SPECIAL FOCUS ON NONRACEMIC AZIRIDINES AND OXAZOLINES

Aldrichimica ACTA

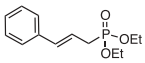
VOL. 36, NO. 2 • 2003

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

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

New Products from Aldrich R&D

Diethyl *trans*-cinnamylphosphonate, 98%

59,438-5  5g, 25g

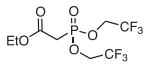
Diethyl (2-methylallyl)phosphonate, 97%

59,309-5  1g

These phosphonates were utilized in the Horner–Wadsworth–Emmons reaction to form conjugated carbon–carbon double bonds.[1] They were also employed as starting materials in an efficient and regiospecific synthesis of 4-oxo-2-alkenylphosphonates, which can serve as building blocks for the construction of polyethylenic chains.[2]

(1) Oestreich, M.; Hoppe, D. *Tetrahedron Lett.* **1999**, *40*, 1881. (2) Lee, B. S. et al. *J. Org. Chem.* **2000**, *65,* 4175.

Ethyl [Bis(2,2,2-trifluoroethoxy)phosphinyl]acetate

59,557-8  5g, 10g

This compound was exploited in the Horner–Wadsworth–Emmons reaction to synthesize α,β-unsaturated esters derived from 6-methoxytetrahydropyran-3-one.

López Tudanca, P. L. et al. *J. Chem. Soc., Perkin Trans. 1* **1992**, 533.

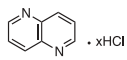
2,6-Dichloropyridine-1-oxide, 99%

59,405-9  1g, 5g

It oxidizes alkenes to epoxides[1] and alkanes to alcohols[2] in the presence of ruthenium catalysts.

(1) Zhang, J.-L.; Che, C.-M. *Org. Lett.* **2002**, *4*, 1911. (2) Yamaguchi, M. et al. *Chem. Lett.* **2002**, 434.

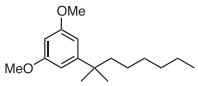
1,5-Naphthyridine hydrochloride

59,416-4  1g, 5g

Serves as a precursor of diaza-*cis*-decalins, a structurally novel class of diamine ligands.[1] Has also been used in the synthesis of one member of a series of antimicrobial parenteral 3′-quaternary ammonium cephalosporins.[2]

(1) Li, X. et al. *Org. Lett.* **2000**, *2*, 875. (2) Brown, R. F. et al. *J. Med. Chem.* **1990**, *33,* 2114.

1-(1,1-Dimethylheptyl)-3,5-dimethoxybenzene, 97%

59,522-5  1g, 5g

Employed as a starting material in the synthesis of a number of THC analogs that were evaluated for their binding affinity towards cannabinoid receptors.

Gareau, Y. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 189.

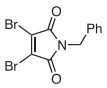
2,3-Dibromo-*N*-methylmaleimide

59,593-4  1g, 5g

2,3-Dibromomaleimide, 97%

55,360-3  1g, 5g

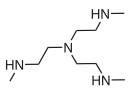
N-Benzyl-2,3-dibromomaleimide, 97%

55,778-1  1g, 5g

Dihalogenated maleimides can be used either as dienophiles or as electrophiles. 2,3-Dibromo-*N*-methylmaleimide is a key starting material in the synthesis of rebeccamycin[1] and 7-azarebeccamycin analogs.[2] These analogs were then evaluated for their antitumor activities.

Marminon, C. et al. *Bioorg. Med. Chem.* **2003**, *11*, 679. (2) Marminon, C. et al. *J. Med. Chem.* **2003**, *46*, 609.

Tris[(methylamino)ethyl]amine, 97%

46,353-1  5g, 10g, 25g

A tripodal metal chelating agent that has been employed in the preparation of *N*-methyl superbase (Aldrich Cat. No. **46,355-8**),[1] and its stilbene and bismuth azaatrane analogs:[2] *N,N′,N″*-trimethylazastibatrane and *N,N′,N″*-trimethylazabismatrane.

(1) Tang, J.-s.; Verkade, J. G. *Tetrahedron Lett.* **1993**, *34*, 2903. (2) Shutov, P. L. et al. *Inorg. Chem.* **2002**, *41*, 6147.

N,N-Diethyl-1,1-dimethylsilylamine, 97%

58,624-2  1g, 5g

Complements $NaBH_3CN$, and has been used in the Lewis acid catalyzed reductive amination of carbonyl compounds.

Miura, K. et al. *Synlett* **2001**, 1617.

Please see pages 54–55 for additional new products.

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About Our Cover

The Railway (oil on canvas, 93.3 x 111.5 cm) was painted in 1873 by the French painter Edouard Manet. When it was exhibited in the following year, it was severely criticized by both the critics and the public, who were greatly puzzled by the subject of the picture, or rather by the fact that it seemed to have no real subject. In late 19th-century France, the most highly valued subjects in art were religious, mythological, historical, or literary. At the same time, a contrary naturalistic movement, paralleled in literature by the writings of reformist authors such as Émile Zola, favored subjects that portrayed the lower classes, like scenes of peasants working in the fields.

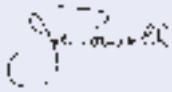
Photograph © Board of Trustees, National Gallery of Art, Washington.

Manet's picture, however, does not represent an imaginary literary subject or a glorious historical event, nor does it portray the travails of the poor or idealize the dignity of manual labor. It simply shows a young woman, who is neither rich nor poor, pausing to rest on a bench with a puppy in her lap, accompanied by a little girl with her back to us who grasps the bars of an iron fence. It does not even seem to show what is indicated by the title of the painting, and the only clue to this is the steam rising in the background.

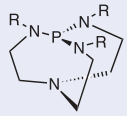
The clear outdoor light and bright color and the broad brushstrokes of his technique seem to link Manet with the impressionists, and indeed, a year after he painted *The Railway*, he was at Argenteuil painting in the open air alongside Renoir and Monet. Manet is not truly an impressionist painter, however. This is not a quickly executed representation of a chance moment, captured by the painter as a photographer makes a snapshot, but a carefully planned work. Manet sketched in the basic composition before carrying the canvas outdoors to work directly from the models. Such details as the placement of one figure facing out and the other into the picture, and the color scheme of the dresses, one white on blue and the other blue on white, show the calculation that underlies his representation of *The Railway*, a phenomenon common to modern life.

This painting is a gift of Horace Havemeyer to the National Gallery of Art, Washington, DC, in memory of his mother, Louisine W. Havemeyer.

"Please Bother Us."



Joe Porwoll, President



R = Me, *i*-Pr, *i*-Bu

Professor John G. Verkade of the Department of Chemistry at Iowa State University kindly suggested that we provide the following three proazaphosphatrane nonionic bases. This family of superbases has broad applications[1] including recently as ligands in the Pd-catalyzed amination of aryl bromides and iodides.[2]

(1) Wroblewski, A. E.; Bansal, V.; Kisanga, P.; Verkade, J. G. *Tetrahedron* **2003**, *59*, 561. (2) Urgaonkar, S.; Nagarajan, M.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 452.

46,355-8
2,8,9-Trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

55,695-5
2,8,9-Triisopropyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

56,588-1
2,8,9-Triisobutyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane

Naturally, we made these valuable superbases. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page or on the inside back cover.

Table of Contents

Lab Notes

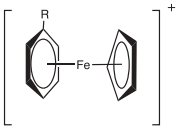
Use of the Microwave Oven for Sublimation: Flash Sublimation

Sublimation is a useful technique for the purification[1–3] or isolation[2–4] of some organic, inorganic, or organometallic compounds. Generally, if a compound can be sublimed, sublimation can be a good alternative to recrystallization or distillation. Sublimation has been known since alchemical times and, in the past, was carried out by simply heating the compound in a porcelain dish covered with a common filter paper.[5] Nowadays, a sublimation apparatus or, sometimes, a Kugelrohr oven[3,4] is used under ambient or reduced pressure.

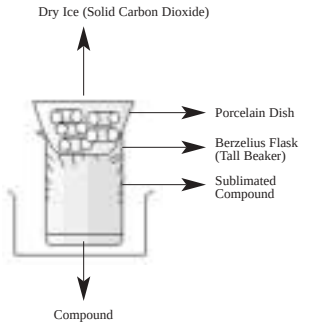
We have recently developed an improved method for the synthesis of arenocenium salts using a simple assembly for reactions under microwave conditions.[6a] It consists of a crystallizing dish and a 250-mL, tall beaker (Berzelius flask) that is covered with a porcelain dish containing dry ice. Dry ice does not absorb microwaves and, therefore, does not vaporize under microwave irradiation conditions.[6b] We found that this simple device may also be used for sublimations. Microwave sublimation has been utilized to manufacture and isolate carbon nanotubes[7] and essential powders from fresh animal, plant, or microbial matter.[8]

We have carried out the sublimation, under microwave heating, of some representative inorganic, organometallic, and organic compounds in the apparatus shown here. The sublimations were fast and easy to carry out. Collection of the sublimate with a spatula was also straightforward. The compounds tested and the "yields" of the corresponding sublimates are presented in **Table 1**. Even certain slightly air-sensitive compounds (Table 1, entries 7, 8, and 10), that are generally purified by sublimation under reduced pressure, may be purified by this method.

Acetyl ferrocene,[9] decadeuteroferrocene,[4] and (cyclopentadienyl)manganese tricarbonyl[3] were prepared by published procedures. Bromopentacarbonylmanganese was prepared by reaction of dimanganese decacarbonyl (Aldrich Cat. No. 24,526-7) and bromine. We tested all the recommended solvents for this reaction: CS_2,[10] dichloromethane,[10] carbon tetrachloride,[11] and hexane (used for the rhenium analog[12]), but found that benzene[13] was the best solvent. $Mn(CO)_5Br$ was obtained in 96% yield, in practically pure form, without formation of manganese(II) bromide as side product.[11] All other compounds in Table 1 were obtained from commercial sources.



(η^6-Arene)(η^5-cyclopentadienyl)iron(II) salts
(arenocenium salts)



References: (1) *Purification of Laboratory Chemicals*, 4th ed.; Perrin, D. D., Armarego, W. L., Eds.; Butterworth Publishers: New York, 1996. (2) Verberne, M. C.; Brouwer, N.; Delbianco, F.; Linthorst, H. J. M.; Bol, J. F.; Verpoorte, R. *Phytochem. Anal.* **2002**, *13*, 45. (3) Federman Neto, A.; Borges, A. D. L.; Miller, J.; Darin, V. A. *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 1299. (4) Federman Neto, A.; Borges, A. D. L.; de Arruda Campos, I. P.; Miller, J. *Synth. React. Inorg. Met.-Org. Chem.* **1997**, *27*, 1543. (5) (a) Engel, R. *Traité Élémentaire de Chimie*; Librairie J.-B. Baillière et Fils (Publisher): Paris, France, 1896; p 13. (b) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Scientific & Technical: Harlow, U.K., 1989; pp 153–155. (6) (a) Federman Neto, A. *An. Acad. Bras. Cienc.* **2003**, in press. (b) Dabirmanesh, Q.; Fernando, S. I. S.; Roberts, R. M. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 743. (7) Mochizuki, T.; Yoshizawa, H. Jpn. Patent 2000 272,913, October 3, 2000; *Chem. Abstr.* **2000**, *133*, 254543z. (8) Maghami, P. Fr. Patent 2,618,450, January 27, 1989; *Chem. Abstr.* **1989**, *111*, 150119v. (9) Darin, V. A.; Federman Neto, A.; Miller, J.; de Freitas Afonso, M. M.; Fonsatti, H. C.; Borges, A. D. L. *J. Prakt. Chem.* **1999**, *341*, 588. (10) Quick, M. H.; Angelici, R. J. *Inorg. Synth.* **1979**, *19*, 160. (11) Abel, E. W.; Wilkinson, G. *J. Chem. Soc.* **1959**, 1501. (12) Schimidt, S. P.; Trogler, W. C.; Basolo, F.; Urbancic, M. A.; Shapley, J. R. *Inorg. Synth.* **1985**, *23*, 41. (13) Federman Neto, A.; Oliveira, W. J. S.; Borges, A. D. L. University of São Paulo, Ribeirão Preto, Brazil. Unpublished work, 2003.

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Editor's Note: *Caution*. Sigma-Aldrich scientists have not tested this procedure in-house and do not have any experience with it. Its publication in this magazine should not be construed as being endorsed or recommended by Sigma-Aldrich. The user should base his/her decision to use this technique solely on the claims made by the authors.

Microwave Synthesis: Chemistry at the Speed of Light by Dr. B. L. Hayes (Aldrich Cat. No. Z55,386-7). See pages 50 and 72 for more details.

Table 1. Sublimation Using a Microwave Oven[a]

Entry	Compound Sublimed: Formula or Name	Amount (g)	Microwave Setting (%)[b]	Heating Time (s)	"Yield" of Sublimate (%)
1	I_2	1.0	60	360	>99
2	$AlCl_3$	0.5	60	180	64
3	Hg_2Cl_2	0.5	60 and 80	360	–[c]
4	$(C_{10}H_{10})Fe$	0.5	30	60	92
5	$(C_{10}D_{10})Fe$	0.1	30	45	96
6	Acetyl ferrocene	0.5	60	60	15[d]
7	$Mn_2(CO)_{10}$	0.1	40	40	58
8	$Mn(CO)_5Br$	0.1	30	40	33[e]
9	$Mo(CO)_6$	0.3	30	60	81
10	$(C_5H_5)Mn(CO)_3$	0.1	30	30	72[e]
11	(–)-Menthol	0.5	30	180	98
12	(±)-Camphor	0.5	20	60	84
13	Vanillin	0.5	10	30	–[f]
14	Piperonal	0.5	80	20	66
15	Biphenyl	0.5	40	150	78
16	Naphthalene	0.5	40	120	96
17	Anthracene	0.5	40	360	89
18	Salicylic acid	0.5	40	120	97
19	Benzophenone	0.5	80	90	71
20	Benzoic acid	0.5	60	60	89

[a] Sharp microwave oven, model Carousel III; manufactured by SANYO®: Manaus, Amazonas State, AM, Brazil. Of all the conditions tested, the best ones are shown in this table. [b] Setting as a percent of maximum power of 800 W. [c] Hg_2Cl_2 appears to sublime only at higher temperatures. [d] With extensive decomposition. [e] With some decomposition. [f] The material sublimed easily, but the vapors were lost without good condensation, even when low power was used.

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

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Outline

1. Introduction

Aziridines and oxazolines are interesting heterocycles that are present as structural motifs in a wide variety of strongly biologically active compounds. Examples of such compounds include azinomycins A and B,[1] which are potent antitumor and antibiotic agents that are isolated from the fermentation broth of *Streptomyces griseofuscus S42227*. The antineoplastic activity of mitomycins A, B, and C,[2a] produced by *Streptomyces caespitosus*, is associated with the high reactivity of the strained heterocycle. Furthermore, some synthetic aziridines show strong activity as enzyme inhibitors,[2b] or are versatile intermediates for enzyme inhibitors.[2c]

Moreover, a great number of oxazoline-containing biologically active compounds have been isolated from marine organisms, primarily sponges and ascidians. Ascidiacyclamide and lissoclinamide, for instance, are cyclic, oxazoline-containing antineoplastic peptides obtained from the tunicate *Lissoclinum patella*.[3] Their favorable cytotoxic and antineoplastic activities, as well as their role as chelating metabolites, have inspired synthetic and structural studies. As protected forms of hydroxyamino acids and amino alcohols, chiral oxazolines are also versatile building blocks for the synthesis of polyfunctionalized compounds, and are widely utilized as chiral ligands in asymmetric synthesis.

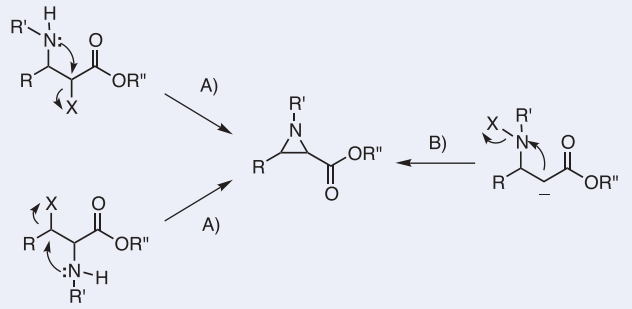
Since their discovery by Gabriel,[4] aziridines have attracted attention as starting materials for further transformations. The ring strain of aziridines, which amounts to 26–27 kcal/mol, renders these compounds susceptible to ring opening[5] and allows their use as precursors of a variety of nitrogen-containing compounds. The use of aziridine-2-carboxylates as intermediates in the synthesis of optically active amino acids, both natural and unnatural, is a subject of current interest.

While the reactivity of N-unsubstituted aziridines is relatively low, high reactivity is associated with aziridines incorporating an electron-withdrawing group on the nitrogen atom. For instance, the presence of an acyl group strongly activates the ring toward opening by a nucleophile. This reaction is generally favored by the presence of Lewis acids and proceeds with inversion of configuration at the stereogenic center of the aziridine. Another important reaction that is characteristic of *N*-acylaziridines is their isomerization to the corresponding oxazolines. This reaction generally occurs in the presence of a Lewis acid and leads to retention of configuration.

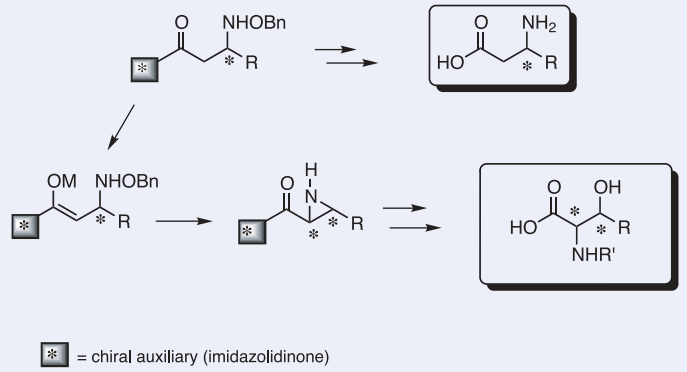
This short review covers primarily the literature of the past five years, and focuses on new syntheses of aziridines and oxazolines, which allow the preparation of a number of hydroxyamino acids in a stereoselective fashion.

2. Recent Advances in the Synthesis of Aziridinecarboxylates

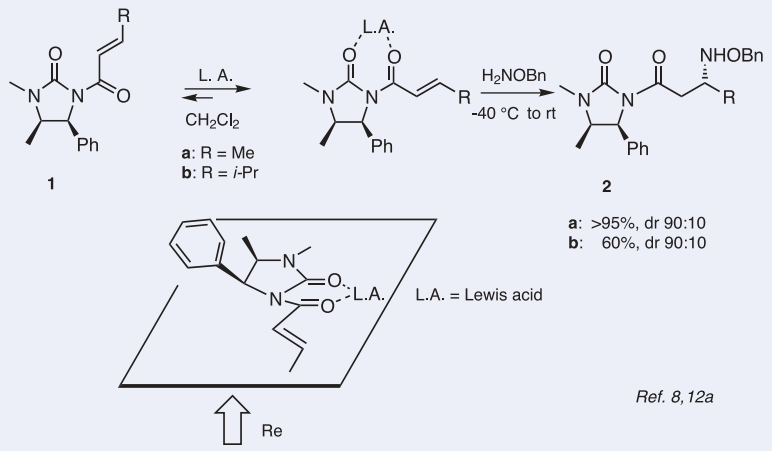
Excellent and exhaustive reviews[6] have surveyed the asymmetric syntheses of aziridines. Herein, we focus our attention on the more recent syntheses and transformations of aziridinecarboxylates, because of their structural similarities to α- or β-amino acids. Other aspects of the reactivity of aziridines are reported on in the review by Lee and Ha in this same issue. Two general approaches to the asymmetric synthesis of aziridines are illustrated in **Scheme 1**. In pathway A, a nucleophilic nitrogen atom affords the aziridine ring by attack on an adjacent carbon atom bearing a leaving group. The well-known Gabriel–Cromwell method,[7] modified with the use of chiral auxiliaries, and the cyclization of hydroxyamino acids are examples of this approach. In pathway B, the formation of a stabilized carbanion allows ring closure on an electrophilic nitrogen carrying a good leaving group.



Scheme 1. General Approaches to the Asymmetric Synthesis of Aziridines.



Scheme 2. Stereospecific Synthesis of Substituted Aziridinecarboxylates.



Scheme 3. Diastereoselectivity of the Nucleophilic Addition to α,β-Unsaturated Chiral Imides.

We have developed a new stereospecific method for preparing substituted aziridinecarboxylates for use as precursors of naturally occurring, nonproteinogenic β-hydroxy-α-amino acids. Our strategy mimics pathway B and starts with the diastereoselective β introduction of *O*-benzylhydroxylamine into α,β-unsaturated chiral imides in the presence of a Lewis acid.[8] This is followed by cyclization of the intermediate enolates to aziridines (**Scheme 2**).

The diastereoselectivity of the first step has been controlled by use of the chiral auxiliaries (+)- or (–)-1,5-dimethyl-4-phenylimidazolidin-2-one (**Scheme 3**),[9] both of which are commercially available in enantiomerically pure forms. MM^+ calculations performed on the ground state conformation of the starting unsaturated imide **1** reveal that the anti arrangement of the carbonyl groups is more stable than the syn conformation by ca. 5 kcal.[10] Nevertheless, the diastereofacial selectivity of the addition to the carbon–carbon double bond depends on the conformational changes induced by the presence of coordinating metals capable of binding both carbonyl groups. Spectroscopic evidence of the coordination of carbonyl groups with a metal atom has been reported in the literature.[8,11] Due to the presence of the substituents on the imidazolidin-2-one ring, preferential attack occurs on the less hindered face of the *s–cis* conformation. Among the variety of Lewis acids tested (Al, Ti, Zn, Mg, Yb, Sc salts, etc.), the best levels of diastereoselectivity have been obtained with BF_3•Et_2O (90:10 dr) and $Bu_2B(OTf)$ (>97:3 dr) in CH_2Cl_2.[12] This reaction allows the synthesis of β-amino acids, whose *S* or *R* configuration depends on the chiral imidazolidin-2-one used as auxiliary. An alternative, highly enantioselective route for the β introduction of a C–N bond involves the 1,4 addition of *O*-benzylhydroxylamine to pyrazole-derived crotonamides catalyzed by chiral $MgBr_2$ complexes.[13]

The 1,4 addition[14] is followed by cyclization of **2** to the corresponding aziridine[15] through the formation of a titanium[16] or aluminum enolate (**Scheme 4**). This reaction is highly diastereoselective affording exclusively the trans aziridine **3**. Since the configurations of the two new stereogenic centers depend on the initial 1,4-addition step, the chiral auxiliary and the Lewis acid selected determine the stereochemical outcome of the whole sequence. The nondestructive removal of the chiral auxiliary has been carried out by treatment with lithium hydroperoxide in tetrahydrofuran–water to afford the corresponding carboxylic acid, with methanol–toluene to afford the corresponding methyl ester, or with neat allylamine to give the corresponding amide.[17]

On the basis of the pathways shown in Schemes 3 and 4, we have developed a one-pot sequence for the preparation of *N*-Boc-3-*un*substituted aziridines (**Scheme 5**).[18] *N*-Boc-*O*-benzoylhydroxylamine, deprotonated with BuLi, reacts with acryloyl imide, and the intermediate enolate spontaneously cyclizes to aziridine **4** in 91% yield and 80:20 dr.

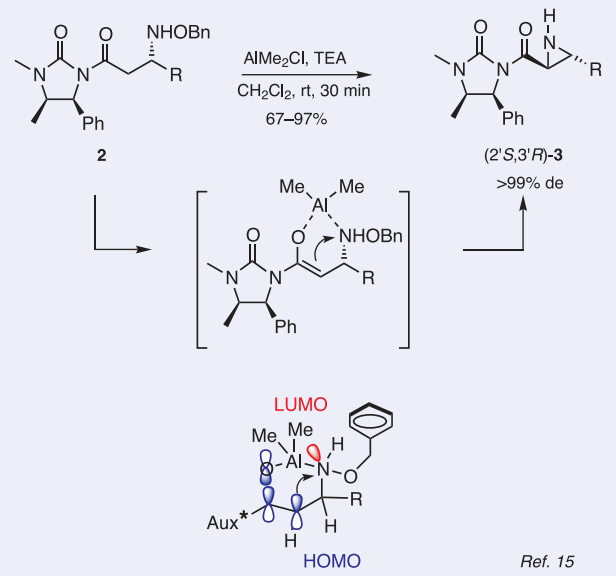
Enantiopure, cis aziridinecarboxylates have been synthesized by a recently disclosed methodology using the anion of optically pure chloroallyl phosphonamide with different oximes.[19] The reaction of the anion, generated using NaHMDS, with *tert*-butyl glyoxylate *O*-benzyl oxime led to the

corresponding cis aziridine in 78% yield as a single diastereoisomer (**Scheme 6**). Cleavage of the phosphonamide moiety by ozonolysis afforded enantiomerically pure cis aziridine **5**.

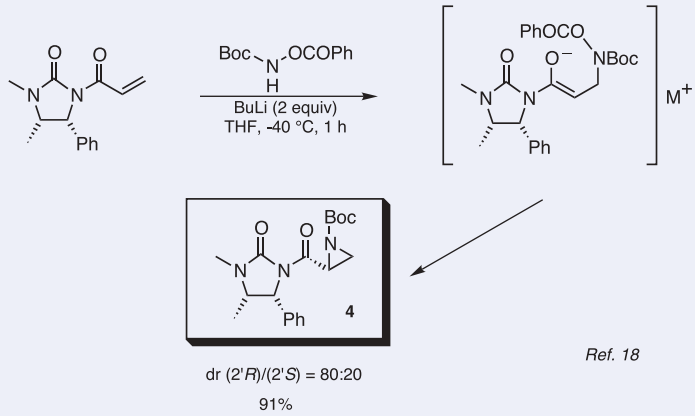
Synthetic 2,2-disubstituted aziridines show activity as protease inhibitors; for example, 2-(4-amino-4-carboxybutyl)aziridine-2-carboxylic acid[20] is a potent irreversible inhibitor of the bacterial enzyme diaminopimelic acid epimerase, while 2-(3-carboxypropyl)aziridine-2-carboxylic acid[21] is an irreversible inhibitor of glutamate racemase. Aziridine-2,3-dicarboxylates have been introduced in peptidomimetics as modified aspartic acid moieties for the purpose of preparing cysteine protease inhibitors.[22] Aiming to develop a similar application, racemic aziridine-2,2-dicarboxylates have been obtained through a Michael-type addition of *S,S*-diphenylsulfimide to arylidene malonates.[23]

We have recently turned our attention to the asymmetric synthesis of aziridine-2,2-dicarboxylates via a 1,4-addition reaction. A variety of methods exist for the synthesis of chiral, nonracemic aziridines through the metal-catalyzed aziridination[24] of olefins.[25] For example, the use of [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) in the presence of bis(oxazoline)-copper complexes as chiral catalysts has resulted in the aziridination of styrene in 97% yield and 61% ee.[26] Our procedure[27] involved the conjugate addition of commercially available *N,O*-bis(trimethylsilyl)hydroxylamine to unsaturated malonates,[28] followed by cyclization under very mild basic conditions (**Scheme 7**). The hydroxylamine derivative reacted both as a nucleophile, during the addition step, and as an electrophile during the cyclization to aziridine **6** with the OTMS group behaving as a good leaving group. The presence of a chiral Lewis acid catalyst induced chirality during nucleophilic attack onto the alkylidenemalonates. $Cu(OTf)_2$ showed good catalytic activity, and the use of bis(benzyloxazoline) as ligand furnished the best results.

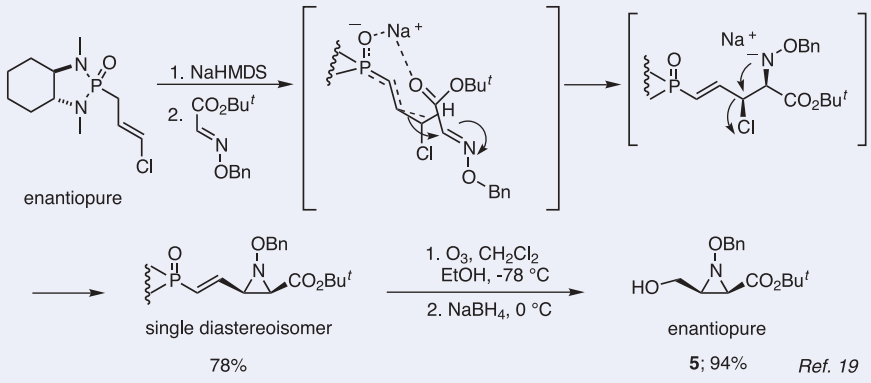
In an alternative strategy, racemic *N*-benzoylamidoaziridine diester **7** was regiospecifically hydrolyzed under mild basic conditions (**Scheme 8**). The resulting monoester, **8**, is a useful intermediate, which can be easily transformed into a mixture of diastereomeric derivatives, **9**, by use of (*S*)-α-methylbenzylamine. Upon slow crystallization from MeOH–H_2O, this mixture afforded a complete diastereomeric separation of **9a** and **9b**.[27d] Besides malonates, α-carbonyl enoates are also good substrates for aziridination. In fact, a simple



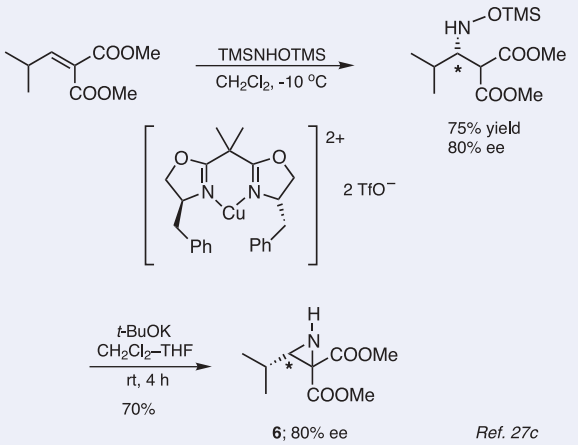
Scheme 4. Diastereoselective Aziridine Formation.



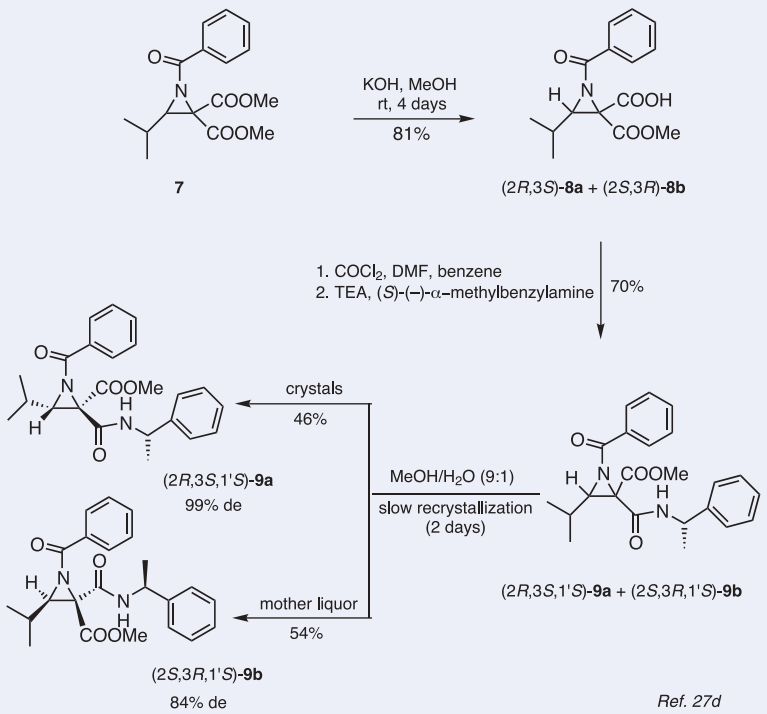
Scheme 5. Diastereoselective, One-Pot Aziridine Formation.



Scheme 6. Recent Method for Preparing Enantiomerically Pure Cis Aziridinecarboxylates.



Scheme 7. Synthesis of Aziridine-2,2-dicarboxylates by a 1,4-Addition Reaction.



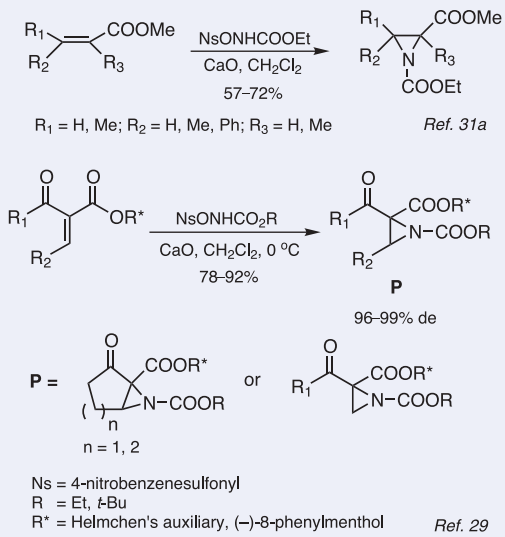
Scheme 8. Diastereomeric Resolution of Aziridine-2,2-dicarboxylates.

and efficient diastereoselective aziridination of chiral α-carbonyl enoates[29] has recently been reported using ethyl or *tert*-butyl nosyloxycarbamate.[30] In situ generated (ethoxycarbonyl)nitrene (NCO_2Et) reacts readily with electron-rich alkenes, but more slowly with electron-deficient ones. Inorganic bases, such as CaO, have been employed to facilitate nitrene formation, which allows the preparation of aziridines from α,β-unsaturated esters and ketones (**Scheme 9**).[31] The same reaction occurs with high diastereoselectivity (96–99% de) with chiral α-carbonyl enoates[29] derived from commercially available chiral alcohols such as Helmchen's auxiliary.[32]

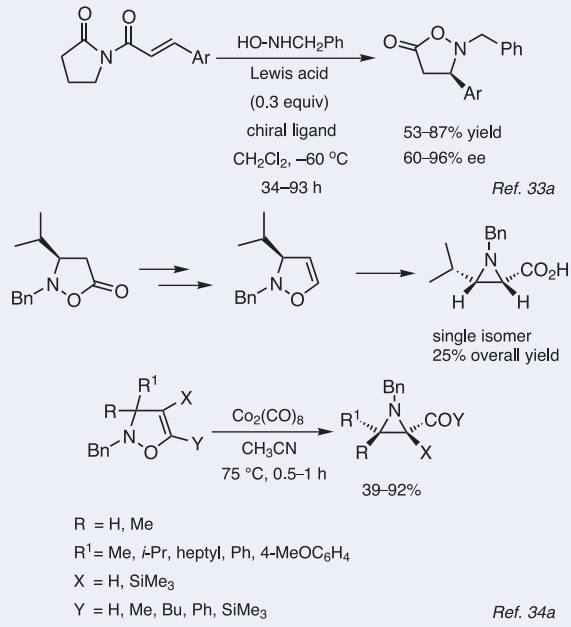
A ring contraction of 4-isoxazolines (2,3-dihydroisoxazoles) to aziridines is illustrated in **Scheme 10**. The conjugate addition of *N*-benzylhydroxylamine to achiral pyrrolidinones and oxazolidinones, in the presence of a chiral ligand, affords chiral 5-isoxazolidinones as precursors of 4-isoxazolines with moderate-to-good chemical yields.[33] 4-Isoxazolines have been utilized for the synthesis of acylaziridines through a $Co_2(CO)_8$ promoted rearrangement.[34]

The use of oxazolidinones as excellent achiral templates has been applied to a variety of enantioselective transformations.[35] For instance, the enantioselective aziridination of *N*-enoyloxazolidinones with *N*-aminophthalimide in the presence of lead tetraacetate and a chiral ligand, provides *N*-phthalimidoaziridines in 15 minutes at 0 °C in good-to-high enantiomeric excesses (**eq 1**).[36]

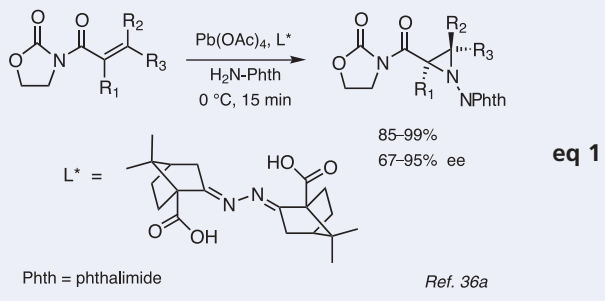
Finally, oxazolinylaziridines were synthesized in good yields and high diastereoselectivities by a Darzens-like reaction between 2-(1-chloroethyl)-2-oxazoline and Schiff bases (**eq 2**).[37]



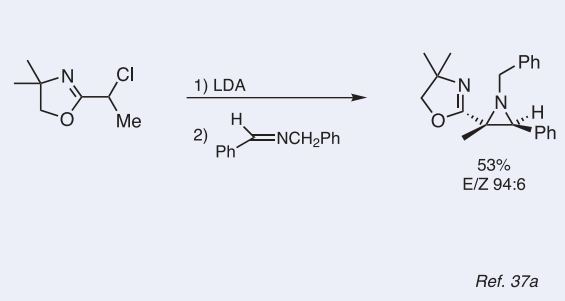
Scheme 9. Aziridination of α,β-Unsaturated Esters by Nosyloxycarbamate.



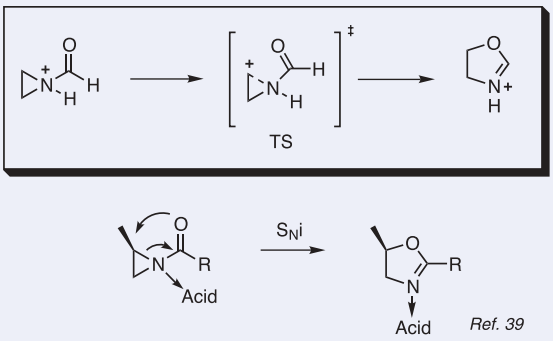
Scheme 10. Enantioselective Synthesis and Ring Contraction of 4-Isoxazolines.



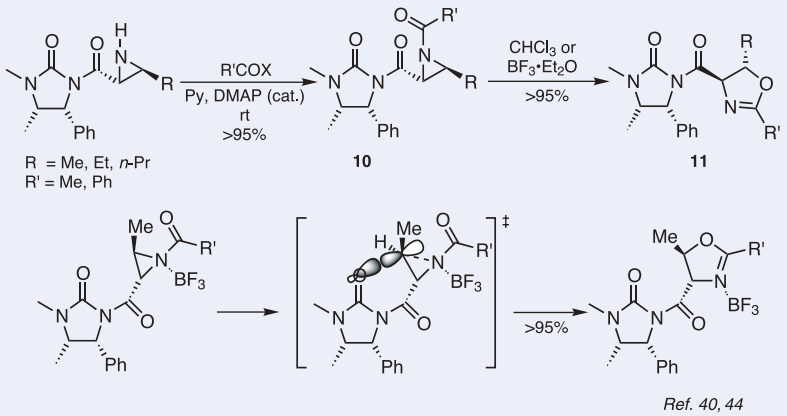
eq 1



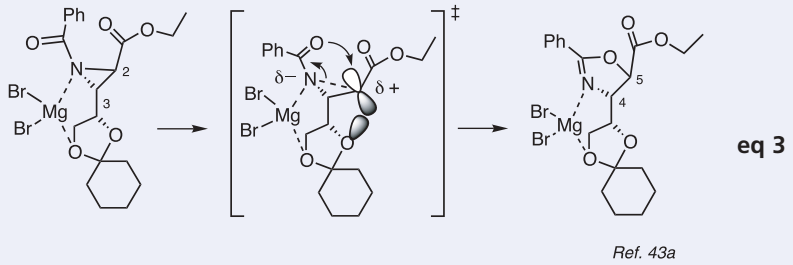
eq 2



Scheme 11. Retention of Configuration in the Ring Expansion of Aziridines to Oxazolines.



Scheme 12. Effect of the Imide Auxiliary on the Ring Expansion Rate and Regioselectivity.



3. Synthesis of Oxazolines

Oxazolines can be synthesized by several routes.[38] The most general methods are: (a) the ring-expansion reaction of acylaziridines; (b) the N-cyclofunctionalization of a double bond starting from a vicinal O-functionality, or the O-cyclofunctionalization of a double bond starting from an N-functionality; or (c) the formation of a C–C bond by an aldol condensation. Herein, we present some recent, original strategies that have been utilized in the synthesis of chiral oxazolines.

3.1. Ring-Expansion Reactions

The ring expansion of acylaziridines to oxazolines promoted by Lewis acids is a well-known reaction that has recently received renewed attention. Both chemical evidence and ab initio calculations have shown that this reaction occurs with retention of configuration of the stereogenic centers (**Scheme 11**).[39] We have confirmed these findings by following the spontaneous ring expansion of an *N*-acyl-3-ethylaziridine-2-imide by ^{1}H NMR spectroscopy.[40] The spectra showed a slow decrease of the intensity of the signals from the aziridine and a corresponding increase of the intensity of the signals from the trans oxazoline-4-imide ($J_{4,5}$ = 5.0 Hz).[41] No intermediate was observed in the reaction mixture. The ring expansion of 3-substituted aziridine-2-imides **10** is completely regioselective, affording oxazolines **11** as the only products (**Scheme 12**). It is generally assumed that the regioselectivity is driven by the stability of an incipient carbocation. Semiempirical calculations suggest that the imidazolidin-2-one chiral auxiliary could be responsible for the accelerated reaction rate and for the regiochemistry.[42] The aziridine presumably adopts a preferred conformation in which the endocyclic carbonyl oxygen is in proximity of the aziridine C3', thus stabilizing the incipient positive charge. This model is also in accord with our experimental observations that the ring expansion of aziridine-2-esters is slower than that of aziridine-2-imides, while the same reaction does not occur for aziridine-2-amides.

A similar neighboring-group-participation effect has recently been observed[43] in the ring expansion of a glyceraldehyde-derived aziridine-2-carboxylate. The oxygen of the cyclohexylidene protecting group appears to stabilize the incipient carbocation and to drive the regiochemistry of the ring expansion toward the formation of the oxazoline-5-carboxylate (**eq 3**).

N-Acyl-3-methylaziridine-2-imides underwent ring expansion to give the corresponding trans oxazoline-4-imides in good yields (see Scheme 12). The mild acid hydrolysis of the heterocycles, followed by the nondestructive removal of the chiral imidazolidinone auxiliary, furnished optically active threonines.[40] This reaction was also applied to a variety of *N*-acyl-3-alkylaziridine-2-imides to afford precursors of *threo*-β-hydroxy-α-amino acids.[44]

The removal of the chiral auxiliary in an earlier stage of the procedure, to transform the aziridine-2-imide into an aziridine-2-ester or an aziridine-2-amide, allowed us to perform the ring opening of the three-membered ring with acetic acid by following the published procedure.[45] This yielded the protected form of optically active *allo*-threonine, a nonproteinogenic amino acid present in many bioactive peptides and glycopeptides associated with biological recognition and selectivity.

Ring expansion and ring opening of aziridine derivatives are complementary: starting from trans acylaziridines, ring opening by an oxygen nucleophile affords

the anti amino acids, while ring expansion followed by hydrolysis leads to the syn isomers. Furthermore, depending on the chiral imidazolidin-2-one auxiliary used, *R* or *S* amino acids may be isolated.

3.2. C–O Bond Formation

We have recently developed a simple, direct, and general synthesis of nonracemic α-hydroxy-β-amino acids[46] through the intermediacy of chiral oxazoline-5-carboxylates **13** (**Scheme 13**).[47] This approach starts from chiral β-amido esters, and is based on the previously reported results by Seebach and Estermann[48] for the highly diastereoselective alkylation of *N*-acyl-β-amino esters. When these two workers quenched the lithium dianion of the amido ester with a range of alkylating agents, the anti α-alkylated products were obtained in high diastereomeric excesses. Our quenching of the dianion of *N*-benzoyl-β-amino esters with iodine at -60 °C afforded trans oxazolines **13** in 80–95% yields and 92–96% de's, after cyclization of the intermediate iodo derivatives. When the reaction was performed on (3*R*)-**12b**, acidic hydrolysis of the corresponding oxazoline, **13b**, afforded enantiopure (2*R*,3*S*)-*N*-benzoylphenylisoserine methyl ester (85% yield), a fragment of the anticancer Taxol® molecule,[49] without any racemization. Although considerable effort has been expended in the last few years toward the synthesis of this biologically important amino acid, our method compares favorably with the reported synthetic procedures in terms of its simplicity and the optical purities obtained.

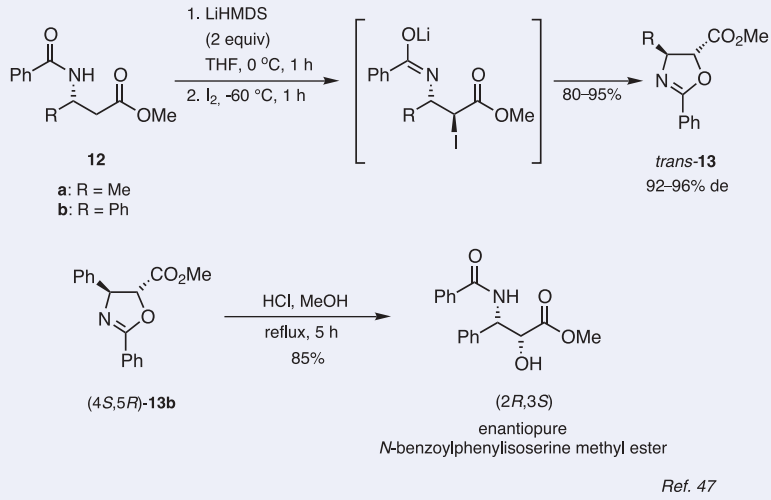
In a similar way, the synthesis of (2*S*,3*S*)-hydroxyaspartic acid,[50] an important component of the antibiotic lysobactin, was performed by deprotonation of *N*-benzoyl dimethyl aspartate at C-3, followed by quenching of the resulting dienolate with I_2 (**Scheme 14**). In this case, the reaction afforded the corresponding trans oxazoline, **14**, in 80% yield, together with the elimination product (20% yield). The hydrolysis with BF_3 in THF–H_2O allowed us to selectively obtain the O-protected amino ester, **16**, which undergoes an intramolecular O→N acyl shift,[51] leading to amido derivative **15**, upon adjusment of the pH of the reaction mixture to 9.5. On the other hand, mild acid hydrolysis of oxazoline **14** furnished amide **15**, while stronger acidic conditions led to the free amino acid.

3.3. C–C Bond Formation

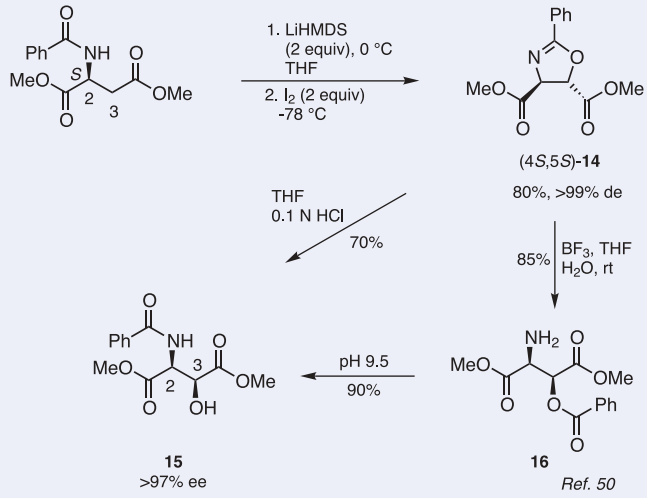
While the preceding method gave access to oxazoline-5-esters, precursors of α-hydroxy-β-amino esters, the regioisomeric (4*R*,5*S*)-*trans*-oxazoline-4-esters, **17**, precursors of phenylserine, have been obtained through an aldol-type reaction catalyzed by chiral Lewis acids. The aldol reaction between aldehydes and methyl isocyanoacetate afforded trans oxazolines through C–C bond formation. The introduction of an optically active ferrocenylphosphine ligand rendered this reaction highly enantio- and diastereoselective.[52] On the other hand, the enantioselective synthesis of *cis*-2-oxazoline-4-carboxylates through a [3+2] cycloaddition of 2-aryl-5-methoxyoxazoles with aromatic aldehydes has been reported.[53] Recently, Evans et al.[54] performed the aldol-type reaction by utilizing chiral aluminum complexes of diaminobinaphthyl-derived ligands[55] and Na_2SO_4 as additive and drying agent (**Scheme 15**). This led to a strong improvement in enantiomeric excesses and yields (>90% yields, 99% ee's).

In addition, the resulting (4*S*,5*S*)-*cis*-oxazolines were easily epimerized to the more stable (4*R*,5*S*)-*trans* isomers, by treatment with a catalytic amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

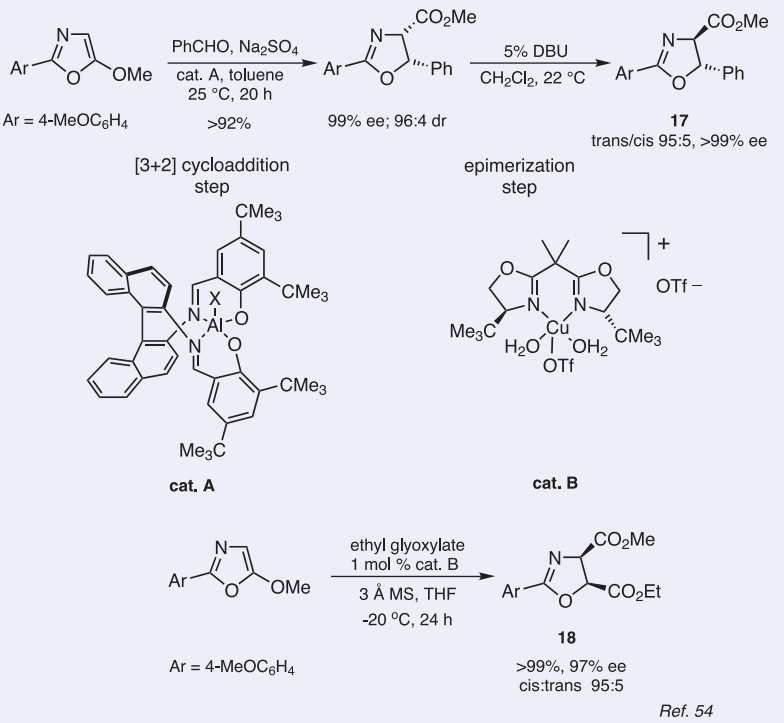
The reaction is not limited to the use of aluminum-derived Lewis acids. When Cu(II)–bisoxazoline complexes were employed in the reaction between ethyl glyoxylate and 5-methoxy-2-(4-methoxyphenyl)oxazole, (4*R*,5*S*)-*cis*-4,5-dialkoxycarbonyl-2-(4-methoxyphenyl)oxazoline (**18**) was obtained in quantitative yield and excellent stereoselectivity (95:5 dr, 97% ee).[54]



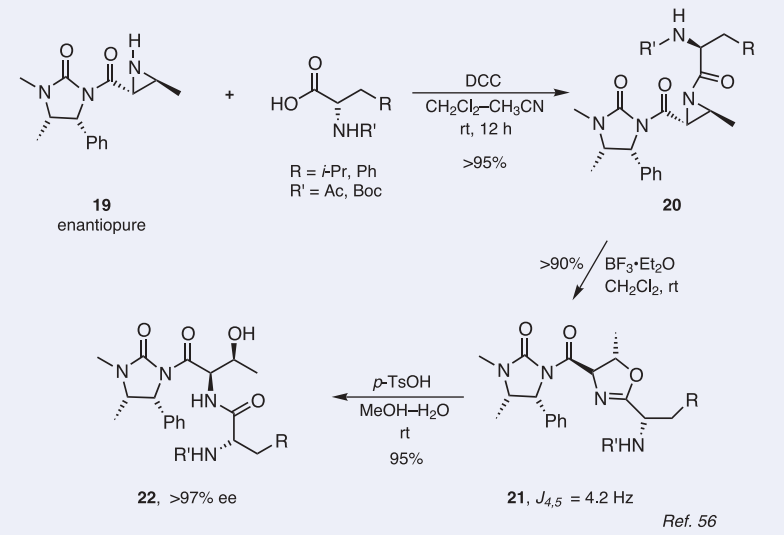
Scheme 13. General Synthesis of Nonracemic α-Hydroxy-β-amino Esters.



Scheme 14. Synthesis of (2*S*,3*S*)-Hydroxyaspartic Acid Derivatives.



Scheme 15. Synthesis of Phenylserine Precursors.



Scheme 16. New and Efficient Strategy for the Synthesis of Threonine-Containing Dipeptides.

4. Synthesis of Threonine-Containing Dipeptides

A new and efficient strategy for the synthesis of threonine-containing dipeptides relies on the ring expansion of enantiomerically pure aziridine-2-imides to oxazolines, which occurs in a regio- and stereocontrolled manner, according to the mechanism described in Section 3.1 (see Schemes 11 and 12, and eq 3).[56] Thus, enantiopure trans aziridine **19** was treated with an N-protected amino acid and DCC to give *N*-(α-aminoacyl)-3-methylaziridine **20** in excellent yield. Conversion of **20** into oxazoline-4-imide **21** and hydrolysis of the five-membered ring with TsOH gave the threonine-containing dipeptide **22** in excellent overall yield (**Scheme 16**). The trans geometry of the starting aziridine **19** was retained in the corresponding oxazoline **21**, as shown by ^{1}H NMR spectroscopy ($J_{4,5}$ = 4.2 Hz).[41]

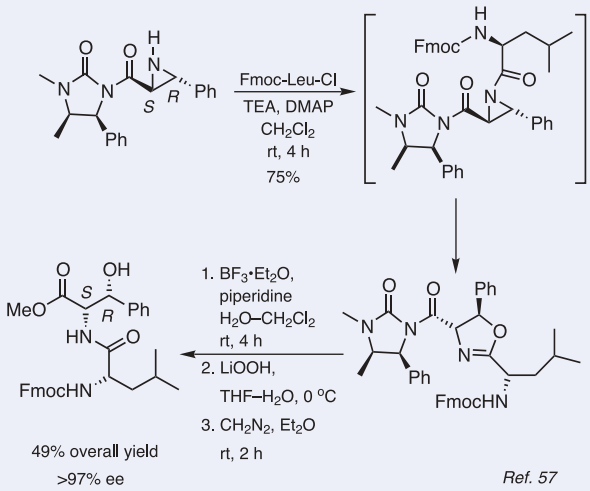
The activation of (2*S*,3*R*)-3-methylaziridine-2-imide with N-protected leucine and phenylalanine gave, after rearrangement, (4*S*,5*R*)-leucyloxazoline and (4*S*,5*R*)-phenylalanyloxazoline. These two fragments are found in the backbone of several cyclic polypeptide metabolites such as ascidiacyclamide and cyclodidemnamide, isolated from the marine organism *Lissoclinum patella*.[3]

The same protocol, shown in Scheme 16, was applied to the corresponding trans 3-phenylaziridine-2-imide, activated with *N*-Fmoc-leucine. Ring expansion, mild acidic hydrolysis, and removal of the chiral auxiliary afforded the dipeptide phenylserine-leucine, a structural fragment in the antibiotic lysobactin (**Scheme 17**).[57]

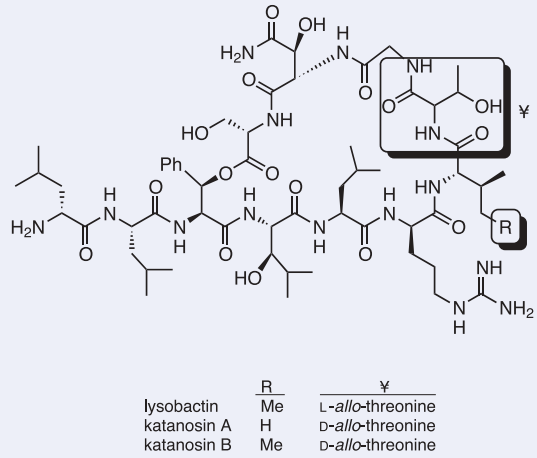
Lysobactin[58] (**Figure 1**) is a depsipeptide antibiotic that was isolated in 1988 from a species of *Lysobacter* (ATCC 53042). The backbone of this macrocycle contains eleven amino acids, five of which are syn or anti β-hydroxy-α-amino acids. Lysobactin is four times more potent than vancomycin,[59] but is slightly more toxic; however, it retains its activity even against vancomycin-resistant bacteria. Katanosins A and B[60] have the same peptide sequence as lysobactin but the opposite stereochemistry at the *allo*-threonine position. These two macrocycles show a high antibiotic activity that is strictly correlated to the inhibition of cell wall biosynthesis.

The methodologies that have been utilized in the synthesis of oligopeptides containing hydroxyamino acids have been easily applied to the preparation of other fragments present in lysobactin. Since activated aziridines give ring opening with inversion of configuration or ring expansion with retention of configuration, we have explored both of these approaches in the synthesis of a threonine or *allo*-threonine dipeptide sequence from a common starting aziridine.[61] For this purpose, a 2'*S*,3'*R* aziridine was acylated with *N*-Boc-isoleucine, and ring-expanded by treatment with BF_3•Et_2O to obtain the corresponding 4*S*,5*R* oxazoline in excellent yield. Hydrolysis of the oxazoline gave a 90% yield of the ester, which was transformed into the corresponding amide by a nucleophilic intramolecular displacement. This sequence led to the preparation of an Ile-Thr derivative.

To introduce *allo*-Thr into a peptide sequence, a different protocol, involving S_N2 aziridine ring opening, was required. In order to obtain the starting aziridine with the



Scheme 17. Preparation of Phenylserine-Leucine Dipeptide, a Structural Fragment in the Antibiotic Lysobactin.



	R	¥
lysobactin	Me	L-*allo*-threonine
katanosin A	H	D-*allo*-threonine
katanosin B	Me	D-*allo*-threonine

Figure 1. Macrocyclic Peptides Exhibiting High Antibiotic Activity.

proper configurations of the stereogenic centers, we performed the conjugate addition step using a (+)-imidazolidinone as chiral auxiliary in the presence of $AlMe_2Cl$. Cyclization of the adduct with $AlMe_2Cl$ led to the desired aziridine. Removal of the chiral imidazolidinone auxiliary by treatment with neat allylamine inhibited aziridine ring expansion and led to aziridine-2-allylamide **23** containing a masked glycine moiety (**Scheme 18**).[61] Coupling of **23** with *N*-Boc-isoleucine followed by ring opening with CH_3COOH gave the *allo*-threonine acetate derivative **25** in good overall yield. Tripeptide derivative Ile-*allo*-Thr-Gly, **26,** was obtained upon treatment of **25** with $KMnO_4/CH_3COOH$.[62]

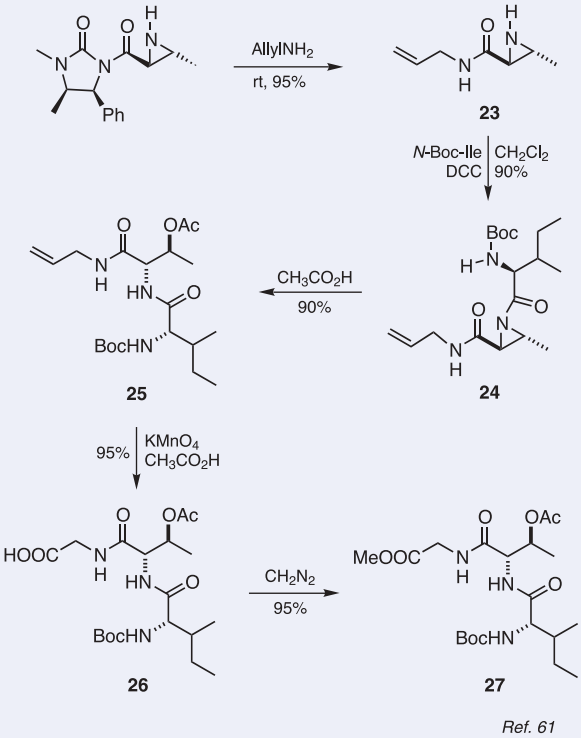
allo-Threonine-containing polypeptide sequences have been synthesized by Wipf and co-workers,[63] starting from the corresponding threonine-containing sequences. The key features of the synthesis include cyclization of the hydroxyamino acid with the Burgess reagent or under Mitsunobu conditions, followed by hydrolysis of the intermediate oxazoline heterocycle (**Scheme 19**).

5. Concluding Remarks

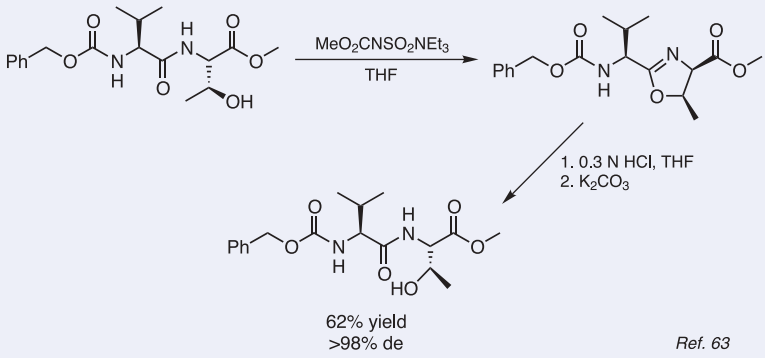
Over the past few decades, an increasing number of researchers have exploited aziridines and oxazolines as starting materials for the synthesis of nitrogen-containing compounds. The use of these heterocycles as intermediates in the synthesis of proteinogenic and nonproteinogenic, optically active amino acids is of current interest. Herein, we have highlighted some of the most recent methods for the asymmetric synthesis of aziridinecarboxylates and oxazolinecarboxylates. Furthermore, particular attention has been paid to the ring expansion of *N*-acylaziridines into oxazolines, which allows the synthesis of syn hydroxyamino acids and their direct insertion into peptide sequences.

6. Acknowledgements

We would like to thank all of the graduate students and postdoctoral fellows, who have developed the chemistry reported herein, and whose names are cited in the references. Furthermore, we gratefully acknowledge the financial support of the University of Bologna, MIUR, CSFM-CNR, ISOF-CNR, C.I.N.M.P.I.S., and NATO for our research, the results of which are presented in this review and in the cited publications.



Scheme 18. Synthesis of *allo*-Threonine Tripeptide Fragment of Lysobactin.



Scheme 19. Conversion of Threonine-Containing Dipeptides into *allo*-Threonine-Containing Dipeptides.

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About the Authors

Giuliana Cardillo has been a professor of organic chemistry at the University of Bologna since 1980. She studied chemistry at the University of Rome, where she received the "Laurea" in chemistry in 1960. She then moved to the Politecnico of Milan, where she accepted a C.N.R. (Consiglio Nazionale delle Ricerche) position and worked under the guidance of Professor A. Quilico on the identification and synthesis of naturally occurring chromenes, active flavons, and polyprenylphenols. The following two years, she worked at the University of Bari with Professor G. Cainelli on the chemistry of 3-methyl-2-butenoic acid dianion, as isoprene unit, and its application to the synthesis of terpenoids and Vitamin A. She was also interested in the preparation and use of supported polymeric reagents such as acetate, carbonate, and chromate ions. For her teaching and research work, she earned the "Habilitation" in natural product chemistry (1970). In 1972, she moved to the University of Bologna where, in 1980, she was promoted to the rank of professor and appointed to the chair of organic chemistry at the same university. From 1986 to 2001, she was director of the Centre for Macromolecular Physics and Chemistry Studies of the C.N.R. (Rome). She has been awarded the 2000 "A. Quilico Memorial Medal" from the Italian Chemical Society for her creative research in the field of natural products. Her current work focuses on the utilization of cyclofunctionalization reactions in the development of new synthetic methods for polyfunctionalized hydroxyl compounds as bioactive carbohydrates and amino acids. This includes new stereoselective syntheses of β-amino acids, peptide synthesis, and conformational analysis of modified, physiologically active peptides. The asymmetric conjugate addition of nitrogen nucleophiles, via chiral auxiliaries or chiral Lewis acids, has allowed Cardillo's group to develop new methods for the synthesis of aziridines and oxazolines, useful intermediates in the preparation of hydroxyamino acids.

Luca Gentilucci received his "Laurea" in chemistry in 1992 from the University of Bologna under the supervision of Professor C. Trombini, and his Ph.D. in 1996 under the direction of Professor G. Cardillo for research done on the conjugate addition in the synthesis of substituted amino acids. He spent a period of time in 1994 in Professor B. Zwanenburg's group at the Katholieke Universiteit Nijimegen (The Netherlands), working on the synthesis of aziridines and azirines. In 1996, he was a research assistant at the Interdepartmental Centre of Biotechnological Research of the University of Bologna. In 1997, he got a postdoctoral fellowship from the same university to develop research in the field of asymmetric synthesis of small heterocycles, and received the "Bracco Award for Young Researchers in Organic Chemistry" administered by Bracco S.p.A. Pharmaceuticals (Milan). Since 1998, he has been a research associate in Professor G. Cardillo's group working on the asymmetric synthesis of aziridines and other small heterocycles and the synthesis of opioid peptide analogues exhibiting analgesic activity.

Alessandra Tolomelli received her "Laurea" in chemistry from the University of Bologna in 1994 under the supervision of Professor G. Cardillo. In 1997, she spent a period of time in Professor J. Konopelski's laboratories at the University of California, Santa Cruz, working on the synthesis of pharmacologically active polypeptides. In 1999, she obtained her Ph.D. degree from the University of Bologna for research on the synthesis of polyfunctionalized biologically active compounds, which was carried out under the direction of Professor Cardillo. Currently, she works in the same group on the asymmetric synthesis of aziridines and oxazolines by the conjugate addition of nitrogen nucleophiles to unsaturated compounds.

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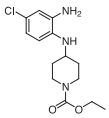
L15,785-6

$C_{14}H_{20}ClN_3O_2$
MW 297.79
250mg



L18,292-3

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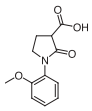
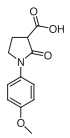
250mg



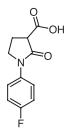
L18,295-8

$C_{12}H_{13}NO_4$
MW 235.24
250mg



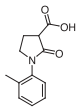
L18,296-6

$C_{11}H_{10}FNO_3$
MW 223.21
250mg



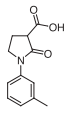
L18,297-4

$C_{12}H_{13}NO_3$
MW 219.24
250mg



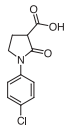
L18,298-2

$C_{12}H_{13}NO_3$
MW 219.24
250mg



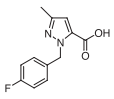
L18,300-8

$C_{11}H_{10}ClNO_3$
MW 239.66
250mg



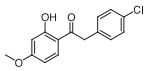
L20,130-8

$C_{12}H_{11}FN_2O_2$
MW 234.23
250mg



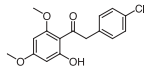
L25,115-1

$C_{15}H_{13}ClO_3$
MW 276.72
250mg



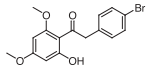
L25,126-7

$C_{16}H_{15}ClO_4$
MW 306.75
250mg



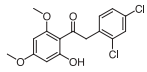
L25,129-1

$C_{16}H_{15}BrO_4$
MW 351.20
250mg



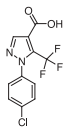
L25,130-5

$C_{16}H_{14}Cl_2O_4$
MW 341.19
250mg



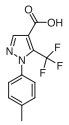
L25,137-2

$C_{11}H_6ClF_3N_2O_2$
MW 290.63
250mg



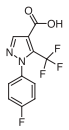
L25,138-0

$C_{12}H_9F_3N_2O_2$
MW 270.21
250mg



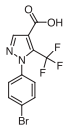
L25,140-2

$C_{11}H_6F_4N_2O_2$
MW 274.18
250mg



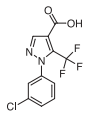
L25,141-0

$C_{11}H_6BrF_3N_2O_2$
MW 335.08
250mg



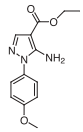
L25,142-9

$C_{11}H_6ClF_3N_2O_2$
MW 290.63
250mg



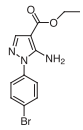
L25,146-1

$C_{13}H_{15}N_3O_3$
MW 261.28
250mg



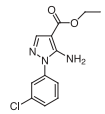
L25,149-6

$C_{12}H_{12}BrN_3O_2$
MW 310.15
250mg



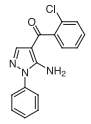
L25,151-8

$C_{12}H_{12}ClN_3O_2$
MW 265.70
250mg



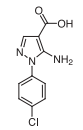
L25,168-2

$C_{16}H_{12}ClN_3O$
MW 297.75
250mg



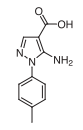
L25,199-2

$C_{10}H_8ClN_3O_2$
MW 237.65
250mg



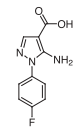
L25,201-8

$C_{11}H_{11}N_3O_2$
MW 217.23
250mg



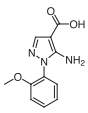
L25,203-4

$C_{10}H_8FN_3O_2$
MW 221.19
250mg



L25,207-7

$C_{11}H_{11}N_3O_3$
MW 233.23
250mg



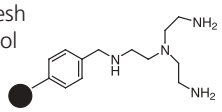
For more information on these products, or to view other similar products, please call us at 800-333-7306 (USA) or email us at bwandler@sial.com.

Scavenger Resins from Aldrich

Since their discovery,[1] scavenger resins have found increasing use not only in combinatorial chemistry, but in classical single-reaction chemistry as well. These resins mimic the limiting reagent(s) in the reaction mixture, and selectively react with excess reagents. The resins can then be simply removed by filtration, thus easing reaction workup. The choice of scavenger resin strongly depends on the type of reagent or byproduct that needs to be removed from the reaction mixture. Listed below are the scavenger resins available from Aldrich and the reagents they react with. If you have any questions on these resins, or have ideas for new resin products, please contact bseitz@sial.com.

Tris(2-aminoethyl)amine, polymer-bound[1a,1g]

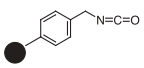
47,210-7 200–400 mesh, 4.5–5.0 mmol — 5g, 25g, 100g



Reacts with:
$RCOCl$, RSO_2Cl, RNCS, RNCO, H^+

Isocyanate, polymer-bound[1a,1b]

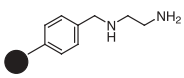
47,368-5 200–400 mesh, *ca.* 2.0 mmol — 1g, 5g, 25g



Reacts with:
RNH_2, R_2NH

Ethylenediamine, polymer-bound

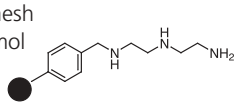
47,209-3 200–400 mesh, 2.5–3.0 mmol — 5g, 25g, 100g



Reacts with:
$RCOCl$, RSO_2Cl, RNCS, RNCO, H^+

Diethylenetriamine, polymer-bound[1c,1d]

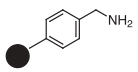
49,438-0 200–400 mesh, 4.0–5.0 mmol — 5g, 25g



Reacts with:
RCHO, RCO_2H, $RCOCl$, anhydrides

Poly(styrene-*co*-divinylbenzene), aminomethylated[1a,1e]

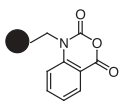
47,367-7 200–400 mesh, *ca.* 4.0 mmol — 5g, 25g, 100g



Reacts with:
$RCOCl$, RSO_2Cl, RNCS, RNCO, H^+

Isatoic anhydride, polymer-bound[2]

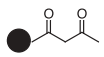
51,437-3 200–400 mesh, 2.0–2.5 mmol — 5g, 25g



Reacts with:
Amines

Activated ketone, polymer-bound[3,4]

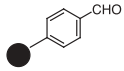
55,147-3 50–90 mesh, *ca.* 3.0 mmol — 5g, 25g, 100g



Reacts with:
Selectively binds primary amines in the presence of secondary amines

Formylpolystyrene, polymer-bound[1g]

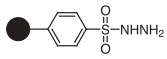
53,242-8 100–200 mesh, 2.0–3.0 mmol — 1g, 5g, 25g



Reacts with:
$RNHNH_2$, NH_2OR, RNH_2

p-Toluenesulfonyl hydrazide, polymer-bound[5]

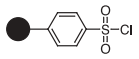
53,232-0 100–200 mesh, *ca.* 2.5 mmol — 1g, 5g, 25g



Reacts with:
Carbonyls

Sulfonyl chloride, polymer-bound[6]

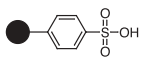
49,821-1 100–200 mesh, 1.0–3.0 mmol — 5g, 25g, 100g



Reacts with:
ROH, anilines

p-Toluenesulfonic acid, polymer-bound, macroporous[1d,1f,7]

53,231-2 30–60 mesh, 2.0–3.0 mmol — 5g, 25g, 100g



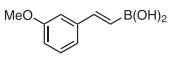
Reacts with:
Amines

References: (1) (a) Booth, R. J.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882. (b) Kaldor, S.W. et al. *Tetrahedron Lett.* **1996**, *37*, 7193. (c) Parlow, J. J. et al. *J. Org. Chem.* **1997**, *62*, 5908. (d) Flynn, D. L. et al. *J. Am. Chem. Soc.* **1997**, *119*, 4874. (e) Kaldor, S. W. et al. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041. (f) Parlow, J. J.; Flynn, D. L. *Tetrahedron* **1998**, *54*, 4013. (g) Cresswell, M. W. et al. *ibid.* **1998**, *54*, 3983. (2) Coppola, G. M. *Tetrahedron Lett.* **1998**, *39*, 8233. (3) Yu, Z. et al. *ibid.* **2000**, *41*, 8963. (4) Yu, Z. et al. *J. Chem. Soc., Perkin I* **2001**, 1947. (5) Emerson, D. W. et al. *J. Org. Chem.* **1979**, *44*, 4634. (6) (a) Zhong, H. E. et al. *J. Org. Chem.* **1997**, *62*, 9326. (b) Rueter, J.K. et al. *Tetrahedron Lett.* **1998**, *39*, 975. (c) Baxter, E. W. et al. *ibid.* **1998**, *39*, 979. (d) Takahashi, T. et al. *ibid.* **1998**, *39*, 1369. (e) Hunt, J. A.; Roush, W. R. *J. Am. Chem. Soc.* **1996**, *118*, 9998. (7) Shuker, A. J. et al. *Tetrahedron Lett.* **1997**, *38*, 6149.

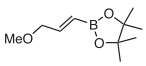
More New Products from Aldrich R&D

Boron Compounds

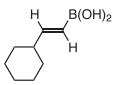
52,786-6
$C_9H_{11}BO_3$ — 1g, 10g



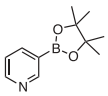
59,293-5
$C_{10}H_{19}BO_3$ — 1g, 10g



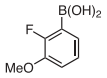
59,625-6
$C_8H_{15}BO_2$ — 1g, 10g



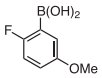
57,656-5
$C_{11}H_{16}BNO_2$ — 1g, 5g



59,425-3
$C_7H_8BFO_3$ — 1g, 5g



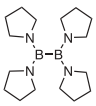
59,711-2
$C_7H_8BFO_3$ — 5g



59,306-0
$C_7H_7BF_2O_3$ — 1g, 5g

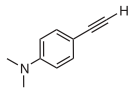
59,798-8
$C_3H_7BO_2$ — 1g, 5g

59,349-4
$C_{16}H_{32}B_2N_4$ — 1g, 5g

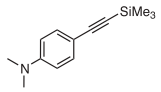


Arylacetylenes

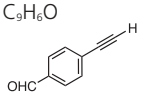
59,260-9
$C_{10}H_{11}N$ — 1g, 5g



59,283-8
$C_{13}H_{19}NSi$ — 1g, 5g



59,743-0
C_9H_6O — 1g, 5g

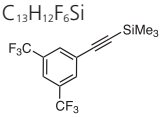


46,722-7
C_9H_8O — 1g, 5g

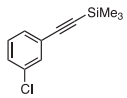
63,026-8
C_8H_5Cl — 1g, 5g

59,765-1
C_8H_7N — 1g, 5g

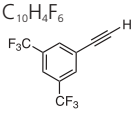
59,780-5
$C_{13}H_{12}F_6Si$ — 1g, 5g



59,770-8
$C_{11}H_{13}ClSi$ — 1g, 5g

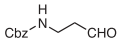


63,024-1
$C_{10}H_4F_6$ — 1g

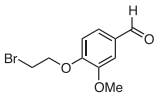


Organic Building Blocks

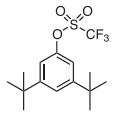
59,295-1
$C_{11}H_{13}NO_3$ — 1g



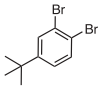
59,747-3
$C_{10}H_{11}BrO_3$ — 1g, 5g



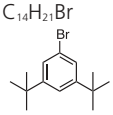
59,322-2
$C_{15}H_{21}F_3O_3S$ — 1g, 5g



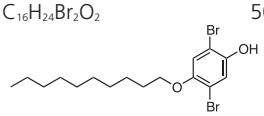
59,338-9
$C_{10}H_{12}Br_2$ — 1g, 5g



59,216-1
$C_{14}H_{21}Br$ — 1g, 5g

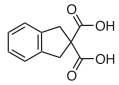


63,054-3
$C_{16}H_{24}Br_2O_2$ — 500mg, 1g

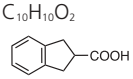


46,846-0
$C_{12}H_{12}O_2$ — 1g, 5g

59,545-4
$C_{11}H_{10}O_4$ — 1g

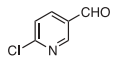


59,555-1
$C_{10}H_{10}O_2$ — 1g, 5g

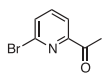


Organic Building Blocks (continued)

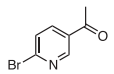
59,617-5
C_6H_4ClNO — 1g, 5g



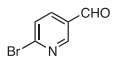
59,787-2
C_7H_6BrNO — 1g, 5g



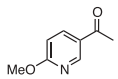
59,594-2
C_7H_6BrNO — 1g, 5g



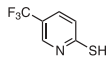
59,628-0
C_6H_4BrNO — 1g, 5g



59,776-7
$C_8H_9NO_2$ — 1g, 5g

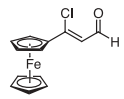


59,076-2
$C_6H_4F_3NS$ — 1g, 5g

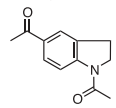


58,699-4
$C_5H_3ClO_2S$ — 1g, 5g

59,359-1
$C_{13}H_{11}ClFeO$ — 1g, 5g



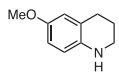
59,327-3
$C_{12}H_{13}NO_2$ — 1g, 5g



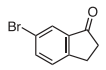
59,426-1
C_9H_6BrN — 1g, 5g

59,726-0
$C_8H_7FO_2$ — 1g, 5g

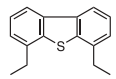
59,614-0
$C_{10}H_{13}NO$ — 1g



59,714-7
C_9H_7BrO — 1g, 5g



59,799-6
$C_{16}H_{16}S$ — 1g

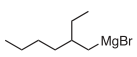


Miscellaneous Products

59,437-7
$C_6H_{15}B$ — 100mL

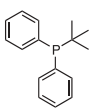
Triethylborane, 2.0M solution in diethyl ether

63,055-1
$C_8H_{17}BrMg$ — 100mL, 800mL



(2-Ethylhexyl)magnesium bromide, 1M solution in diethyl ether

59,168-8
$C_{16}H_{19}P$ — 1g, 5g



59,655-8
$C_{10}H_{15}P$ — 1g, 5g

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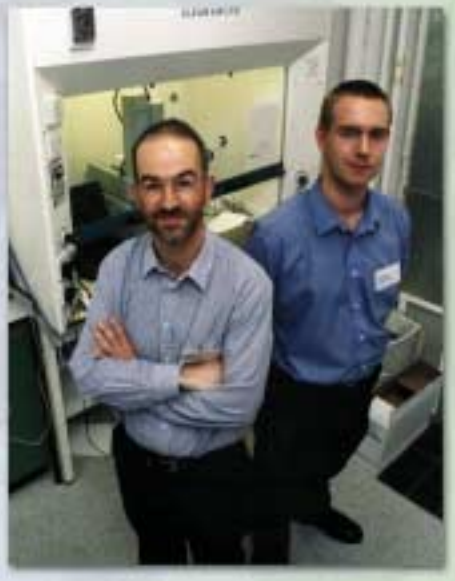
For competitive quotes on larger quantities contact **www.sigma-aldrich.com/safc**.

Kirk Malone—Winner of Sigma-Aldrich Award



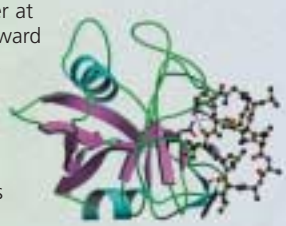
Nick Turner (left) and Kirk Malone in their laboratory at the Edinburgh Protein Interaction Centre. Photo © Jonathan Littlejohn.

Kirk Malone, a Ph.D. student in the laboratory of Professor Nick Turner at the University of Edinburgh, is the winner of a three-year research award from Sigma-Aldrich Company Ltd., U.K. Kirk's winning research project focuses on the "*Design and Synthesis of High-Affinity Ligands for Human Immunophilins*".

The aim of the project is to develop new classes of nonpeptidic inhibitors for the human immunophilins cyclophilin A (CypA) and FK binding protein (FKBP). Such inhibitors could be further developed as drugs for the treatment of HIV and parasitic infections. In collaboration with Professor Malcolm Walkinshaw at Edinburgh, Turner and Malone have used in silico screening to identify a novel class of ligand for CypA and FKBP. One round of chemical synthesis has led them to a family of compounds with a 20,000-fold increase in binding. The next step in the project is to apply combinatorial chemistry methodology to synthesize a library of potential ligands to further explore the ligand–protein interactions and thereby develop more potent inhibitors.

This leading-edge research is being carried out within the Wellcome Trust funded Edinburgh Protein Interaction Centre (EPIC; www.epic.ed.ac.uk), which is located in the School of Chemistry at the University of Edinburgh. The Centre fosters multidisciplinary research and is equipped with state-of-the-art facilities for the characterization of proteins, along with combinatorial and parallel synthesis equipment for high-throughput chemistry.

For further information, please contact Nick Turner (n.j.turner@ed.ac.uk).



CypA

FKBP

Congratulations to Kirk and Best Wishes for a Successful, World-Class Research Project!

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

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Outline

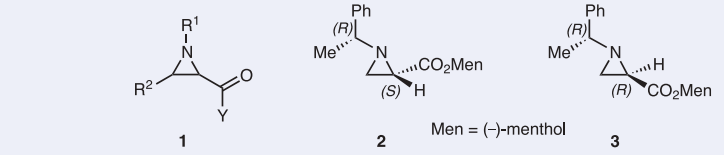
1. Introduction

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.

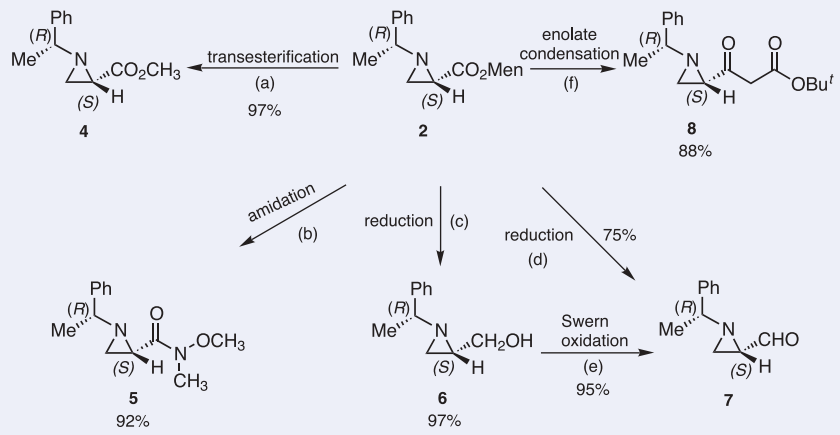
A number of surveys of the chemistry of chiral aziridines have been published.[1] Aziridines **1** in which R^2 is an alkyl or aryl group can be easily prepared, mainly as the trans isomers, from the corresponding imines and olefins. This is not the case for simple aziridine-2-carboxylates in which R^2 = 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

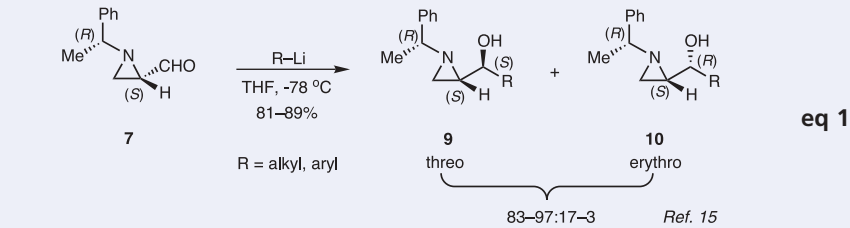


1 2 3

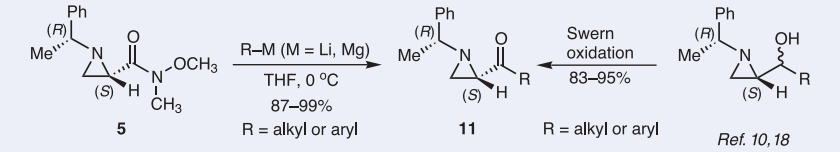


Representative reaction conditions: (a) Mg, CH_3OH, reflux, 2 h; (b) *N,O*-dimethylhydroxylamine hydrochloride, $AlMe_3$, CH_2Cl_2, -10 °C, 2 h; (c) $LiAlH_4$, Et_2O, 0 °C, 1 h; (d) DIBAL-H, toluene, -78 °C, 2 h; (e) DMSO, oxalyl chloride, CH_2Cl_2, NEt_3, -78 °C, 1.5 h; (f) LiHMDS, $CH_3CO_2Bu^t$, THF,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

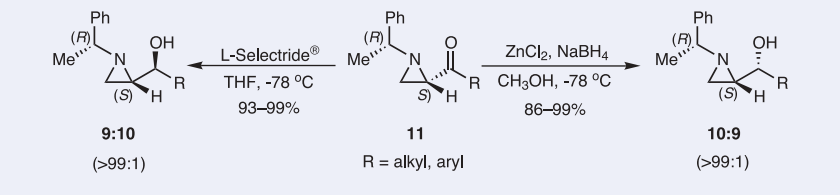
Scheme 1. Elaboration of the C-2 Carboxylate Group.



eq 1



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]

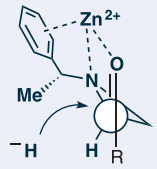
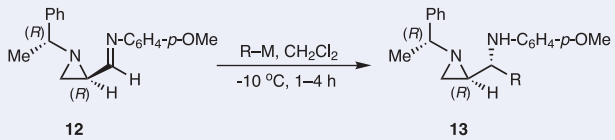
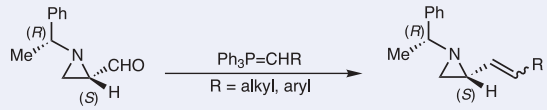


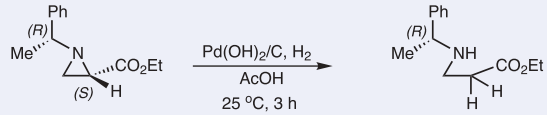
Figure 1. Most Stable Structure of the Chelated Intermediate in the $ZnCl_2$–$NaBH_4$ Reduction of **11**.



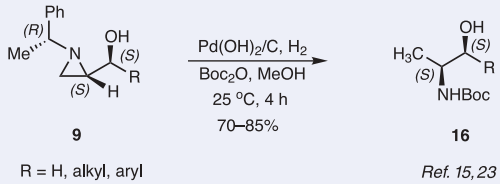
eq 2



eq 3



eq 4



eq 5

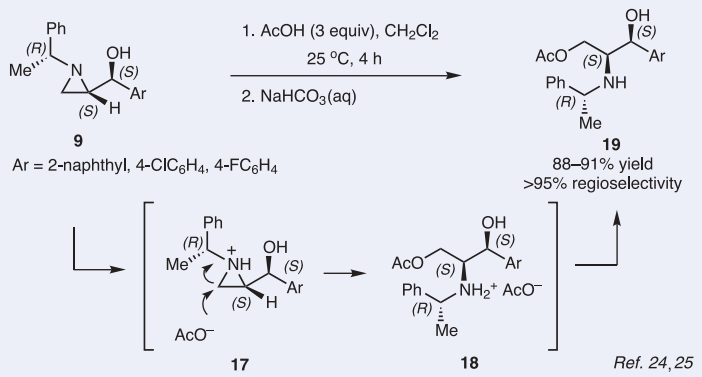
Aziridinylaldimine **12**, formed by the condensation of aldehyde (*R*,*R*)-**7** and *p*-anisidine, readily reacts with organometallics to give the corresponding amines in high yields. In most cases, addition of alkyl or aryl Grignards in the presence of BF_3•OEt_2 yields the chelation-controlled products, **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]

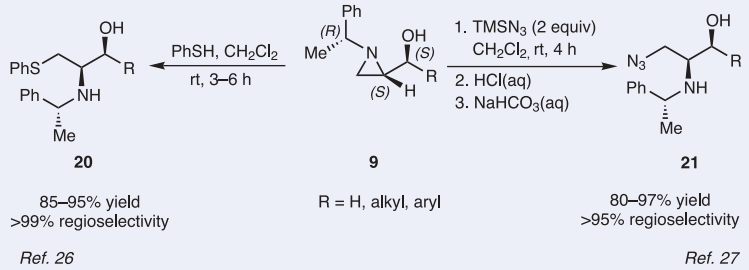
4. Aziridine Ring Opening

4.1. Regioselective Reductive Ring Opening

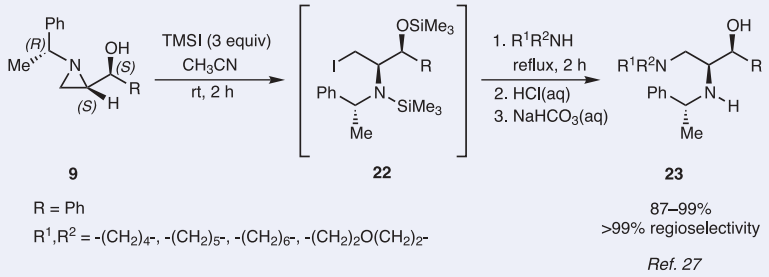
We have found that the regioselectivity of the catalytic hydrogenation of 2-substituted aziridines is controlled by the electronic character of the substituent. With an electron-withdrawing substituent at C-2, the ring-opening reduction takes place at the C(2)–N bond, with a resulting loss of the stereochemistry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



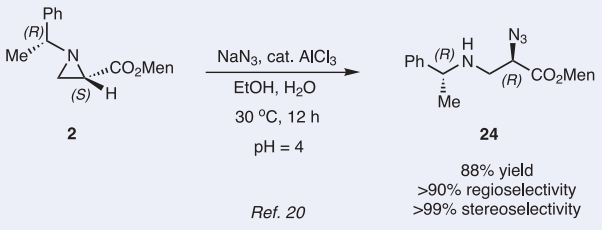
Scheme 4. Regioselective Ring Opening of Nonactivated Aziridines **9**.



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]

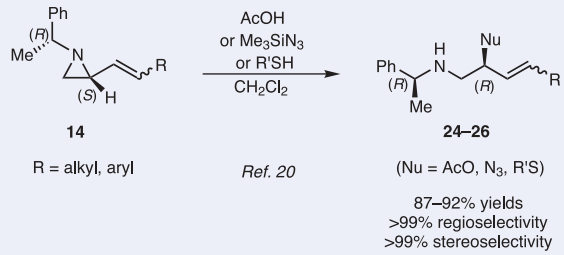
In contrast to the preceding results, a different regioselectivity is observed in the reaction of enantiomerically pure aziridine-2-carboxylate **2** with NaN_3 in aqueous ethanol and in the presence of a catalytic amount of $AlCl_3$ (pH 4). In this reaction, the nucleophile, N_3^-, selectively attacks 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]

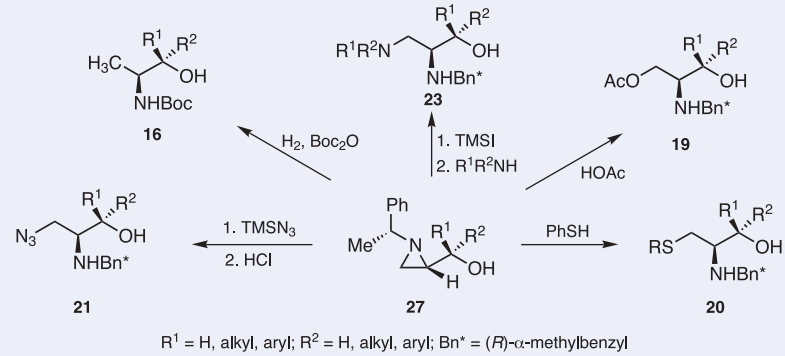
The regioselective ring-opening reactions of enantiomerically pure aziridine-2-methanols with heteroatom nucleophiles are summarized in **Scheme 7**.

5. Ring Expansions Leading to Oxazolidinones[28]

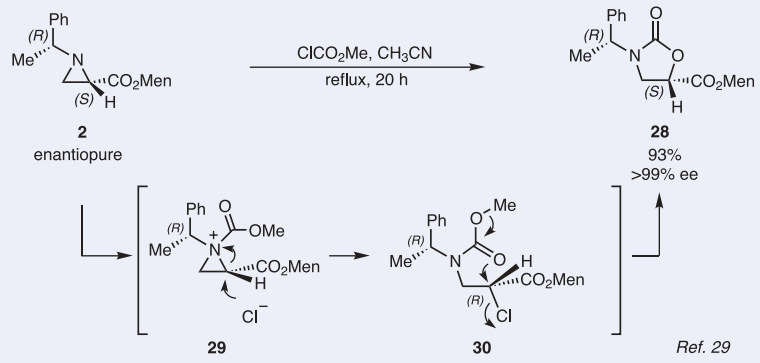
Since the aziridine nitrogen is basic and nucleophilic, we envisaged a regioselective aziridine ring-opening reaction initiated by acylation of the aziridine nitrogen to produce an activated aziridinium species. Reaction of enantiomerically pure aziridine-2-carboxylic acid menthol ester **2** with 1.5 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



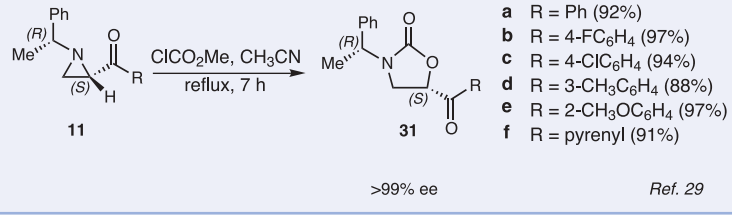
eq 7



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



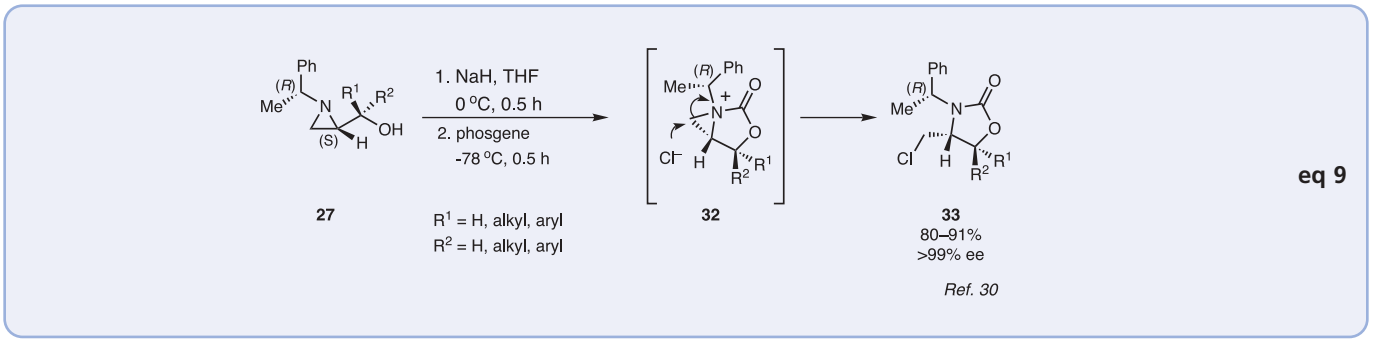
Scheme 8. Ring Expansion of Aziridine-2-carboxylate **2** into the Corresponding Oxazolidinone.



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

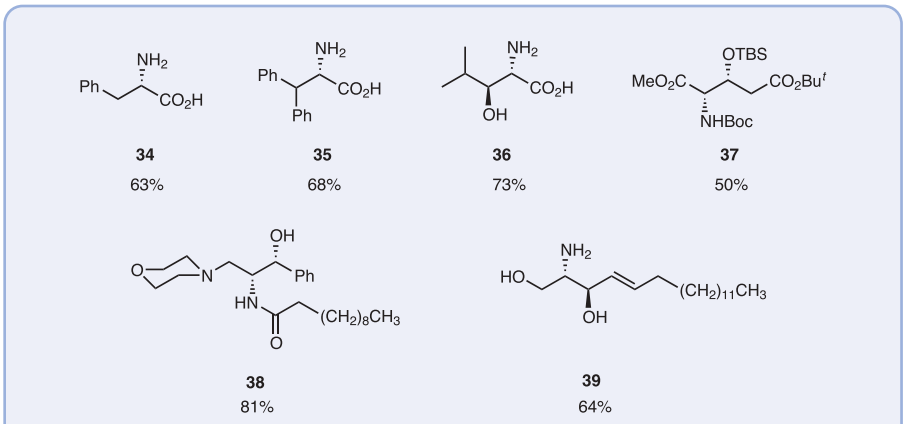


Figure 2. Amine-Containing, Biologically Active Compounds Readily Available from Aziridine-2-carboxylates.

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

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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.

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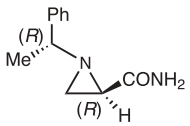
(2*R*)-1-[(1*R*)-1-Phenylethyl]-2-aziridinecarboxamide

57,055-9 — 1g, 5g



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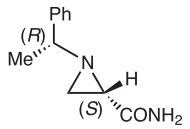
57,052-4 — 1g, 5g



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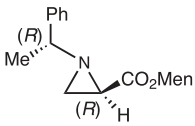
57,054-0 — 5g, 25g



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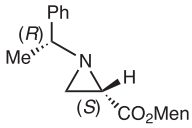
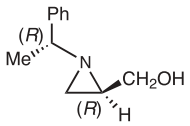
57,051-6 — 5g, 25g



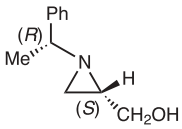
(2*R*)-1-[(1*R*)-1-Phenylethyl]aziridine-2-yl-methanol 98% (98% ee/GLC)

57,056-7 — 1g, 5g



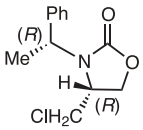
(2*S*)-1-[(1*R*)-1-Phenylethyl]aziridine-2-yl-methanol 98% (98% ee/GLC)

57,053-2 — 1g, 5g



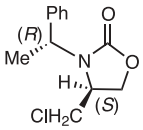
(4*R*)-4-(Chloromethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98% (98% ee/GLC)

57,061-3 — 1g, 5g



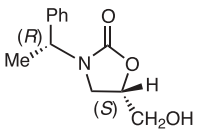
(4*S*)-4-(Chloromethyl)-3-[(1*R*)-1-phenylethyl]-1,3-oxazolidin-2-one, 98% (98% ee/GLC)

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



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- Sample cleanup following organic synthesis
- Dehydrating solvents (desiccation)
- Filtration (particulate removal)
- Isolation of actives from natural products
- Cleanup of natural products
- Scale-up of SPE and flash methods

Reduce Risk, Prevent Problems, Save Time and Money:

- Compressed bed eliminates channeling
- Porous frit helps spread sample across adsorbent bed
- Quality, reliability, and reproducibility
- Increased safety–prepacked to eliminate exposure to inhalable particulates
- Prepacked design saves time in packing, cleaning, and disposal

Bed Description	Wt.	Qty.	Cat. No.
DSC-Si			
55mmID x 30mmH	12.5g	6qty/pk	52591-U
70mmID x 40mmH	25g	6qty/pk	52592-U
90mmID x 48mmH	50g	6qty/pk	52593-U
110mmID x 66mmH	100g	3qty/pk	52594-U
Merck-Si			
55mmID x 30mmH	12.5g	6qty/pk	2026-U
70mmID x 40mmH	25g	6qty/pk	2027-U
90mmID x 48mmH	50g	6qty/pk	2028-U
110mmID x 66mmH	100g	3qty/pk	2029-U
Charcoal			
55mmID x 30mmH	12.5g	6qty/pk	2031-U
70mmID x 40mmH	25g	6qty/pk	2032-U
90mmID x 48mmH	50g	6qty/pk	2033-U
110mmID x 66mmH	100g	3qty/pk	2034-U
Magnesium Sulfate			
55mmID x 30mmH	12.5g	6qty/pk	2037-U
70mmID x 40mmH	25g	6qty/pk	2041-U
90mmID x 48mmH	50g	6qty/pk	2043-U
110mmID x 66mmH	100g	3qty/pk	2044-U
Celite®			
55mmID x 30mmH	12.5g	6qty/pk	2047-U
70mmID x 40mmH	25g	6qty/pk	2048-U
90mmID x 48mmH	50g	6qty/pk	2049-U
110mmID x 66mmH	100g	3qty/pk	2064-U

Bed Description	Wt.	Qty.	Cat. No.
Florisil®			
55mmID x 30mmH	12.5g	6qty/pk	2074-U
70mmID x 40mmH	25g	6qty/pk	2076-U
90mmID x 48mmH	50g	6qty/pk	2077-U
110mmID x 66mmH	100g	3qty/pk	2078-U
Alumina-A			
55mmID x 30mmH	12.5g	6qty/pk	2084-U
70mmID x 40mmH	25g	6qty/pk	2087-U
90mmID x 48mmH	50g	6qty/pk	2088-U
110mmID x 66mmH	100g	3qty/pk	2089-U
Alumina-N			
55mmID x 30mmH	12.5g	6qty/pk	2091-U
70mmID x 40mmH	25g	6qty/pk	2092-U
90mmID x 48mmH	50g	6qty/pk	2093-U
110mmID x 66mmH	100g	3qty/pk	2094-U
Alumina-B			
55mmID x 30mmH	12.5g	6qty/pk	2096-U
70mmID x 40mmH	25g	6qty/pk	2097-U
90mmID x 48mmH	50g	6qty/pk	2098-U
110mmID x 66mmH	100g	3qty/pk	2099-U
DPA-6S			
55mmID x 30mmH	6g	6qty/pk	2079-U
70mmID x 40mmH	12.5g	6qty/pk	2081-U
90mmID x 48mmH	25g	6qty/pk	2082-U
110mmID x 66mmH	50g	6qty/pk	2083-U

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Catalog No.	Product Name	Unit
56,542-3	Acetonitrile with 0.035% TFA	4x4L 18L
57,472-4	Acetonitrile with 0.05% TFA	4x4L 18L
57,473-2	Acetonitrile with 0.10% TFA	4x4L 18L
57,694-8	Acetonitrile with 0.035% formic acid	4L 18L
57,854-1	Acetonitrile with 0.05% formic acid	4L 18L
57,695-6	Acetonitrile with 0.10% formic acid	4x4L 18L
59,750-3	Acetonitrile with 0.035% acetic acid	4x4L 18L
59,739-2	Acetonitrile with 0.05% acetic acid	4x4L 18L
59,075-4	Acetonitrile with 0.10% acetic acid	4x4L 18L
57,789-8	Methyl alcohol with 0.10% TFA	4x4L 18L
63,254-6	Methyl alcohol with 0.10% formic acid	4x4L 18L
59,014-2	Water with 0.05% TFA	4x4L 18L

Catalog No.	Product Name	Unit
59,015-0	Water with 0.06% TFA	4x4L 18L
57,690-5	Water with 0.10% TFA	4x4L 18L
57,691-3	Water with 0.10% formic acid	4x4L 18L
59,772-4	Water with 0.035% acetic acid	4x4L 18L
59,761-9	Water with 0.05% acetic acid	4x4L 18L
59,116-5	Water with 0.10% acetic acid	4x4L 18L
57,696-4	Acetonitrile with 0.10% formic acid, 0.01% TFA	4L 18L
57,692-1	Water with 0.10% formic acid, 0.01% TFA	4L 18L
63,233-3	Acetonitrile with 10% water, 0.10% TFA	4x4L 18L
63,232-5	Water with 10% acetonitrile, 0.10% TFA	4x4L 18L
63,245-7	Methyl alcohol with 10% water, 0.10% TFA	4x4L 18L
63,244-9	Water with 10% methyl alcohol, 0.10% TFA	4x4L 18L

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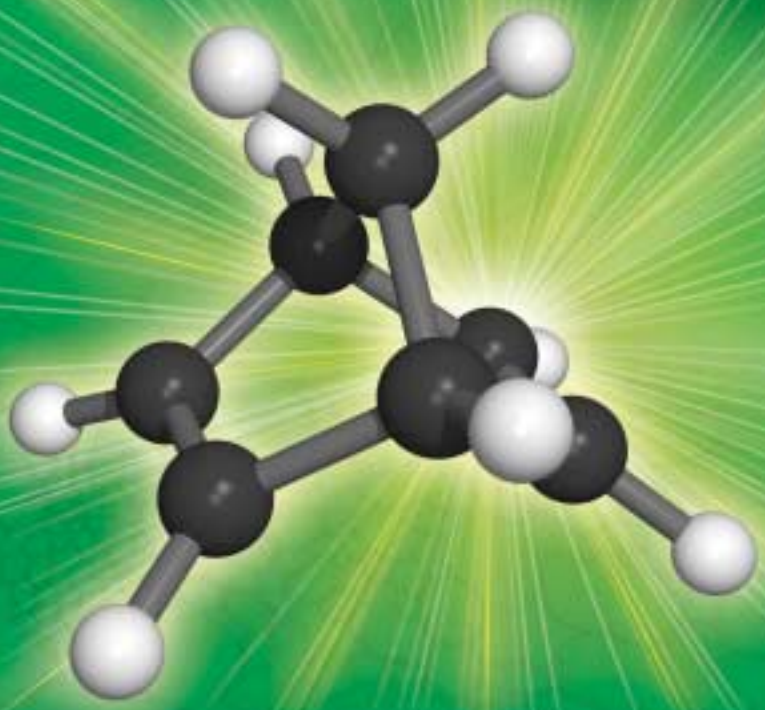
2,5-Norbornadiene

(Bicyclo[2.2.1]hepta-2,5-diene
Product No. B3,380-3, CAS No. 121-46-0)



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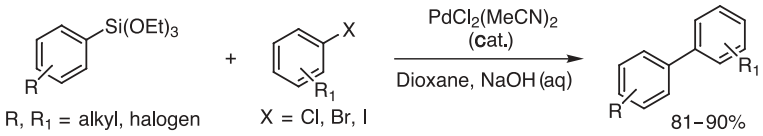
New Alkoxysilanes

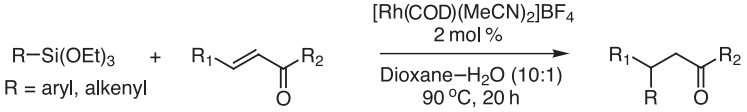
The use of silicon compounds as transmetalation reagents has attracted much attention as a viable alternative to the popular Stille and Suzuki coupling reactions, mainly due to the formation of nontoxic byproducts and the stability of the reagents to many reaction conditions.[1] Silicon-based coupling reactions can be carried out using aryl, heteroaryl, or alkenyl halides and alkoxysilanes in the presence of palladium or rhodium catalysts. Among the various types of silicon compounds available, alkoxysilanes are most effective in the coupling reactions.[2]



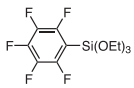
R, R_1 = alkyl, halogen

X = Cl, Br, I

Recently, considerable attention has been paid to the rhodium-catalyzed addition of aryl(trialkoxy)silanes to carbonyl compounds, such as aldehydes, α,β-unsaturated ketones and esters.[3]



59,275-7

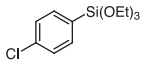


5g
10g
25g

17,556-0

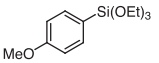
100mL
500mL

59,791-0



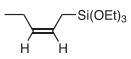
1g
10g

59,701-5



5g
20g

59,264-1



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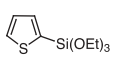
5g

59,700-7



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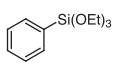
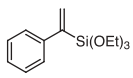
10g

17,560-9



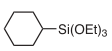
5g
250g
1kg

59,635-3



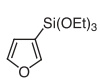
1g
10g

59,242-0



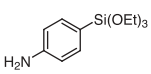
1g
5g

59,231-5



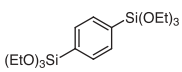
5g

59,647-7



1g
10g

59,803-8



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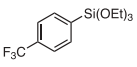
20g

63,043-8



1g
5g

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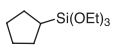
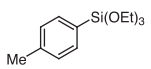


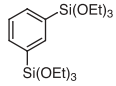
5g

59,157-2



1g
5g

59,813-5



1g
10g

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References: (1) (a) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (b) Chuit, C. et al. *Chem. Rev.* **1993**, *93*, 1371. (c) Horn, K. A. *ibid.* **1995**, *95*, 1317. (d) Hiyama, T.; Shirakawa, E. In *Topics of Current Chemistry*; Miyaura, N., Ed.; Springer-Verlag: Heidelberg, 2002; Vol. 219, p 61. (2) (a) Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835. (b) Tamao, K. et al. *Tetrahedron Lett.* **1989**, *30*, 6051. (c) Shibata, K. et al. *Chem. Commun.* **1997**, 1309. (d) Mowery, M. E.; DeShong, P. *J. Org. Chem.* **1999**, *64*, 1684. (e) Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2140. (f) Lee, H. M.; Nolan, S. P. *ibid.* **2000**, *2*, 2053. (g) Murata, M. et al. *Synthesis* **2001**, 2231. (3) Oi, S. et al. *Org. Lett.* **2002**, *4*, 667.

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Coiled Reflux Condenser

Coolant circulates through the coil. The jacket provides additional cooling capacity by allowing vapors to condense on the inner wall of the jacket. Ʇ24/40 joints.

Overall L (mm)	Cat. No.
200	Z55,360-3
300	Z55,361-1
400	Z55,363-8

Modified Friedrichs Condenser

Molded spiral condensing coolant tube fits closely within jacket to force vapors along the spiral path. The modified feed tube reduces the chance of breakage. Ʇ24/40 joints.

Jacket o.d. (mm)	Overall L (mm)	Cat. No.
37	270	Z55,358-1
37	370	Z55,364-6
54	300	Z55,365-4

Liebig Condenser

Ʇ24/40 outer-top joint with lower, inner, drip-tip joint.

Overall L (mm)	Cat. No.
200	Z55,366-2
300	Z55,367-0
400	Z55,368-9

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Dry Ice Condenser Trap

4mm PTFE stopcock. Use with or without dry ice to condense and collect material in trap.

Reservoir cap. (mL)	Overall L (mm)	Cat. No.
250	450	Z55,355-7
500	470	Z55,356-5
1,000	490	Z55,357-3

Safety Bubbler

Built-in flash arrester bulb prevents backflow. Capacity: 15mL fill mark.

Z55,387-5

Chromatography Sprayer

Provides a fine, uniform spray that is optimized for the development of TLC plates. Also suited for use in electrophoresis.

- Adjustable spray pattern using thumb on vent hole
- Greaseless, screw-threaded T joint will not seize; a simple turn of the threaded cap pulls joint apart safely
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Flask size (mL)	Cat. No.
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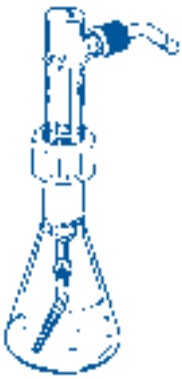
50	Z52,972-9
125	Z52,973-7
250	Z52,974-5

Replacement SafetyBarbs™	
Consists of PBT cap, PP barbed connector, and silicone rubber seal. Choice of straight or angled barb.	
Straight barb	Z54,778-6
Angled barb	Z54,788-3

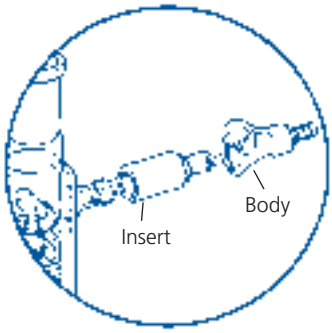


Automatic Shut-Off Quick-Disconnects

Replace removable tubing connectors with these new quick-disconnect fittings, which are made specifically for use with Aldrich glassware. To install quick-disconnects, unscrew tubing connectors on glassware and replace with coupling inserts Z55,337-9 listed below. Order one coupling insert and one coupling body for each glass connection.

Chemically resistant acetal coupling insert and body are spring-loaded, locking, and have 316 SS springs and EPR seals. When pulled apart, both sides seal quickly and automatically. For use with flexible ¼-in. i.d. tubing.

Coupling insert, GL 14 inner thread Z55,337-9
Coupling body, ¼ in. i.d. tubing connection Z55,338-7



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BioNMR in Drug Research

R. Mannhold, G. Folkers, H. Kubinyi, and O. Zerbe, Eds., John Wiley & Sons, New York, NY, 2003, 450pp. Hardcover.

Presents the theoretical background on NMR of biomolecules, and the use of NMR techniques in determining the structures of proteins and nucleic acids. BioNMR spectroscopy offers a universal tool for examining the binding of an active substance to its target protein, thereby benefiting drug development.

Z70,054-1

Characterization of Materials (2-Volume Set)

E. N. Kaufmann, Ed., John Wiley & Sons, New York, NY, 2003, 1464pp. Hardcover.

Provides comprehensive coverage of materials characterization techniques including computational and theoretical methods, crystallography, mechanical testing, thermal analysis, optical imaging and spectroscopy.

Z55,373-5

Handbook of Radiopharmaceuticals

M.J. Welch and C.S. Redvanly, Eds., John Wiley & Sons, New York, NY, 2003, 848pp. Hardcover.

Covers radiochemistry and clinical applications including the production of various radionuclides, positron emission tomography (PET), and drug development. Discussions on the uses of radiopharmaceuticals in the diagnosis and therapy of cancer and other diseases are also included.

Z55,369-7

Handbook of Free Radical Initiators

E. T. Denisov, T. G. Denisova, and T. S. Pokidova, John Wiley & Sons, New York, NY, 2003, 879pp. Hardcover.

This book presents physicochemical data on radical initiators and reactions that generate radicals. Free radical initiators serve as reactive intermediates in organic and polymer syntheses, and play an important role in research on oligomerization, network formation, and kinetics.

Z55,382-4

Solvent-free Organic Synthesis

K. Tanaka, John Wiley & Sons, New York, NY, 2003, 433pp. Hardcover.

Supplies alternative answers to the demand for increasingly clean and efficient chemical syntheses.

Z55,370-0

The Laboratory Quality Assurance System: A Manual of Quality Procedures and Forms (with CD-ROM)

3rd ed., Thomas A. Ratliff, John Wiley & Sons, New York, 2003, 236pp. Softcover.

Incorporates changes to ANSI/ISO/ASQ 9001-2000 pertaining to laboratories and provides information on the inter-relationship of ANSI/ISO 17025:1999 and ANSI/ISO/ASQ. Also provides blank forms used in preparing a quality manual.

Z55,340-9

Wiley Guide to Chemical Incompatibilities

R. P. Pohanish and S.A. Greene, John Wiley & Sons, New York, NY, 2003, 1408pp. Hardcover.

Compiles hard-to-find data on over 11,000 chemical compounds, describing a wide range of chemical reactions that produce undesirable results in uncontrolled situations.

Z55,348-4

The Pilot Plant Real Book

F. X. McConville, FXM Engineering and Design, Worchester, MA, 2002, 312pp. Softcover.

A practical handbook for chemists, chemical engineers, technicians, and students working in chemical process development or tech transfer to pilot or commercial plants.

Z55,385-9

Candid Science: Conversations with Famous Chemists

I. Hargittai, Imperial College Press, London, UK, 2000, 516pp. Softcover.

36 chemists discuss their lives in science, how they began, their aspirations, and their hardships and triumphs.

Z55,383-2

Candid Science II: Conversations with Famous Biomedical Scientists

I. Hargittai, Imperial College Press, London, UK, 2002, 604pp. Softcover.

Contains 36 interviews that present a cross-section of biomedical science, important research areas, and discoveries.

Z55,384-0

Purification of Laboratory Chemicals

5th ed., W. L. F. Armarego and C. Chai, Elsevier-Science, 2003, 624pp. Softcover.

Updated to include more detailed descriptions of commonly used techniques. New procedures, ionization constants, and more detail about trivial compound names are included.

Z54,183-4

Microwave Synthesis: Chemistry at the Speed of Light

B. L. Hayes, CEM Publishing, Matthews, NC, 2003, 289 pp. Hardcover.

Benefiting both the practicing chemist and student alike, this book discusses microwave-based chemistry for the organic laboratory. Topics include optimizing reactions, applications in microwave synthesis, atmospheric and pressurized reactions, choosing the best solvent for a microwave-assisted reaction, solvent-free reactions, and the fundamentals of microwave theory.

Z55,386-7

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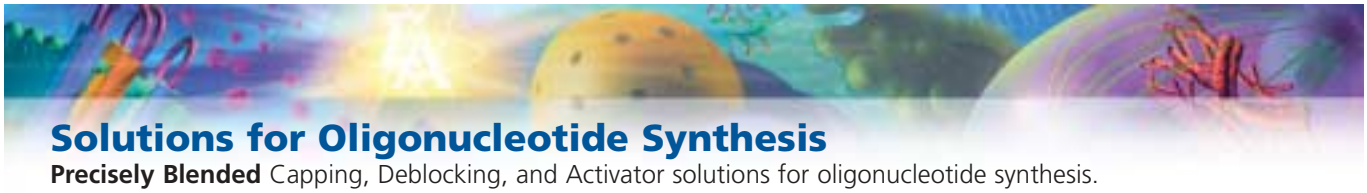

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55,533-9	**Cap Mix A, with pyridine** (Contains 80% tetrahydrofuran: 10% acetic anhydride: 10% pyridine)	1L 2L
55,532-0	**Cap Mix B** (Contains 84% tetrahydrofuran: 16% 1-methylimidazole)	1L 2L

Catalog No.	Product Name	Unit
55,535-5	**Cap Mix B, with pyridine** (Contains 80% tetrahydrofuran: 10% pyridine: 10% 1-methylimidazole)	1L 2L
56,193-2	**Deblock** (Contains 3% trichloroacetic acid in dichloromethane)	1L 2L
55,404-9	**Activator** (1-*H*-Tetrazole, 3 wt. % solution in acetonitrile)	1L 2L

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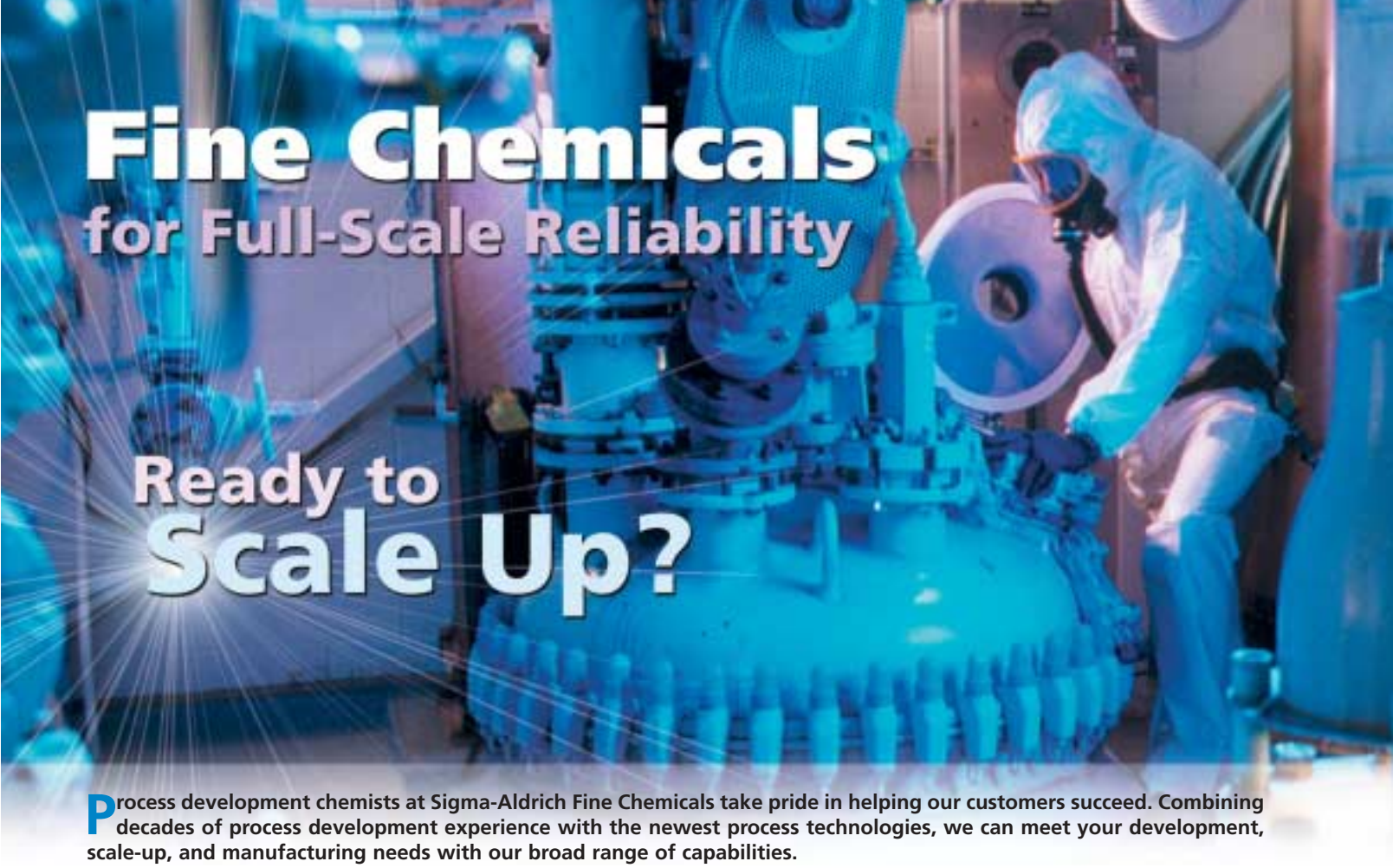

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