrogen of **9** and provides a source of N_3^-, which attacks the less substituted position, C-3. The ring-opened product, **21**, was obtained in high yield, and was further elaborated into the corresponding diamino alcohol by $LiAlH_4$ reduction of the azido group. Similarly, iodotrimethylsilane reacts with **9** and leads to an alkyl iodide intermediate, **22**, which produces 3-hydroxy-1,2-diamines, **23**, in high yields upon reaction with secondary heterocyclic amines (**Scheme 6**).[27]

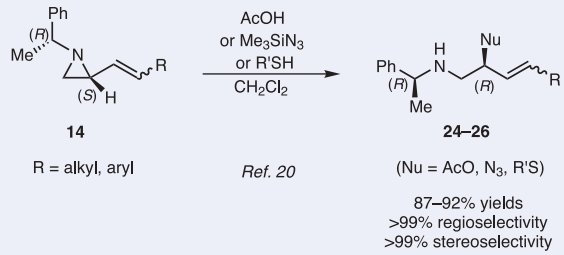
In contrast to the preceding results, a different regioselectivity is observed in the reaction of enantiomerically pure aziridine-2-carboxylate **2** with NaN_3 in aqueous ethanol and in the presence of a catalytic amount of $AlCl_3$ (pH 4). In this reaction, the nucleophile, N_3^-, selectively attacks the more electron-deficient carbon, C-2, to give 2-azido-3-aminopropanoate **24** in high yield and regioselectivity (**eq 6**).[20]

Another example of nucleophilic attack at the more sterically hindered C-2 is provided by the ring-opening reactions of 2-vinylaziridines with heteroatom nucleophiles. Upon allylic activation, the C(2)–N bond is regio- and stereospecifically cleaved by treating 2-vinylaziridines **14** with 2.5 equiv of AcOH, RSH, or $TMSN_3$ in CH_2Cl_2 to provide the ring-opened products **24–26** (**eq 7**).[20]

The regioselective ring-opening reactions of enantiomerically pure aziridine-2-methanols with heteroatom nucleophiles are summarized in **Scheme 7**.

5. Ring Expansions Leading to Oxazolidinones[28]

Since the aziridine nitrogen is basic and nucleophilic, we envisaged a regioselective aziridine ring-opening reaction initiated by acylation of the aziridine nitrogen to produce an activated aziridinium species. Reaction of enantiomerically pure aziridine-2-carboxylic acid menthol ester **2** with 1.5 equiv of methyl or allyl chloroformate in refluxing CH_3CN proceeded smoothly to give oxazolidin-2-one-5-carboxylic acid menthol ester **28** in 93% yield (**Scheme 8**).[29] The crystal structure of **28** enabled us to determine the stereochemical course of the reaction, which occurred with retention of configuration at C-2 of the aziridine. A plausible mechanism involves the formation of α-chlorocarboxylate **30**, which was isolated and characterized from its spectral data including HRMS. Intermediate **30** is formed by S_N2 attack of Cl^- at C-2 of the activated aziridine



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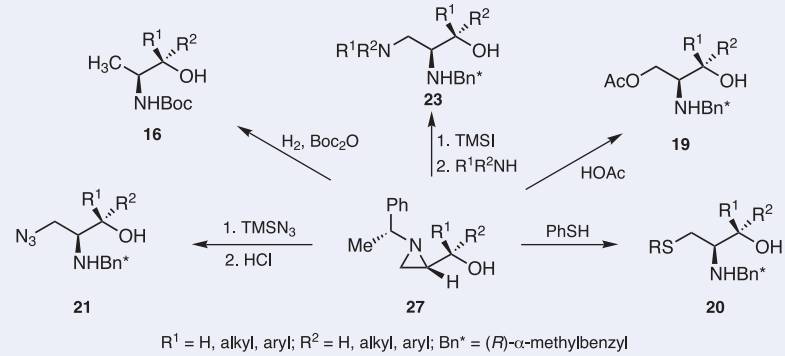
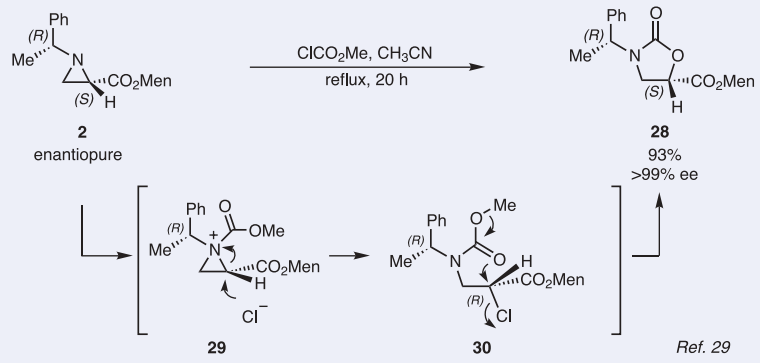
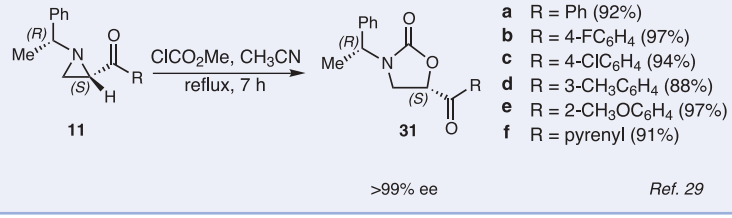


Scheme 7. Conversion of Aziridine-2-methanols, **27**, into More Functionalized Amino Alcohols.



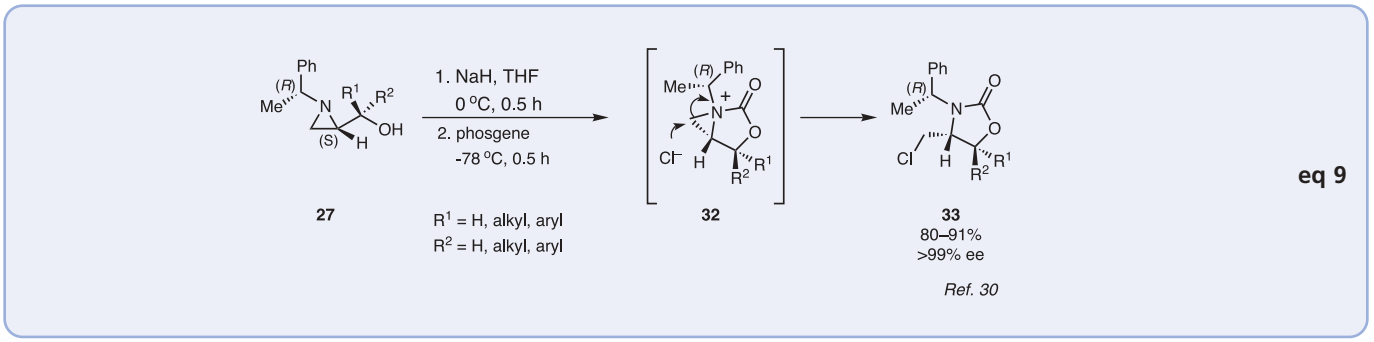
Scheme 8. Ring Expansion of Aziridine-2-carboxylate **2** into the Corresponding Oxazolidinone.



eq 8

29 and concomitant regioselective cleavage of the C(2)–N bond. Subsequent intramolecular cyclization by the carbamate oxygen of **30** provides oxazolidinone **28** with an overall retention of configuration. We have also confirmed that the same reaction with enantiopure **3** provides the corresponding oxazolidin-2-one in excellent yield and enantioselectivity.[29]

The preceding results show that



eq 9

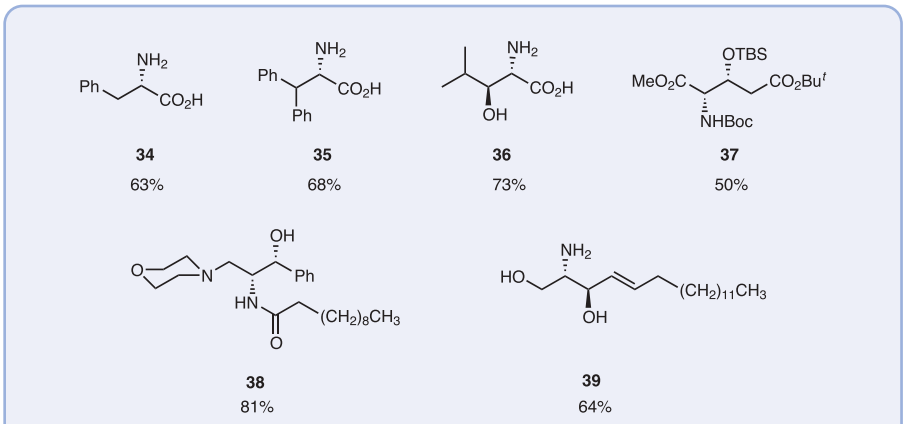


Figure 2. Amine-Containing, Biologically Active Compounds Readily Available from Aziridine-2-carboxylates.

5-functionalized enantiomerically pure oxazolidin-2-ones can be obtained very efficiently with retention of configuration from the corresponding aziridines bearing an electron-withdrawing group at C-2. We have extended the scope of this reaction by employing various C(2)-substituted aziridines to obtain 5-functionalized chiral oxazolidin-2-ones, **31**, in excellent yields and stereoselectivities (**eq 8**).[29]

We have also successfully carried out the ring opening of aziridine-2-methanols with concomitant ring expansion leading to enantiomerically pure 4-functionalized oxazolidin-2-ones.[30] Thus aziridine-2-methanols **27** led, upon treatment with NaH in THF and then phosgene, to (4*R*)-4-chloromethyl-5-substituted oxazolidin-2-ones **33** in good yields and stereoselectivities (**eq 9**). Oxazolidinones **33** presumably arise from chloride attack at the sterically less hindered C-3 of the activated aziridinium intermediates **32**. We were able to establish the absolute configuration at C-4 of **33** indirectly by measuring the coupling constants of the two vicinal protons at C-4 and C-5 in cases where R^1 or R^2 = H.[31]

The preceding results provide a novel route toward functionalized 2-oxazolidinones, which can be utilized as chiral synthons or chiral auxiliaries in a variety of asymmetric transformations.

6. Asymmetric Synthesis of Amino Acids and Alcohols

The versatility of aziridine-2-carboxylates in stereoselective transformations has led to a wide variety of optically pure, amine-containing molecules including natural and unnatural amino acids and their biologically active derivatives. Examples include phenylalanine (**34**),[32] homophenylalanine,[30] diphenylalanine (**35**),[33] 3-hydroxyleucine (**36**), and *threo*-β-hydroxy-L-glutamic acid (**37**).[13] The methodology that leads to 2,3-diamino alcohols (see Scheme 6) provides a way for the efficient synthesis of the glycosylceramide synthase inhibitor D-*threo*-PDMP (**38**)[27] and sphingosine (**39**)[20] from chiral aziridine-2-carboxylates.

7. Conclusion

Both (2*R*)- and (2*S*)-aziridine-2-carboxylates and some of their derivatives are now commercially available in bulk quantities in optically pure forms.[34] Stereo- and regioselective transformations including aziridine ring-opening reactions permit the preparation of a variety of nitrogen-containing molecules. Some of them are useful in practical syntheses of commercially valuable compounds and as starting molecules to generate diverse compound libraries. We hope that the material presented in this review will catch the attention of readers, who are actively engaged in synthesis and other aspects of research and development in many different disciplines.

8. Acknowledgement

We gratefully acknowledge the financial support of the following institutions for our work that is cited in this review: The Korea Science and Engineering Foundation (R01-2000-000-00048-0 to HJH and R14-2002-045-01002-0 to WKL), HUFS fund (2003), and the Korea Research Foundation (KRF-99-042-D00079-D3004 to HJH and KRF-2002-070-C00060 to WKL).

9. References and Notes

(†) WKL dedicates this review to Professor Manfred T. Reetz on the occasion of his 60th birthday.

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About the Authors

Won Koo Lee was born in 1962 in Seoul, Korea. He received a B.S. degree in 1984 and an M.S. degree in 1986 from Sogang University, Seoul, Korea. He obtained his Ph.D. degree in 1991 from the University of Illinois at Urbana-Champaign (with Professor Peter Beak). After two years of postdoctoral work with the late Professor Henry Rapoport at the University of California, Berkeley, he returned to Korea in 1993 as an assistant professor at Sogang University. He was promoted to full professor in 2002. In 2000, he received an Alexander von Humboldt research fellowship and was a visiting professor in Professor Manfred T. Reetz's research group at the Max Planck Institute for Coal Research in Muelheim/Ruhr, Germany. He is a cofounder of ChemBioNex Co., Ltd., and a member of the board of scientists of ImaGene. He is a member of the Korean and American Chemical Societies. His research interests include developing new synthetic methodologies, the synthesis of biologically active molecules, and the elaboration of chiral aziridines.

Hyun-Joon Ha was born in 1959 in Jinju, Korea. He obtained his B.S. degree in chemistry in 1982 from Seoul National University, and his Ph.D. degree in 1987 from Brown University, Providence, RI (with Professor David E. Cane). After a one-year postdoctoral fellowship with Professor Michael C. Pirrung at Stanford University, he returned to Korea in 1988, and accepted the position of senior research scientist at the Korea Institute of Science and Technology (KIST). In 1991, he joined the faculty of the chemistry department at Hankuk University of Foreign Studies, and is now a full professor and chairman of the department. In 1993, he carried out research at Cambridge University, U.K., as a short-term visiting scholar. He is a cofounder of ChemBioNex Co., Ltd., and a member of the board of scientists of ImaGene. His research interests include the exploitation of new methods in organic synthesis, imines and iminium ions, asymmetric synthesis of biologically active molecules, and lipase-mediated chiral resolutions. He has recently become interested in medicinal chemistry for drug discovery, process development for pharmaceuticals, and the design and synthesis of radiopharmaceuticals. He is a member of the Korean and American Chemical Societies and is on the editorial board of the electronic journal *Arkivoc*. He has coauthored over 60 papers and three reviews.

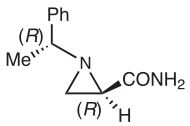
Enantiomerically Pure Aziridines and Oxazolidinones

The review by Professor Cardillo and co-workers and that by Professors Lee and Ha outlined some of the recent and growing applications of aziridines and oxazolidines in a number of synthetically useful organic reactions. Aldrich is pleased to offer its customers a wide range of these useful starting materials and intermediates.

We are always looking to expand our collection of these and other useful compounds, and we welcome your suggestions for new products. If you have questions about any of our products, or would like to suggest we list new ones, please call our Technical Services Department at **800-231-8327 (USA)**. If you would like to place an order, please contact our Customer Services Department at **800-558-9160 (USA)**. International customers, please contact your local Sigma-Aldrich office or visit our website at **sigma-aldrich.com**.

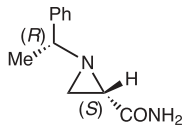
(2*R*)-1-[(1*R*)-1-Phenylethyl]-2-aziridinecarboxamide

57,055-9 — 1g, 5g



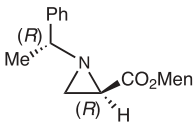
(2*S*)-1-[(1*R*)-1-Phenylethyl]-2-aziridinecarboxamide 98% (98% ee/GLC)

57,052-4 — 1g, 5g



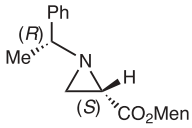
(2*R*)-1-[(1*R*)-1-Phenylethyl]-2-aziridinecarboxylic acid (–)-menthol ester, 98% (98% ee/GLC)

57,054-0 — 5g, 25g



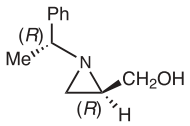
(2*S*)-1-[(1*R*)-1-Phenylethyl]-2-aziridinecarboxylic acid (–)-menthol ester, 98% (98% ee/GLC)

57,051-6 — 5g, 25g



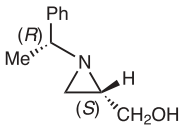
(2*R*)-1-[(1*R*)-1-Phenylethyl]aziridine-2-yl-methanol 98% (98% ee/GLC)

57,056-7 — 1g, 5g



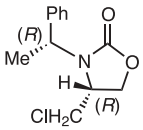
(2*S*)-1-[(1*R*)-1-Phenylethyl]aziridine-2-yl-methanol 98% (98% ee/GLC)

57,053-2 — 1g, 5g



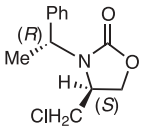
(4*R*)-4-(Chloromethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98% (98% ee/GLC)

57,061-3 — 1g, 5g



(4*S*)-4-(Chloromethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98% (98% ee/GLC)

57,060-5 — 1g, 5g



(5*S*)-5-(Hydroxymethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98%

57,057-5 — 1g, 5g