Pergamon

Tetrahedron Vol. 50, No. 8, pp. 2297-2360, 1994

0040-4020/94 $24.00+0.00

0040-4020(94)E0091-7

TETRAHEDRON REPORT NUMBER 350

THE CHEMISTRY OF 2-OXAZOLINES (1985-PRESENT)

Thomas G. Gant and A. I. Meyers*

Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523, U.S.A.

Contents

I.	Introduction	2298
II.	Preparation of Oxazolines	2298
	A. Carboxylic acids—direct methods	2298
	B. Hydroxyamides—hydroxyl activation	2299
	C. Eneamides—alkene activation	2300
	D. Epoxide/aziridine ring opening reactions	2302
	E. Electrocyclic reactions	2303
	F. Schollkopf method	2304
	G. Other methods	2307
III.	Transformation of Oxazolines into other Functional Groups	2310
IV.	Transformation of Oxazolines into other Heterocycles	2313
V.	Utility as Protecting Group	2316
VI.	Aryl Oxazolines	2317
	A. Nucleophilic substitution	2317
	B. Nucleophilic addition	2321
	C. Metalation and electrophilic substitution	2327
VII.	Aliphatic Oxazolines	2333
	A. Metalations	2333
	B. Pericyclic reactions	2335
	C. Conjugate additions	2338
	D. Other reactions of aliphatic oxazolines	2340
VIII.	Oxazolines as Ligands for Catalysis	2343
IX.	Miscellaneous	2346
X.	Summary	2350

I. INTRODUCTION

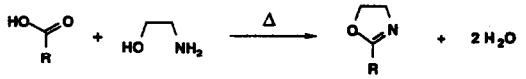
The 2-oxazoline ring system, a simple cyclic imino ester, has demonstrated its vast synthetic potential as a masked carboxylic acid for over 100 years. A number of reviews have appeared[1] and to the authors' delight, the literature still abounds with studies of novel and important synthetic behavior. The purpose of this review is to assemble the literature dealing with the synthesis and ensuing chemical prowess of the 2-oxazoline since its last survey (1985) by the senior author.[1e]

In this age of phenomenal regio- and stereochemical control in synthesis, the 2-oxazoline moiety continues to play a significant role. It has attracted scientists from various areas who have, as the present authors have, discovered its unique properties and its capacity to serve as synthetic precursor or mediator in a multitude of chemical processes. The literature from 1985 until early 1993 has been scanned as thoroughly as possible and, although the most significant studies are represented herein, some surely have eluded careful search and for this the authors apologize and hope that readers will inform them of any omissions so such work may be included in a future discussion of this remarkable molecular system.

II. PREPARATION OF OXAZOLINES

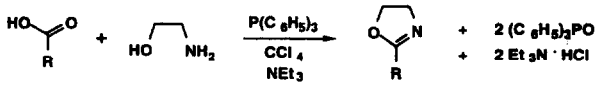
A. *Carboxylic Acids - Direct Methods.*

The 2-oxazoline[2] ring system has been known for more than a century.[3] A number of reliable preparative methods, developed before this heterocycle saw widespread utility, are still valuable and in use today. Simple cyclodehydration of a carboxylic acid and a β-amino alcohol (eq. 1) can yield the oxazoline under conditions of high temperature, azeotropic water removal, or other dehydrative means. This preparation, however, is not very reliable for volatile β-amino alcohols, nor is it useful for sensitive functionality present in the components. It has, nonetheless, found utility in the preparation of high molecular weight oxazolines for the purpose of mass spectral analysis.[4] The



(eq. 1)

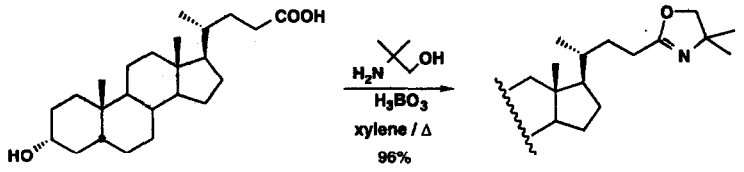
latter approach is not generally useful to the synthetic chemist dealing with a variety of complex materials. An excellent and versatile procedure was developed by Vorbruggen[5] to lower the energy barrier to formation of oxazolines from these simple precursors.[6] By using traditional and modified Appel reaction conditions,[7] the oxazoline can be assembled in a one-pot procedure at room temperature for a variety of acids and amino alcohols.



(eq. 2)

Barton[8] has also described a one-pot procedure for the conversion of carboxylic acids to oxazolines in the absence of labile functionality. The harsh conditions - boric acid, anhydrous

xylene, reflux 48h with azeotropic removal of water - preclude general applicability but may find considerable use in limited cases due to the good yields of oxazolines obtained. Trivedi recently used this approach in the protection of the steroid, lithocholic acid, **1**.[9]

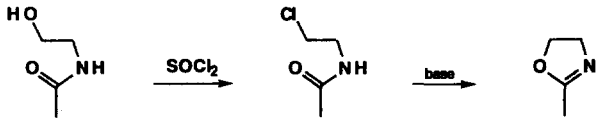


1 **2**

B. *Hydroxyamides - Hydroxyl Activation.*

For simple, sturdy molecular systems, the thionyl chloride induced ring-closure (Scheme 1) of a hydroxyamide precursor, **3**, to the oxazoline, **5**, proceeds particularly well. Occasionally, the problem of chloroamide **4** formation limits the utility of this route,[10] and although the chloroamide can usually be converted to the oxazoline, **5**, the inclusion of a base-mediated additional step is unattractive. Chloroamides such as **4** have also been converted to the respective oxazolines by silver triflate induced cyclization.[11] Again this method suffers because of the additional step required.

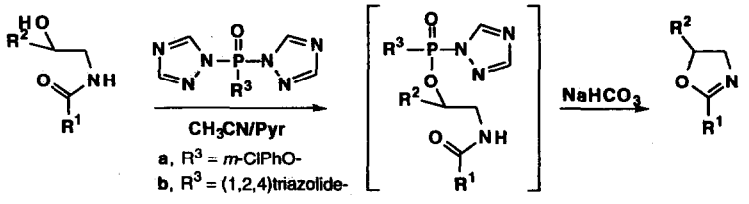
Scheme 1.



3 **4** **5**

Another common limitation observed in the cyclization of hydroxyamides is the indiscriminate reactivity of thionyl chloride. As a result, a number of mild, selective alternatives have been developed to cyclize the easily prepared hydroxyamide precursors.[12] The phosphorous-mediated Appel reaction has been applied in several forms.[13] Recently it was shown (Scheme 2) by Kwiatkowski[14] that treatment of hydroxyamide **6** with the analogous phosphorous hydroxy-activating

Scheme 2.

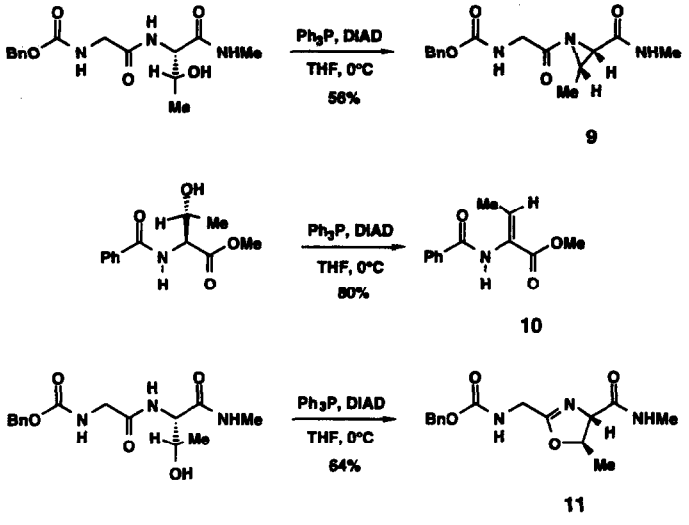


6 **7** **8**

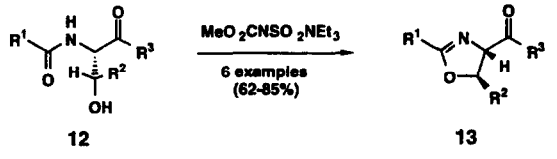
agents, *o*-chlorophenylphosphoro-bis-(1,2,4)-triazolide, **a**, or phosphoro-tris-(1,2,4)-triazolide, **b**, in pyridine at ambient temperature gave aryl- and benzyl- oxazolines **8** in good yields irrespective of the electronics of the aryl ring. Most cyclizations were achieved directly, although base was added in some cases to facilitate closure of the presumed intermediate **7**.

Galeotti employed the Mitsunobu conditions (DEAD/PPh_3) in the cyclization of dipeptides possessing serine or threonine residues[15] and the method gave generally satisfactory results. By contrast, Wipf found that similar conditions (diisopropylazadiester "DIAD"/PPh_3) showed a lack of generality[16], affording aziridines, **9**, and alkenes, **10**, in addition to the expected oxazolines, **11** (Scheme 3). Wipf reported that this problem can be circumvented through the use of the Burgess

Scheme 3.



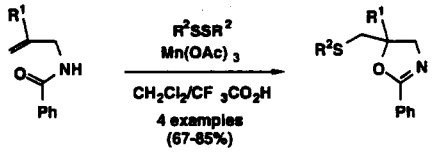
reagent.[17] A number of oxazolines **13** as well as thiazolines, were prepared from the corresponding dipeptides **12** in this manner in good yields, thus opening efficient routes to conformationally restricted peptides -- an area of increasing importance in medicinal chemistry.



C. *Eneamides - Alkene Activation.*

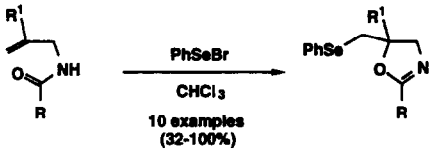
In the cyclization of *N*-(allyl)amides, the π-electrons of the double bond act as the leaving group. In the early literature, this transformation was accomplished through the use of concentrated H_2SO_4.[18] Once again the need arose for milder reagents to perform this transformation. Sulphenylation employed by Mellor,[19] afforded 5-thiomethoxymethylether substituted oxazolines **15**

from the alkene **14** in good yield. This technique appears to be limited to arylamides since the only example of an aliphatic amide reported gave low yield (10%) of cyclized product.



14 **15**

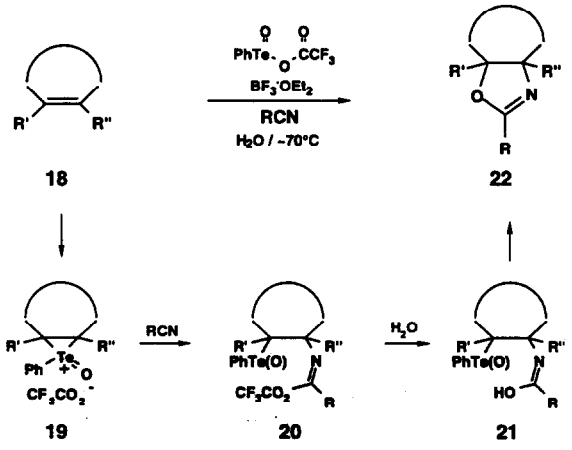
A similar approach recently described by Engman[20] extends this 5-exo-trigonal cyclization manifold to non-aromatic eneamides. Alkene activation with phenylselenenyl bromide proved practical for both aryl- and alkyl- eneamides, **16**, leading to phenylselenenylmethyl-substituted oxazolines, **17**.



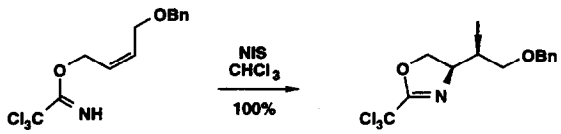
16 **17**

A more convergent and general approach developed by Ogura[21] utilizes *inter-* rather than *intra-* molecular formation of oxazolines by way of an amidotellurinylation of alkenes (Scheme 4). A variety of alkenes, **18**, was treated with an electrophilic tellurium reagent affording presumed metallacycle, **19**. Subsequent Ritter reaction[22] (*vide infra*) with various nitriles gave oxazolines **22** via likely intermediates **20** and **21**. The method was used to give a unique array of bicyclic systems and was found to be general for acyclic- as well as cyclic- alkenes.[23]

Scheme 4.



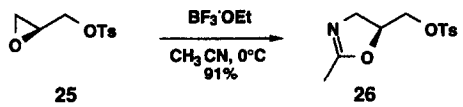
Cardillo[24] has used the enamide approach quite effectively in the synthesis of acyclic amino sugars. The *O*-allyl iminoether **23** was activated toward cyclization with *N*-iodosuccinimide and gave the oxazoline **24** in quantitative yield. The process was quite substrate dependant and some imidates gave the 6-membered oxazine ring (6-endo-trigonal cyclization) as the primary product.



23 **24**

D. *Epoxide/Aziridine Ring Opening Reactions.*

Several reports have described strained-ring-opening reactions in the formation of oxazolines.[25] Recent advances in the preparation of appropriate starting materials have created a new impetus for further study in this area. The asymmetric epoxidation developed by Katsuki and Sharpless[26] was recently applied to an oxazoline synthesis.[27] The readily prepared glycidyl tosylate **25**, an enantiomerically enriched epoxide obtained from the Sharpless epoxidation, was subjected to acid-catalyzed ring opening.[28] The optically active oxazoline **26** was obtained in an efficient one-step process, presumably via the nitrilium ion in a Ritter-type reaction.

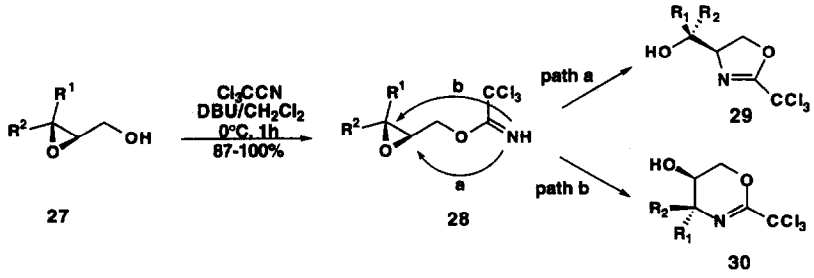


25 **26**

Other reagents have been employed to generate the oxazoline from an epoxide and a nitrile including Amberlyst A 26,[29] $CoCl_2$,[30] $HClO_4$,[31] TMS-CN,[32] and SiF_4,[33] presumably all proceed via the Ritter nitrilium salt.[34]

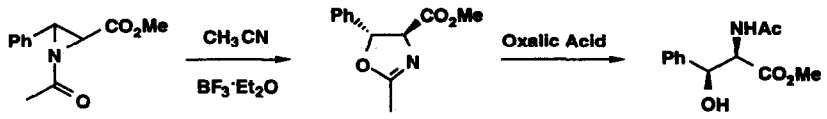
A similar approach (Scheme 5) by Schmidt[35] incorporated the hydroxyl moiety in **27** into the ring by way of the readily formed imidic ester, **28**. Two cyclization manifolds exist. The oxazoline, **29**, predominated over the six-membered oxazine, **30**, when methanesulfonic acid was used as catalyst.

Scheme 5.



27 **28** **29** **30**

In an analogous system, *N*-(acyl)aziridine **31** has been converted to the oxazoline, **32**, by acid catalysis according to an earlier route described by Heime.[36] Zwanenburg utilized this approach in the synthesis of phenylalanine derivatives,[37] **33**.

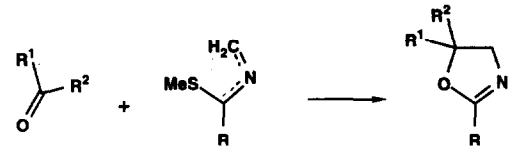


31 32 33

Laurent and Stamm[38] reported a reductive electrocatalytic method whereby single electron transfer to the *N*-acylaziridine was purported to set in motion a series of events culminating in oxazoline formation. The yields were low (25-42%) and so the thermal route remains the method of choice.

E. *Electrocyclic Reactions.*

Azomethine ylides have been combined with acyl substrates in [3+2] cycloadditions to yield oxazolines (eq. 3). The ylide must bear a leaving group so the incorporated ring nitrogen may dehydrate yielding the imine. Utilization of either aldehydes or ketones as substrate affords

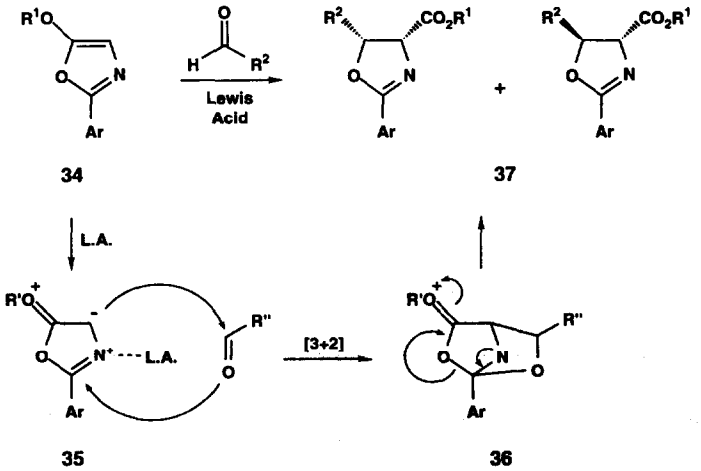


(eq. 3)

oxazolines regioselectively provided the appropriate conditions are used. Padwa[39] found that regioselectivity was achieved under conditions favoring stepwise addition of the 1,3-dipole to carbonyl compounds. Tsuge[40] reported that aromatic carbonyl compounds gave favorable results while their aliphatic counterparts failed to react. These, and other limitations, relegate this method to a list of potentially useful, if currently unpractical, synthetic methods.

Another theoretically interesting, if limited, approach to 2-oxazoline preparation calls upon the [3+2] cycloaddition of aldehydes with 5-alkoxyoxazoles **34** to produce the *cis/trans* mixture, **37**.[41]

Scheme 6.

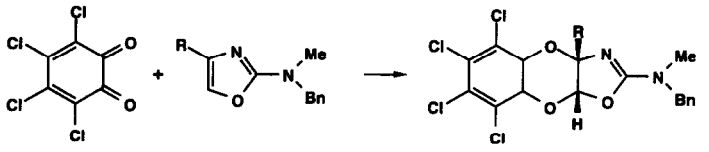


34 37

35 36

This Lewis acid catalyzed reaction was optimized for electron-poor aromatic aldehydes while other aldehydes gave less impressive results. Intermediates **35** and **36** are simplified representations of the likely [3+2] pathway.

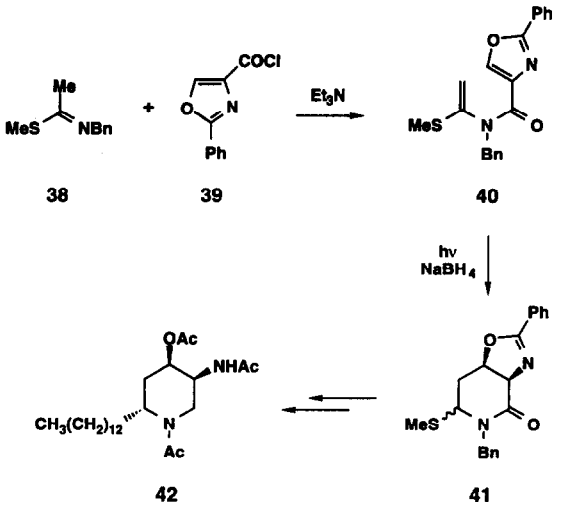
An oxazole precursor was used by Dondoni[42] to produce oxazolines (eq. 4) via a [4+2] process to functionalize electron poor dienes. The inverse-demand hetero-Diels-Alder afforded 2-amine substituted oxazolines in good yield.



(eq. 4)

A resourceful approach to 3-amino-4-alkoxypiperidines (Scheme 7) was described by Naito.[43] Oxazole **40** was readily prepared from acylation of thioimidate **38** with oxazole acid chloride **39**. A photoinduced electrocyclic (3,3) rearrangement followed by iminium reduction with $NaBH_4$ gave the fused piperidinone/oxazoline **41** in good yield. Further manipulations provided the first total synthesis of the neoplastic alkaloid pseudodistomin tetrahydroacetate, **42**.

Scheme 7.

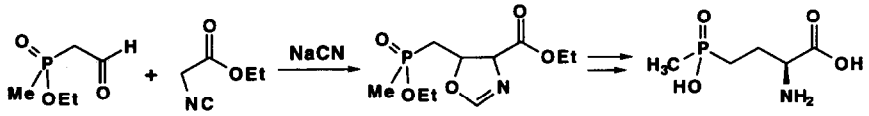


F. *Schollkopf Method.*

The combination of aldehydes with isocyanides produces oxazolines under basic or acidic catalysis[44] and exhibits a remarkable level of generality. Among the scores of papers that have appeared having this reaction in some key step, a few are illustrated below to exemplify the range of catalysts and substrates.

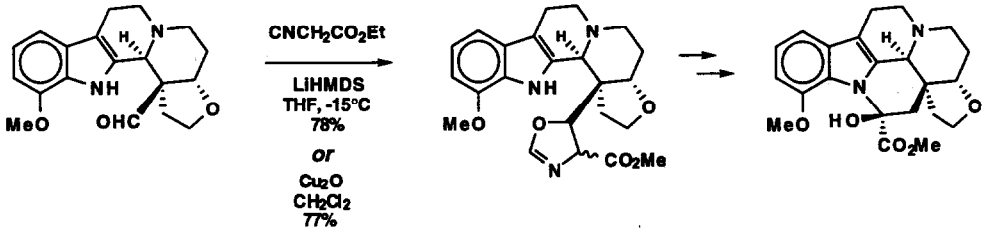
Bases commonly employed to mediate this transformation include cyanide,[45] *t*-butoxide,[46] hydroxide[47] and amines.[48] Zeiss[49] recently used sodium cyanide in the homologation of

phosphinate aldehyde **43** with ethyl isocyanoacetate **44** to afford the carboxyoxazoline, **45**. The oxazoline was carried on to the naturally-occurring amino acid phosphinothricin, **46**.



43 **44** **45** **46**

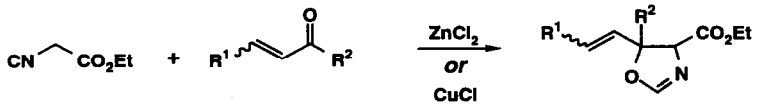
Several transition metal catalysts have proven effective for the isocyanide carbonyl condensation. Langlois,[50] using the aldehyde **47** and the isocyano ester, produced oxazoline **48**



47 **48** **49**

under basic conditions or alternatively through transition metal catalysis. The oxazoline **48** was taken on to the indole alkaloid cuanzine, **49**, a close relative of the well-known Eburna alkaloid, vincamine.

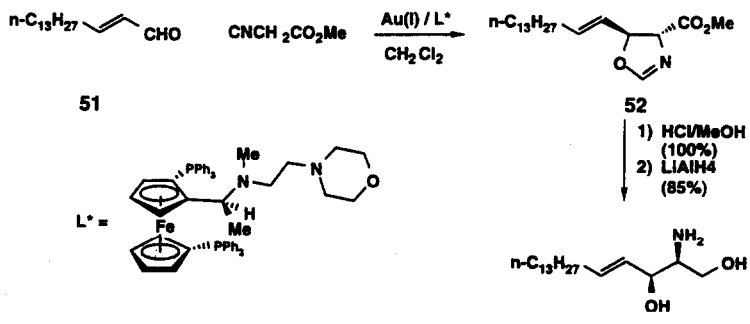
Ito has used $ZnCl_2$, as well as CuCl to effect the formation of 5-vinyl substituted oxazolines,[51] **50**, in good yields although *cis:trans* mixtures were often obtained.



50

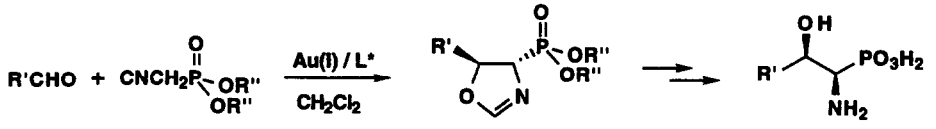
A particularly fruitful application of the Scholikopf method was developed by Ito and Hayashi,[52] producing non-racemic oxazolines through asymmetric catalysis (Scheme 8). It was shown that addition of a chiral non-racemic ferrocenylphosphine-gold(I)[53] or -silver(I)[54] complex (1 mol%) to isocyanoacetate and various aldehydes allowed highly enantioselective syntheses of many valuable targets. A synthesis of *threo*- and *erythro*-sphingosines[55] began with the long chain α,β-unsaturated aldehyde, **51**. The acyclic aldehyde was allowed to react with the isocyanoacetate in the presence of the catalyst, **54**. The *trans* oxazoline **52** predominated 89/11 over the *cis* isomer and was obtained in 93% ee. Acidic hydrolysis produced the α-amino ester in quantitative yield. Reduction gave an 85% yield of D-threo-sphingosine, **53**.

Scheme 8.



51 52 54 53

The versatility of this method was extended by Togni and Pastor[56] to phosphonic acid analogs of α-amino acids through a synthesis of oxazolinylphosphonates,[57] **55**. Ito and Hayashi published a virtually identical synthesis, though they carried the derived oxazolines on to the intended targets, **56**.[58]

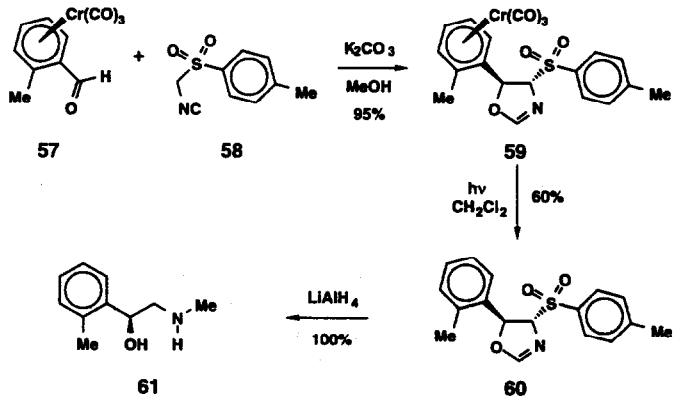


55 56

In a synthesis that takes advantage of chiral non-racemic chromium-tricarbonyl-arenealdehydes as substrates, Solladie-Cavallo and Colonna have found conditions that produce oxazolines diastereospecifically. Three dissimilar bases have been used in this approach with K_2CO_3 (Scheme 9)[59] and LDA (Scheme 10)[60] giving excellent results in various instances. The oft-used cyanide catalyst gave only moderate diastereoselectivity, as is usually the case.

A tosyl group was used to enhance acidity in the coupling partner **58** (Scheme 9) which when combined with chiral complex **57** in the presence of a base afforded an excellent yield of the

Scheme 9.



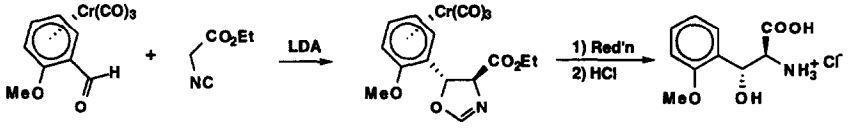
57 58 59 61 60

oxazoline, **59**. The *trans* complex so-produced, was photochemically *de*complexed from the chromium moiety to afford **60**. Reduction with $LiAlH_4$ gave **61** with the desired 4-methylene group α

to the nitrogen illustrating the value of the tosyl group for easy removal. The optically pure halostachine analog **61** was obtained in excellent overall yield.

A carboxyl group at C-4 was, in fact, necessary for a related application (Scheme 10) that used ethyl isocyanoacetate. By use of the same general approach, an α-amino-β-hydroxy acid, **62**, was efficiently assembled.

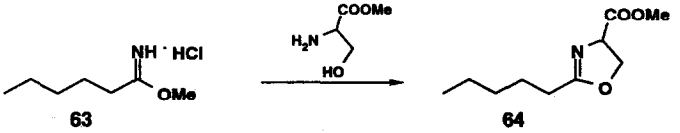
Scheme 10.



62

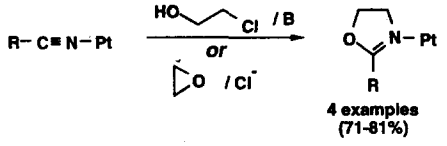
G. *Other Methods.*

A traditional method often employed with acid-stable substrates utilizes amino alcohols in a condensation step with iminoethers as shown by Hajdu in the synthesis of an antitumor phospholipid.[61] In this manner, iminoether **63** (as the HCl salt) was condensed with serine methyl ether to give the methylcarboxyoxazoline **64** directly. Many additional examples of this route have been described.[62]

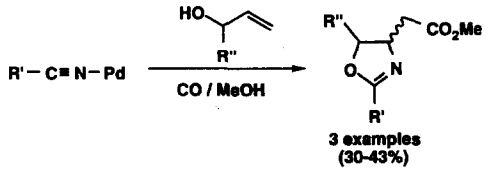


63 **64**

Transition metal coordination compounds have attracted so much interest in recent years, it is not unexpected that oxazolines have been produced this way. Michelin[63] used a platinum complex to effect the synthesis of platinum-oxazoline coordinates from various nitriles (eq. 5). This general route had been previously used by Hegedus,[64] though yields were lower for the palladium-based synthesis (eq. 6).



(eq. 5)

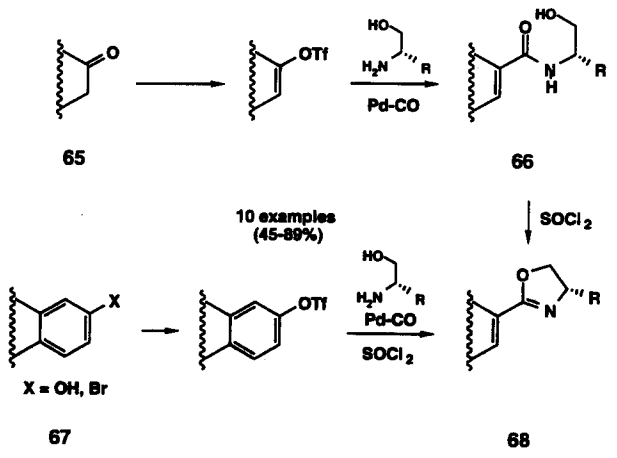


(eq. 6)

A further contribution in the transition metal arena has been aimed at production of an oxazoline precursor, the hydroxyamide.[65] Starting with enol triflates derived from ketones, **65**, as

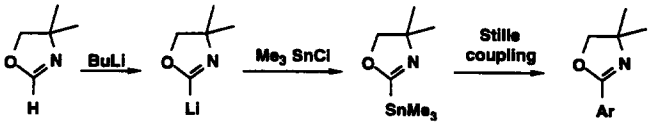
well as phenols and bromides, **67**, a coupling method developed by Stille[66] and modified by Ortar[67] and Overman[68] gave the desired amido alcohols, **66**. Treatment with thionyl chloride afforded good yields of a wide variety of oxazolines, **68** (Scheme 11).

Scheme 11.



Occasionally, it is most efficient to preassemble the oxazoline nucleus then follow with a subsequent homologation of a substrate with the transferable oxazolinyl moiety. Dondoni has aptly transferred oxazolinylstannanes **71** to aromatic halides via a Stille coupling affording aryloxazolines, **72**.[69] The requisite stannane **71** may be readily prepared from the 2-H-oxazoline **69** via lithiation to **70** and subsequent treatment with an appropriate tin electrophile. The generality of the process

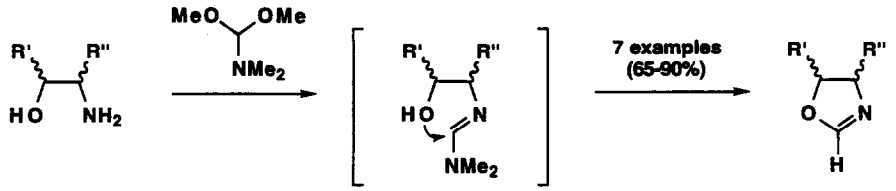
Scheme 12.



with respect to the aromatic substrates was explored and found to be equally efficient with electron-withdrawing groups as well as electron-releasing groups.

The 2-H oxazolines, e.g. **69**, required for the application above (Scheme 12) and others have been prepared by various methods. However, one route that has proven efficient (Scheme 13) was accomplished by treatment of various amino alcohols **73** with dimethylformamide dimethylacetal under azeotropic dehydration conditions, to afford **75**.[70] Presumably, the formamidine **74** is the intermediate through which the cyclization proceeds.

Scheme 13.

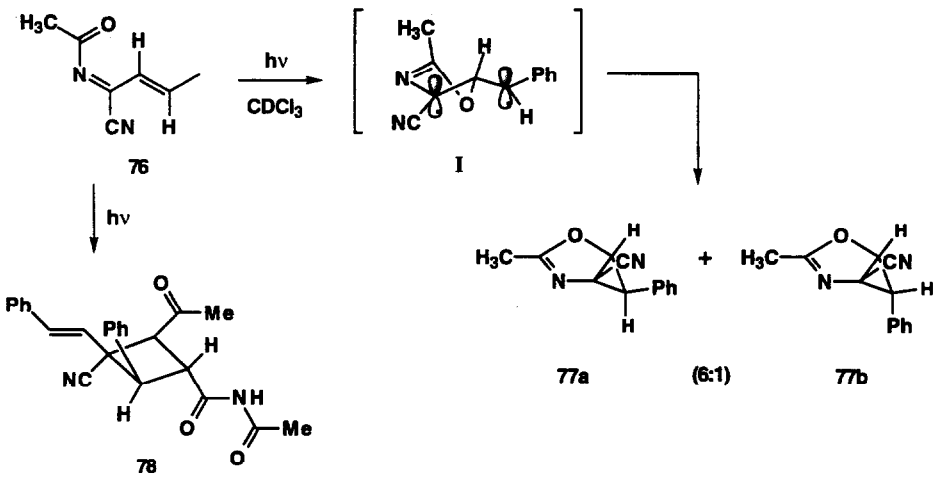


73 74 75

The oxazoline ring system is often encountered inadvertently as a consequence of its thermodynamic stability. In an effort to show the depth of the thermodynamic well in which the oxazoline ring lay, the following examples are included.

A study focusing on the photochemical behavior of azadienes found that the *N*-acyl substrate **76** afforded a 6:1 ratio of fused cyclopropyloxazolines **77a,b** presumably passing through intermediate diradical, **I**.[71] The products were obtained in 98% yield when the reaction was carried out in $CDCl_3$. Alternatively, solid state irradiation produced 2+2 cycloadduct **78** in a 2:1 ratio over the oxazoline.

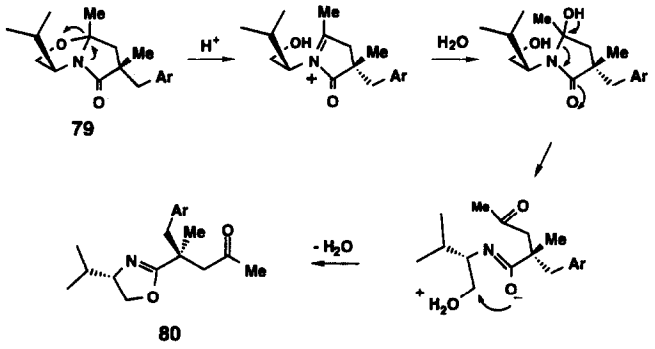
Scheme 14.



76 I 77a 77b 78

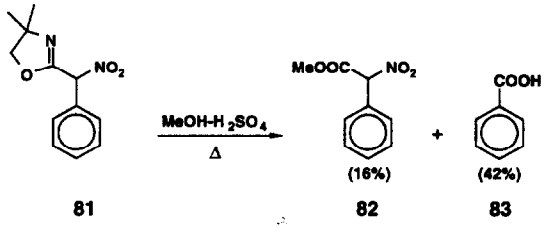
Oxazoline **80** was smoothly produced upon hydrolysis of bicyclic lactam, **79**.[72] The presumed mechanism is outlined in Scheme 15. The harshness of the conditions, triflic acid in 1,2-dichloroethane heated at reflux, survived by the oxazoline shows the stability of the heterocycle to acid. The topic of oxazoline stability will be discussed further in section V.

Scheme 15.

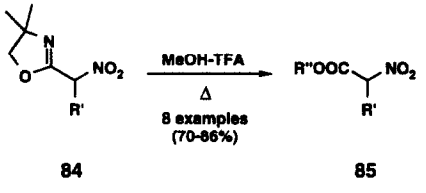


III. TRANSFORMATION OF OXAZOLINES INTO OTHER FUNCTIONAL GROUPS

Many schemes have been developed for the transformation of oxazolines into other functional groups. Simple hydrolysis, under strongly acidic or basic conditions typically affords the carboxylic acid directly, provided that no other labile functionality is present in the substrate.[73] It was recently found by Feuer[74] (eq. 7) that the typical acidic conditions, methanolic sulfuric acid, afforded the Nef product **83** in the case of a 2-(α-nitrobenzyl)-oxazoline **81** in preference to the expected ester **82**. This pathway was circumvented through the use of trifluoroacetic acid in methanol (eq. 8). A number of similar nitro derivatives **84** gave the corresponding methyl ester **85**



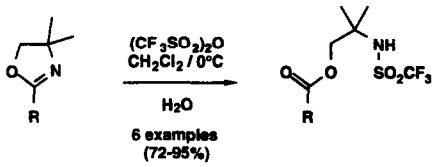
(eq. 7)



(eq. 8)

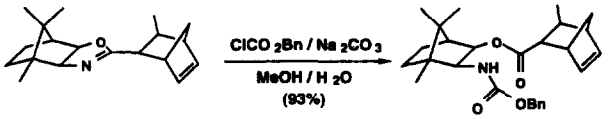
directly and in high yield. Trifluoroacetic acid (TFA) has been previously reported[75] to hydrolyze the oxazoline to the amino ester in the presence of Na_2SO_4.

Other techniques for oxazoline cleavage have been developed to circumvent side reactions associated with the use of strong protic acids. Weinreb[76] described an *N*-chlorination method using bleach to allow more facile hydrolysis to produce the carboxylic acids. However, this has proven to be substrate sensitive. In response to this limitation, Phillion[77] employed trifluoromethanesulfonic anhydride as the *N*-activating reagent and obtained high yields of ester **86**.



86

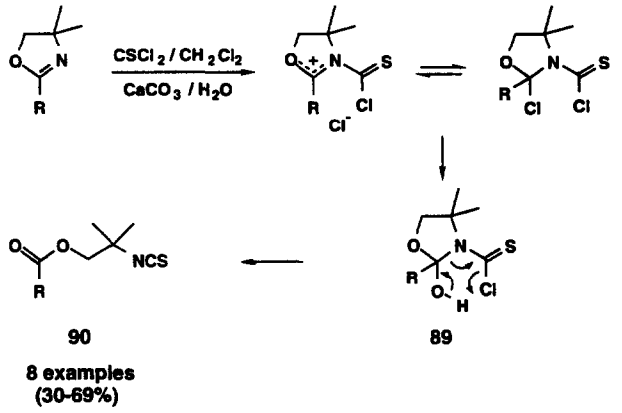
Similarly, Langlois[78] treated a cetol-derived oxazoline **87** under Schotten-Baumann conditions to effect an efficient hydrolysis to the ester, **88**. This process appears to overcome the failure of both the chlorination method and direct acidic hydrolysis described above.



87 88

An unusual ring-opening (Scheme 16) employing thiophosgene provided isothiocyanate esters **90** in moderate yields.[79] The authors suggested a mechanism wherein *N*-thioacylation was followed by hydroxide attack at the iminium bond. Loss of HCl from intermediate **89** accounts for the breakdown to the observed products.

Scheme 16.

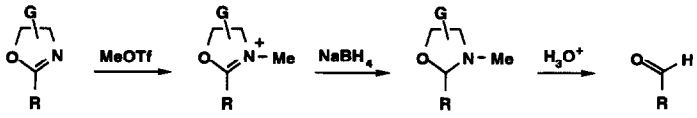


90 89

8 examples
(30-69%)

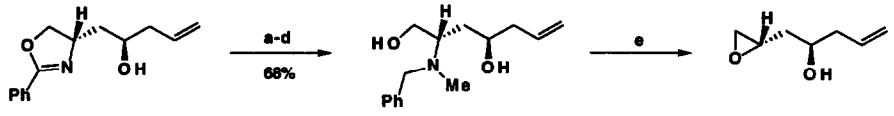
The facile conversion of oxazolines to nitriles by use of $POCl_3$ has also been described.[80] This is another very useful route, in the absence of labile functionality, to reach an alternative functional group in the acid-oxidation state. Although this and the methods described above are useful, frequently a reductive removal of the oxazoline is more attractive. The transformation of oxazolines to aldehydes (Scheme 17) has been found to be both versatile and efficient in a number of instances.[1e] Typically the oxazoline is quaternized thus activating the imine π-system toward nucleophilic attack. For example, treatment of an oxazoline, **91**, with methyl triflate gives the oxazolinium species **92** now susceptible to borohydride reduction. The resultant *N*-methyl oxazolidine **93** can be readily hydrolyzed to the aldehyde, **94**, under mildly acidic conditions.

Scheme 17.



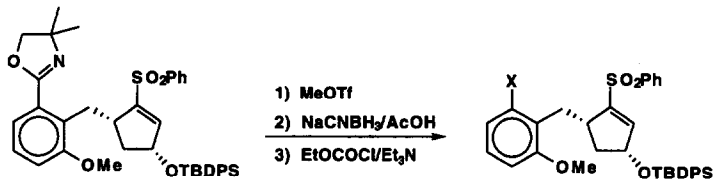
Reduction of the oxazoline to the amino alcohol has recently allowed conversion to an epoxide (Scheme 18). Using the procedure developed by Castedo,[81] an "epoxide-oxazoline equivalency" study by McGarvey showed the interconversion of the two heterocycles.[82] Reduction of oxazoline **95** was followed by a two-step methylation of the nitrogen to afford amine **96**. The tertiary amine could then be converted to epoxide **97** in the presence of dichlorocarbene.It is noteworthy to recall the converse transformation, which allowed a ready formation of oxazolines from epoxides (Section II C).

Scheme 18.



Key: (a) TBSOTf, Et_3N, 0°C; (b) DIBAL, $PhCH_3$, 0°C; (c) HCHO, PhH, Dean-Stark (-H_2O); (d) DIBAL, $PhCH_3$, -78°C; (e) $CHCl_3$, 50% NaOH (aq.), Bu_4NCl (cat.).

Fuchs[83] reported a one-pot procedure to reach the chloromethyl group by treatment of oxazoline **98** with methyl triflate followed by acid catalyzed sodium cyanoborohydride reduction to give the tertiary amine, **99**. Addition of a large excess of ethyl chloroformate led to the chloride, **101**,

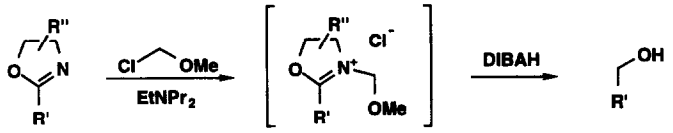


98

99: X = $CH_2NMeCMe_2CH_2OH$
100: X = $CH_2NMeCMe_2CH_2OCO_2Et$
101: X = CH_2Cl

via carbonate **100** in 88% yield overall. Reductive conversion of oxazolines to amines has been accomplished by electroreduction[84] as well as by hydride reducing agents as noted above.

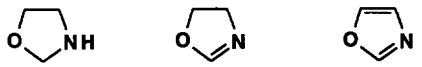
The conversion of oxazolines to carbinols has been accomplished frequently by various two-step procedures. Recently the first example of a one-pot procedure (eq. 9) was developed utilizing chloromethyl methyl ether (MOMCl) or (trimethylsilyl) ethoxymethyl chloride (SEMCl) as activating agent followed by diisobutylaluminum hydride (DIBAH) reduction.[85] Various aryloxazolines were reduced to the respective alcohols in moderate to good yield.



(eq. 9)

IV. TRANSFORMATION OF OXAZOLINES INTO OTHER HETEROCYCLES

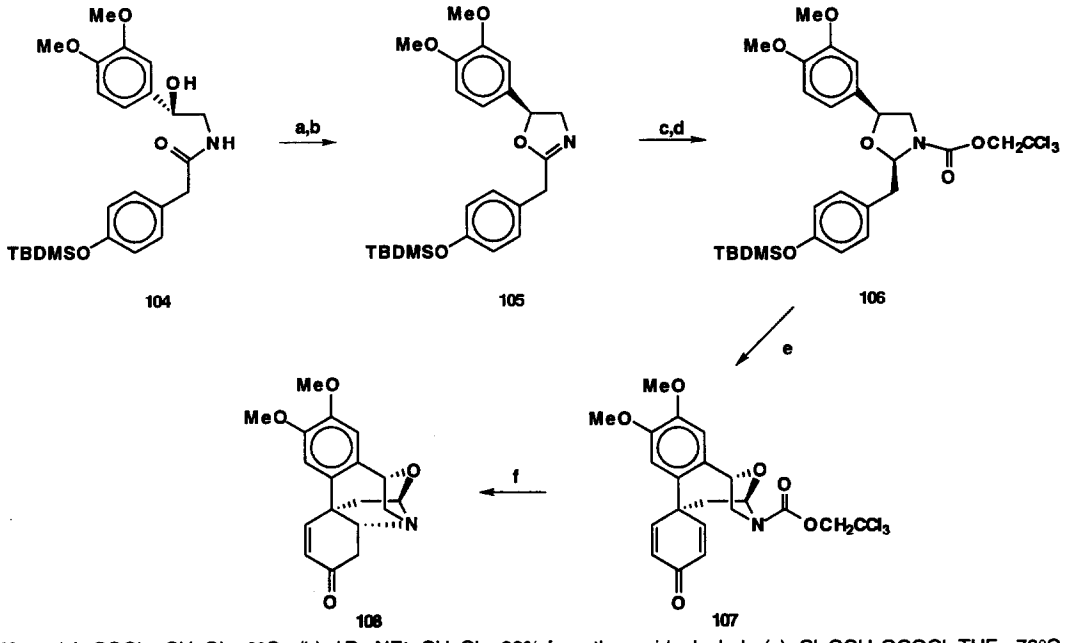
Oxazolines have long been recognized as precursors to various other heterocycles by relatively simple transformations. For example, the closely related systems, oxazolidine **102**, and oxazole **103**, are constituents of many natural products and are often accessed by either oxazoline reduction or oxidation, respectively.



102 **103**

An example of the former method was demonstrated recently in White's synthesis[86] of a hasbanane alkaloid analog (Scheme 19). The oxazoline, **105**, was prepared from hydroxyamide

Scheme 19.

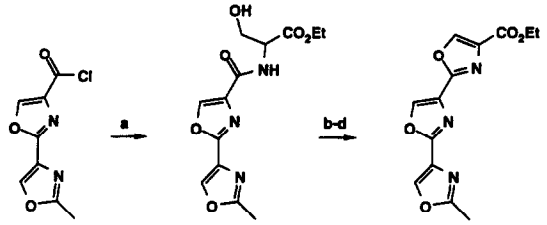


Key: (a) $SOCl_2$, CH_2Cl_2, 0°C; (b) *i*-Pr_2NEt, CH_2Cl_2, 82% from the amidoalcohol; (c) Cl_3CCH_2OCOCl, THF, -78°C, then $NaBH_3CN$, THF-EtOH, 65%; (d) *n*-Bu_4NF, THF, 25°C, 76%; (e) VOF_3, $(CF_3CO)_2O$, TFA, CH_2Cl_2, -78°C to -10°C, 98%; (f) Zn, MeOH, reflux, 50%.

104 by the thionyl chloride route. In this instance the chloroamide was obtained, necessitating base-induced ring closure. Acylation of **105** with a chloroformate followed by sodium cyanoborohydride reduction produced the requisite oxazolidine, **106**. A subsequent phenolic

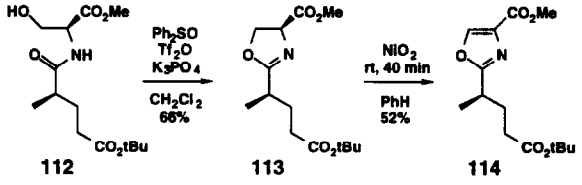
oxidative coupling wherein the oxazolidine acts as a template, or diastereocontrol element, gave polycyclic alkaloid **107**. Reductive removal of the *N*-acyl group led to spontaneous Michael addition and the desired alkaloid system, **108**.

Syntheses of oxazoles abound, and oxazolines are frequently their synthetic precursors. An approach to this ring system was developed,[87] involving the oxidation of oxazolines with NiO_2 in hexane or benzene and was shown to provide generally satisfactory results. However, this oxidation technique, as simple as it may be, often gives yields below 50%. Pattenden[88] employed these conditions several times in the synthesis of the tris-oxazole array found in the *ulapualides*, the final sequence of which is shown below. The oxazoline was assembled from condensation of the bis-oxazole acid chloride, **109**, with ethyl serine followed by an efficient cyclization[89] of hydroxyamide **110**, which was subjected to nickel peroxide oxidation furnishing the tris-oxazole, **111**.



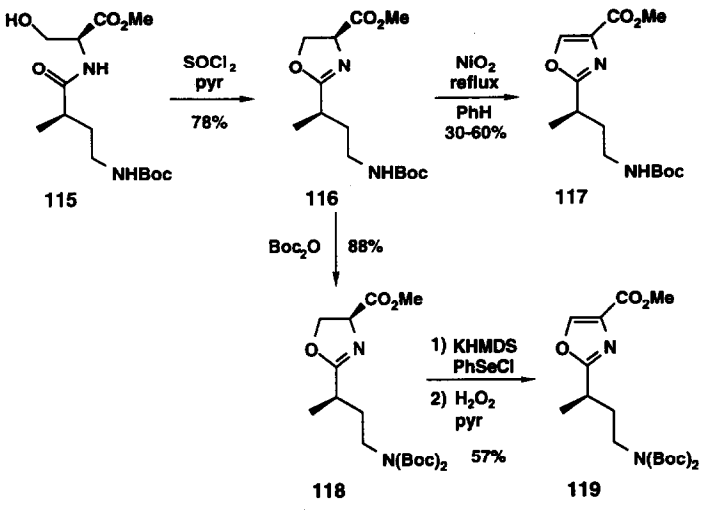
Key: (a) Serine ethyl ester; (b) $SOCl_2$; (c) AgOTf; (d) NiO_2, PhH, reflux 6h.

Nickel peroxide has also been utilized to prepare oxazoles present in the calyculins. Hamada and Shioiri[90] found that unusual conditions, diphenylsulfoxide, triflic anhydride, and potassium phosphate, were required to effect cyclization of hydroxyamide **112** without epimerization of the α-center. The subsequent nickel peroxide oxidation of oxazoline **113** produced a 52% yield of optically pure oxazole **114** without any effect upon the stereocenter of the C-2 side chain.

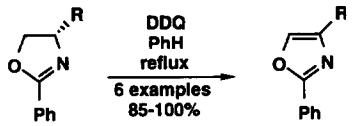


Using a very similar approach to the calyculins, Evans[91] simultaneously described conversion of oxazolines to oxazoles (Scheme 20) using a two-step procedure having, in this instance, greater reproducibility than they had found with the NiO_2 method. Starting with hydroxyamide **115**, thionyl chloride-induced ring closure gave oxazoline **116** in good yield. When nickel peroxide was employed, 30-60% yields of oxazole **117** were obtained, and the process was said to be resistant to large-scale attempts. Alternatively, conversion of Boc-protected amine **116** to the *bis*-Boc imide **118** allowed deprotonation of the oxazoline ester and selenation. Oxidation of the selenide with H_2O_2 led to the expected elimination in 87% yield. The combination of these steps gave a reproducible 50% yield of the oxazole, **119**. It is not clear whether the two-step procedure provides any significant advantage over the simple single-step procedure involving NiO_2 in a general sense.

Scheme 20.

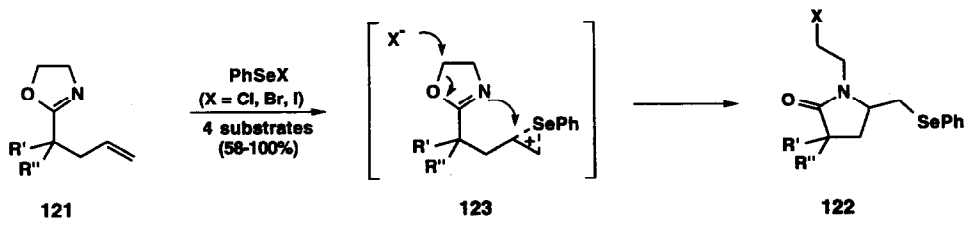


Other oxidants have been successfully employed in specific cases, for example by McGarvey who used DDQ in benzene at reflux.[92] However, all cases studied were 2-phenyl-substituted oxazolines **120**, and this method has proved less than satisfactory with 4-carboxy oxazolines.[93]



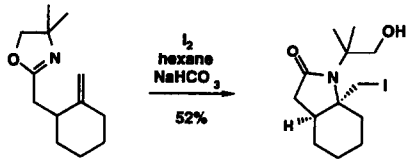
Similarly, MnO_2 has been used successfully in the oxidation of a 2-styrenyl oxazoline to the corresponding oxazole.[94] It should be noted that there still is a strong need for a general, high-yielding oxidation protocol for oxazoles from oxazolines and efforts in this direction warrant serious consideration, especially in view of the numerous important biological substances containing the oxazole system.

Toshimitsu[95] used phenylselenenyl halides as an alkene activator, inducing cyclization of γ,δ-unsaturated oxazolines, **121** to the lactam **122**. This rearrangement is postulated to pass through the intermediate **123**. Varying the halide did not significantly affect yields of the highly substituted lactams in most cases.



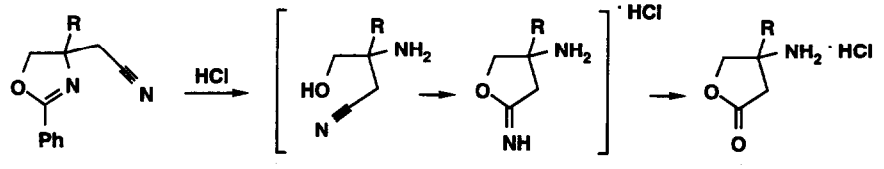
Kurth[96] has investigated the stereoselectivity of this reaction on substrates possessing chiral oxazolines. Iodine was used in place of selenium electrophiles in a reaction with oxazoline **124**. Oxazoline-based asymmetry did not provide for any selectivity: iodolactamization of oxazoline **124** gave a 1:1 mixture of lactam diastereomers, **125**. On the other hand, diastereospecificity was achieved in the production of bicyclic lactam **127** from its racemic predecessor, **126**.

124 **125**



126 **127**

An interesting rearrangement was observed whereby 4-cyanomethyl substituted oxazolines **128** underwent ring-opening on exposure to mineral acid and recyclized on the pendant nitrile, to furnish β-aminoacid derivatives **130**.[97] Presumably the product was formed from the intermediate hydroxycyanide, **129**, which underwent a 5-exo-digonal ring closure.



128 **129** **130**

R = CH_3 **(60%)**
R = H **(68%)**

V. UTILITY AS PROTECTING GROUP

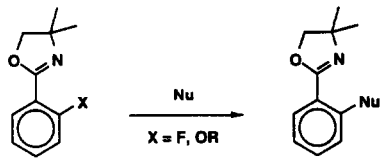
The oxazoline has acted as a protecting group (while fulfilling various other functions) for many of the reactions described herein. To influence transformations without itself being consumed, this heterocycle must resist a variety of reagents. Indeed, aside from the susceptibility to mineral-, as well as Lewis- acids described in other sections, this carboxylic acid masking-agent is virtually impervious to most other reagents. In fact, Greene's popular monograph, *"Protective Groups in Organic Synthesis"*, ably summarizes this behavior.[98] Of particular interest, it is noted that the oxazoline resists nucleophiles, bases, radicals, and even a number of acids as well or better than other carboxyl masking groups surveyed. This stability will be indirectly demonstrated in examples in following sections.

VI. ARYL OXAZOLINES

The influence of an oxazoline moiety on an aromatic system allows heretofore difficult transformations to occur with great predictability.[99] Thus, substitutions, additions, and metalations on aromatic nuclei are among the most useful for this ubiquitous heterocycle.

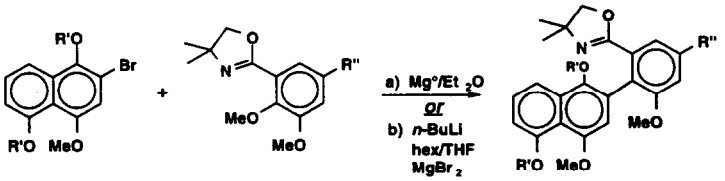
A. *Nucleophilic Substitution.*

Although a number of methods exist for the functionalization of aromatic systems, few are general and allow predictably high yields in carbon-carbon bond forming reactions.[100] As a result, the oxazoline-mediated substitution method has been extensively utilized in the synthesis of numerous important aromatic targets. The general principles for its use are simple. The oxazoline moiety readily promotes displacement (eq. 10) of *ortho* -alkoxy and -flouro[101] groups by strong nucleophiles. This favorable behavior has seen considerable use in biaryl syntheses. Few other methods are available for the formation of mixed biaryl systems.[102]

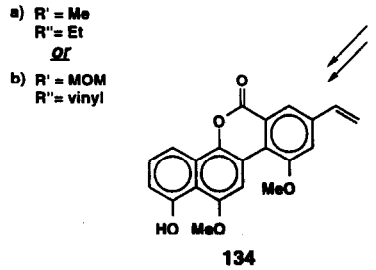


(eq. 10)

This reaction was used to advantage in similar though independent syntheses of the ravidomycin aglycone, defucogilvocarcin V, **134**, by Findlay[103] and Danishefsky.[104] In the first instance, Findlay added the Grignard reagent of bromide **131a** to the *ortho*-methoxy oxazoline, **132a**. The displacement proceeded in 81% yield. Four efficient steps completed the synthesis from biaryloxazoline **133a**.



131a,b **132a,b** **133a,b**

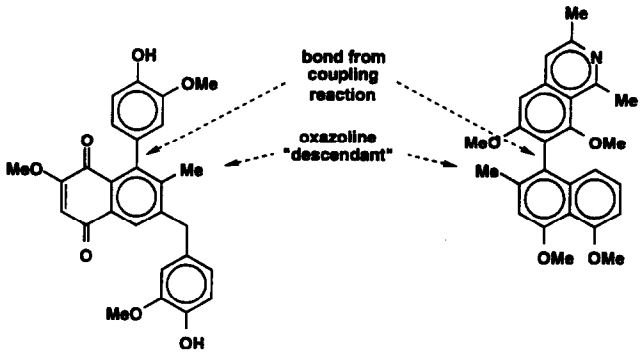


134

Danishefsky employed a lithium-halogen exchange on bromide **131b** followed by transmetalation with magnesium bromide to produce the desired Grignard reagent. Treatment of this nucleophile with *ortho*-methoxy oxazoline **132b** led to the biaryl product **133b** in 50-60% yield. Treatment of **133b** with aqueous mineral acid gave the desired product, **134**, directly in 86% yield.

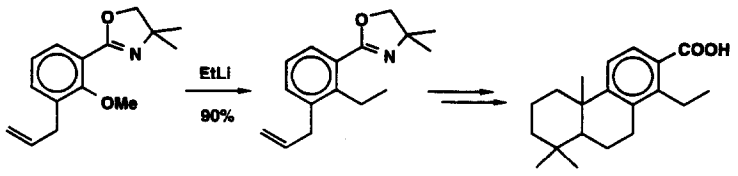
Similarly, the cytotoxic naphthoquinone larreantin, **135** (Figure 1), was synthesized by Sargent using the appropriate Grignard reagent as outlined above.[105] Likewise the degradation product of the isoquinoline alkaloid, ancistrocladisine, **136**, was efficiently assembled.[106] In both cases the oxazoline was reduced to the methyl group after its purpose had been served.

Figure 1.



135 **136**

In a synthesis of veadeiroic acid, **139**, Nasipuri[107] treated *o*-methoxyphenyloxazoline **137** with ethyllithium to effect the coupling leading to *o*-ethyl phenyloxazoline, **138**. The use of alkyllithium reagents has been shown to require lower temperatures to avoid addition to the C=N bond or attack at the carbon of the methoxy group.[108]

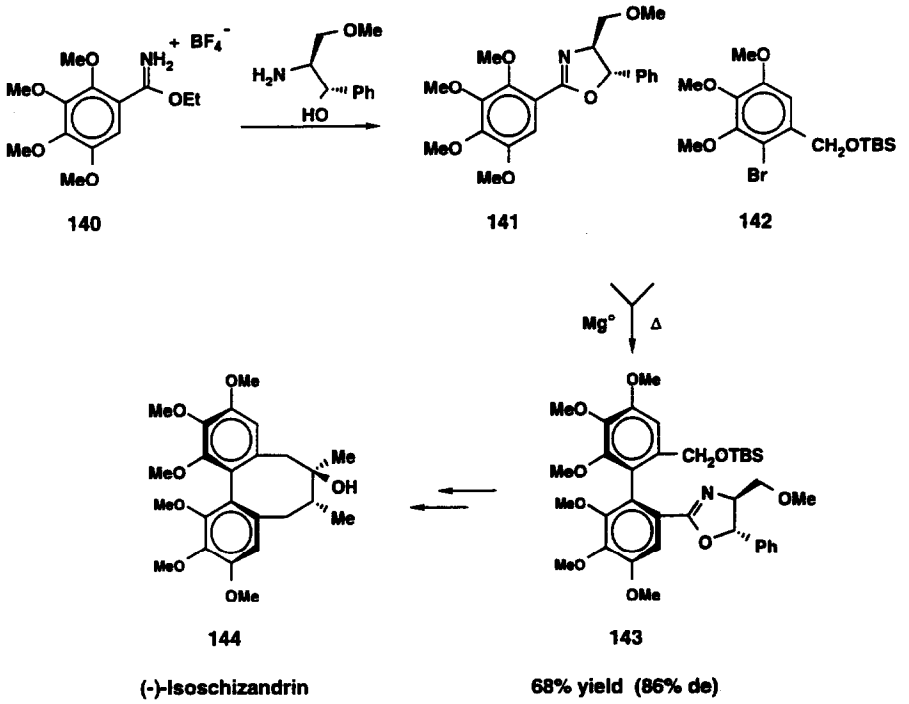


137 **138** **139**

All the coupling reactions described above were mediated by an achiral oxazoline. Most natural products of this genre, however, possess axial chirality at the bond formed in this reaction. Consequently, the asymmetric variant utilizing an oxazoline derived from an enantiomerically pure amino alcohol has been brought into play. The oxazoline, **141**, in Scheme 21[109] was formed by condensation of the easily prepared amino alcohol[110] with iminoether **140**. Subsequent treatment of a mixture of **141** and bromide **142** with Mg° in THF at reflux sequentially formed the Grignard

reagent and led to displacement of the *ortho*-methoxy group. Thus, biaryl **143** was obtained in 68% yield and, of equal significance, the undesired diastereomer could be easily removed by radial chromatography. Several further synthetic steps resulted in the antipode of naturally-occurring schizandrin and also forced a revision of the reported structure of isoschizandrin, **144**.

Scheme 21.



140 **141** **142**

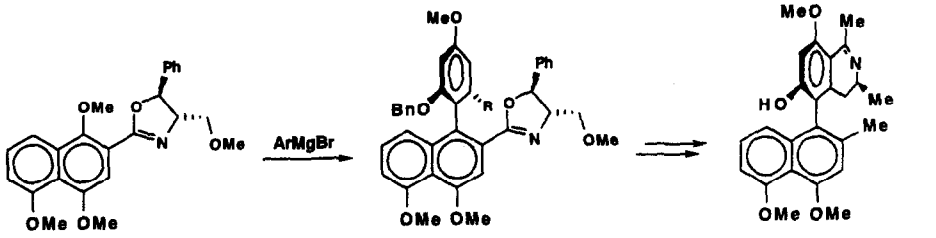
144 **143**

(-)-Isoschizandrin **68% yield (86% de)**

The work described in Scheme 21 was based upon prior efforts[111] to effect diastereoselective conditions for the asymmetric biaryl coupling reaction. Sargent has utilized this paradigm in the efficient syntheses of the natural products (-)-ancistrocladinine (Scheme 22),[112] (-)-O-methylancistrocladine,[113] and related alkaloids. This technique has also been employed in the synthesis of azaphenanthrenes,[114] chiral porphyrins (Scheme 23),[115] and numerous pharmacologically active agents including leukotriene antagonists,[116] cholesterol biosynthesis inhibitors,[117] and antihypertensives.[118]

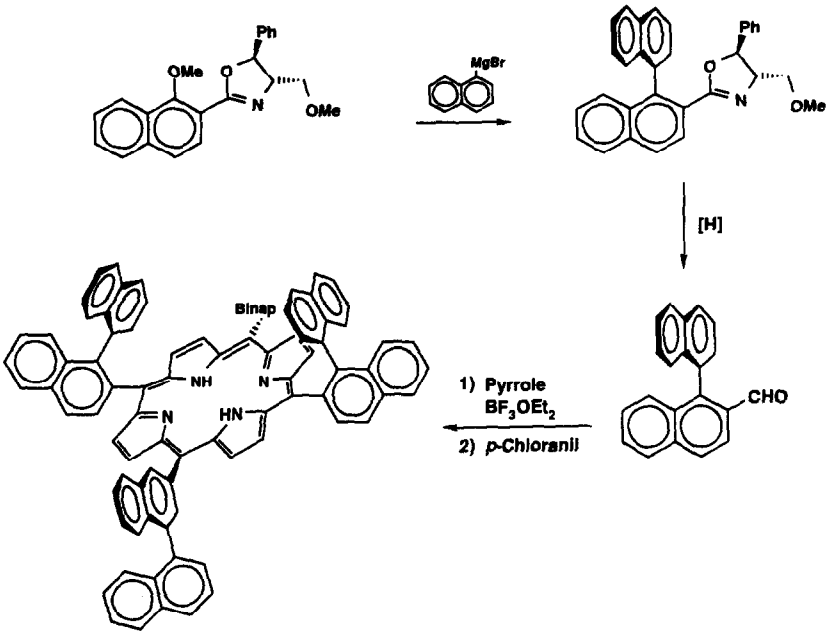
In 1974 one of the earliest examples of an asymmetric reduction of ketones by use of an optically active ligand was reported.[119] In more current studies, axially chiral biaryls are proving to promote asymmetric induction more effectively, while serving as ligands for a number of other transformations as well. The first generation of biaryl ligands, developed by Noyori,[120] consisted of binaphthyl diols and diphosphines and have been used in a wide array of chiral processes. In attempts to improve on the preparative availability and reliability of these chiral ligands, oxazolines have recently been investigated to assess their potential value. (See also Section VIII).

Scheme 22.



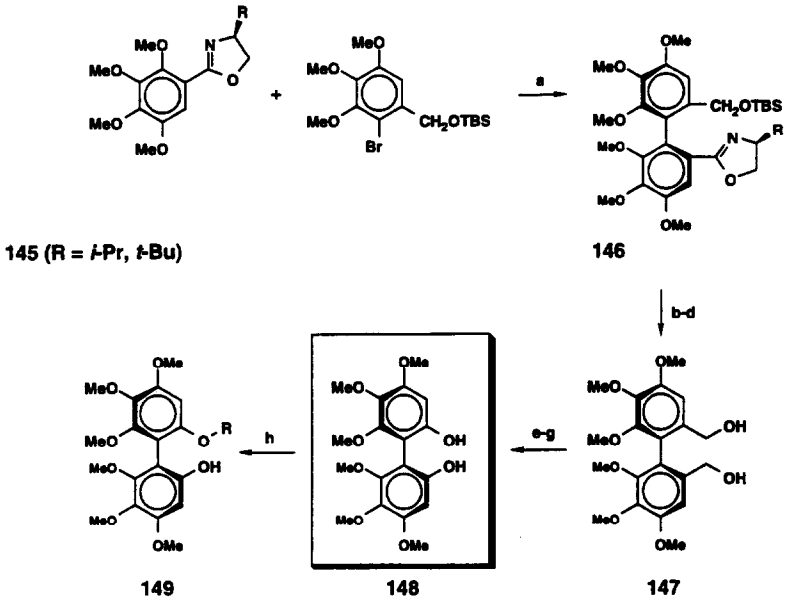
(-)-ancistrocladinine

Scheme 23.



Utilizing protocol developed earlier, (e.g. **143**) it was found that the electron-rich π-system provided the best results in the biaryl coupling (Scheme 24). However, unlike previous cases (Schemes 21, 22, and 23) wherein a chelating-oxazoline was employed, the *tert*-leucinol- and valinol- derived oxazolines, **145**, were evaluated and led to superior yields of coupling products.[121] The resulting biaryl **146** was efficiently converted to the dihydroxymethyl biphenyl **147** which was subsequently oxidized to the dialdehyde, subjected to a Baeyer-Villiger rearrangement, and finally hydrolyzed to give the desired diol, **148**. Enantiomeric purity (>96% ee) was established based on the diastereomeric purity of Mosher's ester **149**.

Scheme 24.



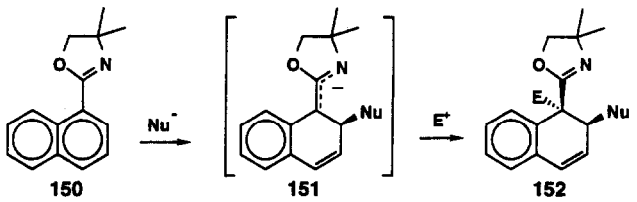
Key: (a) Mg°, THF, reflux (R = i-Pr: 90%, 96% de; R = t-Bu: 60%, >96%de); (b) Na_2SO_4, TFA, H_2O; (c) Ac_2O, Pyr; (d) $LiAlH_4$ (73% from biaryloxazoline); (e) $(COCl)_2$, DMSO, NEt_3; (f) m-CPBA; (g) K_2CO_3, MeOH, H_2O (81% from dihydroxymethylbiaryl); (h) Mosher's acid chloride, DMAP, NEt_3, R = $OCO(CF_3)C(OMe)Ph$.

A series of lithium aluminum hydride reductions in the presence of diol **148** was carried out to assess the viability of the ligand.[122] The results afforded data comparable in enantioselective efficiency to those obtained with BINAL-H.[120] It would appear that certain classes of carbonyl derivatives are particularly amenable to this treatment, and give higher selectivity than those obtained with the binaphthyl ligand.

B. *Nucleophilic Addition.*

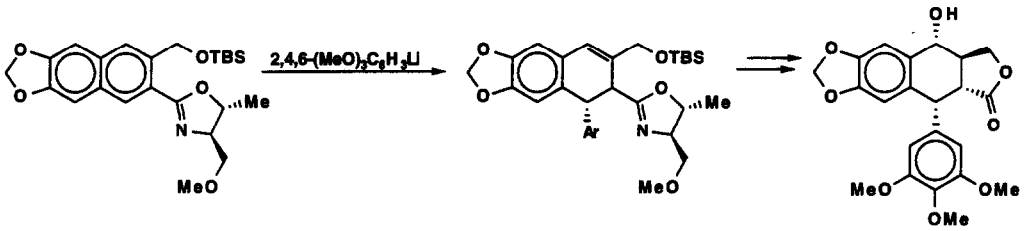
A multitude of annulation methods has been developed over the years to reach elaborated six-membered rings from aliphatic precursors. Approaching this problem from a different perspective, readily available aromatic feedstocks have proven useful through nucleophilic additions to phenyl- and naphthyl- oxazolines.

Nucleophilic additions to the aromatic π-system have been achieved in *naphthyl* systems[123] by direct introduction of alkyllithium reagents.[124] The tandem-addition strategy was an effective tool in the functionalization of naphthyloxazoline **150**[125] as well as its 2-isomer.[126] When carbon and sulfur electrophiles were introduced to intermediate **151**, the *anti* isomer, **152**, was typically isolated to the exclusion of the *syn* adduct. When protio quench (E^+ = H) was employed, careful workup with a strong acid (weak conjugate base) allowed isolation of the now *syn*-disposed product, **152** (effectively still a tandem-adduct). Alternatively the proton-trapped product could be isomerized to the more stable *trans* isomer if a stronger base was introduced.



150 151 152

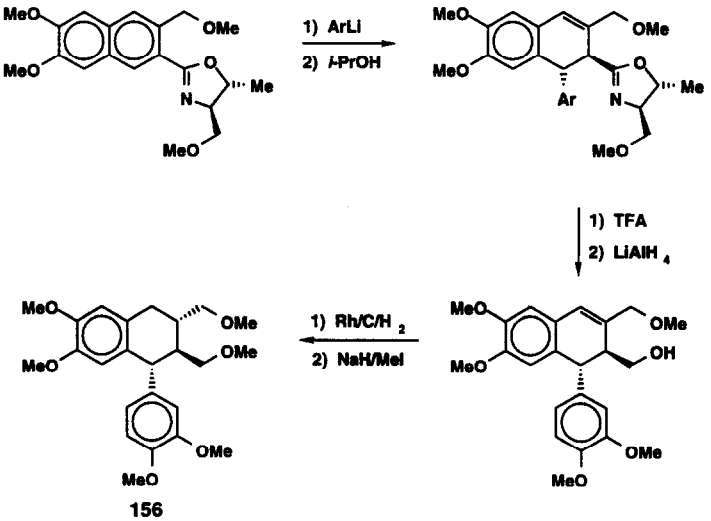
The logical next step was to employ an optically active oxazoline to effect an asymmetric synthesis. This goal was accomplished by use of various 4-methoxymethyl-substituted chelating auxiliaries.[127] Stereochemical results were excellent in most cases. The disubstituted (proton-quenched) addition products **152** (E = H) were obtained with high enantiopurity as well as



153 154 155

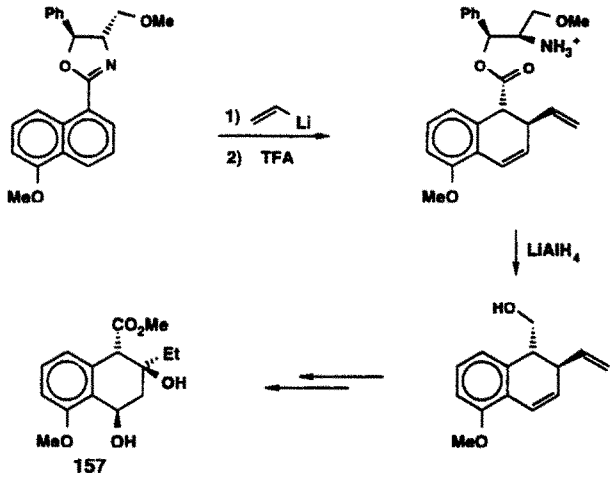
trisubstituted tandem adducts **152** (E = alkyl, thioalkyl). The chiral non-racemic proton-quench method was later employed in various applications including an enantioselective total synthesis of (-)-podophylotoxin, **155**.[128] The key step, addition of an aryllithium reagent to chiral oxazoline **153**, afforded addition product **154** in 70-80% yield with a 92:8 diastereomeric ratio. Similarly, the synthesis of (+)-phyltetralin, **156** (Scheme 25), as well as a total synthesis of the stereochemically endowed AB-ring of aklavinone[129], **157** (Scheme 26), were achieved.

Scheme 25.

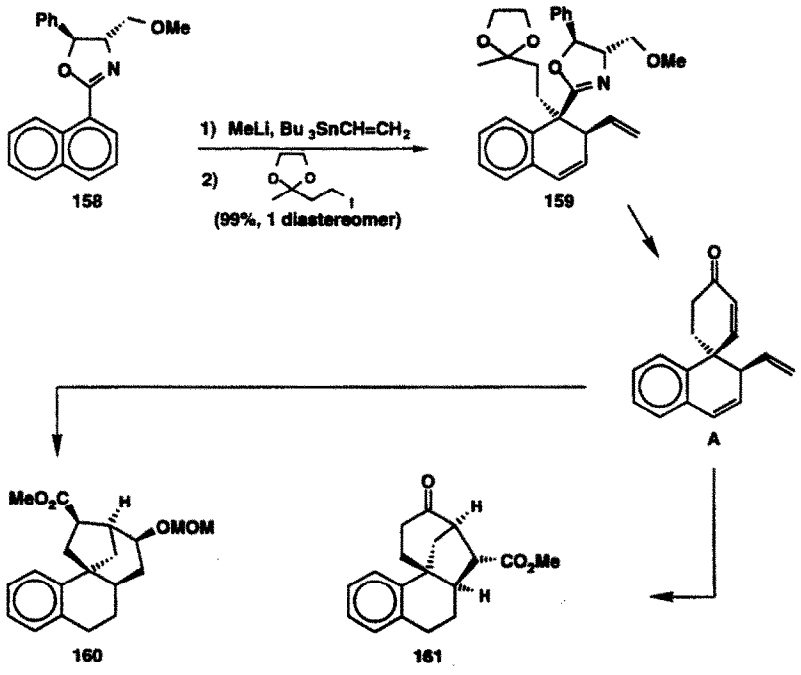


156

Scheme 26.

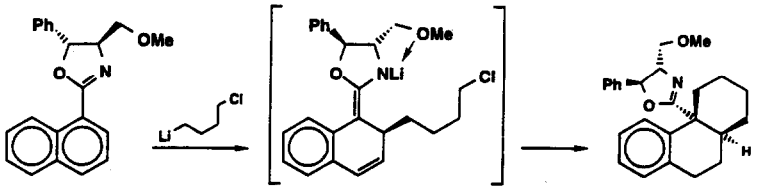


The tandem addition strategy has also been used in the construction of complex polycyclic systems. Enantioselective applications to the chlorothricolide,[130] kaurane, scopadulcic acid, **160**, and aphidocolin, **161**, skeletons have been achieved.[131] The latter two syntheses arose from vinyllithium addition to naphthyloxazoline **158**, followed by electrophilic trap with 2-methyl-2-(2-



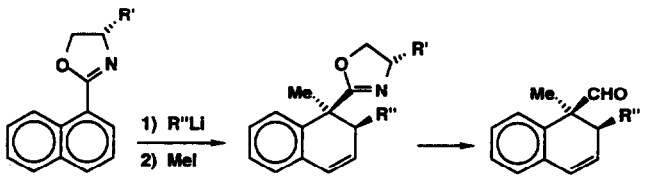
iodoethyl)-1,3-dioxolane to provide a quantitative yield of the stereospecifically disposed *anti*-tandem adduct **159**. With the proper B-ring stereochemistry in place, the pivotal spiroketone, **A**, was rapidly assembled with further synthetic steps to provide the tetracyclic systems **160** and **161**.

Addition of the bifunctional nucleophile, 4-chlorobutyllithium, to chiral oxazoline **158** afforded presumed intermediate **162** which, when warmed, gave the *syn*-disposed tricyclic product **163** in 84% yield.[132] Subsequent transformations supported a 98:2 ratio with regard to the initial facial selectivity of the nucleophile. None of the *trans* product was detected.



158 **162** **163**

In the examples given above, the oxazoline employed possessed a chelating auxiliary generally considered to be important in promoting high stereoselectivity. This concept dates back to the early 70's when this moiety was introduced as an effective component in asymmetric conjugate additions to vinyl systems. Recently, it was determined that appropriate steric factors can also provide high diastereoselectivity. Thus, coordination by a sterically crowded valinol- or *tert*-leucinol- derived oxazoline (**164b** and **164c**, respectively) provided enough diastereofacial bias to produce comparable or superior selectivity in additions to coordinating naphthyloxazolines, **164a**.[133] The *t*-leucinol derived oxazoline, **164c**, provided the highest selectivity. It should also be

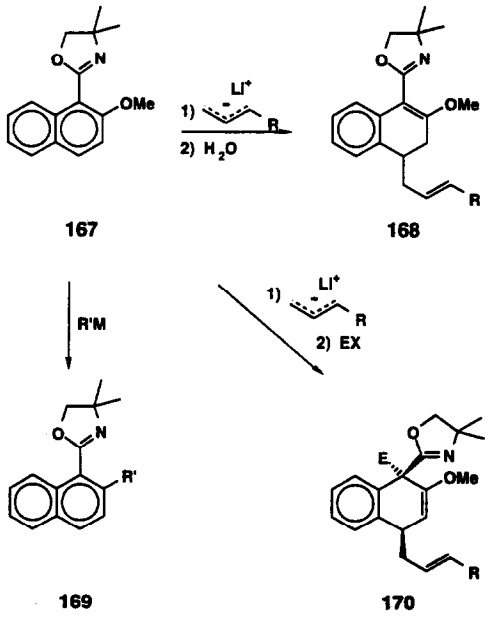


164 **165** **166**

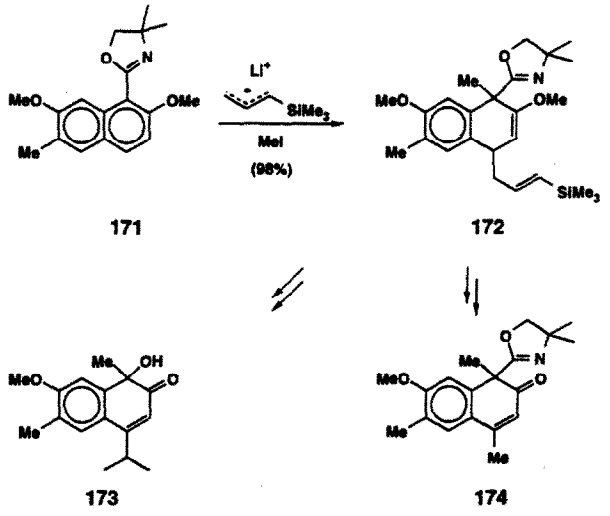
noted that the sense of addition to naphthyloxazolines **164b** and **164c** was identical to that obtained from the chelate-containing species **164a**. The nucleophile entered from the side opposite the pendent 4-alkyl group as represented above. This result has several advantages, not the least of which is the simpler preparation of these systems over the chelating auxiliaries. It was noted, however, that the chelating auxiliaries enhance the rate of addition, thus allowing reaction with certain nucleophiles inert to non-chelating oxazolines.

Recently, 2-methoxynaphthyloxazoline **167** was observed to undergo efficient 1,6-conjugate addition with allyllithiums to give adduct **168** (Scheme 27).[134] This outcome was contrary to the facile and well-precedented *ortho*-displacement observed in other systems mentioned above. The expected *ortho*-methoxy displacement was, in fact, observed for a wide variety of other nucleophiles and afforded elaborated naphthalenes **169** in high yield. Nonetheless, the 1,6-addition manifold was general for a wide variety of allyllithiums as well as for other naphthyloxazolines. Tandem additions with allyllithiums were also carried out with **167** producing, in all cases, only the *anti* product **170**.[135] Thus, when the tetrasubstituted naphthyloxazoline **171** was treated with trimethylsilyl-allyllithium (Scheme 28) followed by trapping with MeI, the tandem-adduct **172** was formed in 98% yield. This sequence was employed in the total synthesis of the byssinotic agent *lacinilene C-7 methyl ether*, **173**, a natural product isolated from various *Gossypium* species[136] as well as a new class of HIV-1 reverse transcriptase inhibitors (e.g. **174**).[137] In contrast to the naphthyl systems above, direct addition of strong nucleophiles to *benzene* derivatives usually leads to *ortho*-deprotonation rather than addition (see Section VI C). However, successful addition to phenyl oxazolines has been accomplished by Kundig[138] through derivitization of the phenyl oxazoline **175** to the tricarbonylchromium complex (Scheme 29).[139] Complex **176**, formed by exchange of naphthaleneCr(CO)$_3$ for phenyloxazoline **175**, was chromatographable and air stable. The highly electrophilic π-system, susceptible to nucleophilic attack, gave the intermediate **177** on treatment with alkyllithiums. The intermediate was either trapped with I_2 to give the rearomatized product (not shown) or, alternatively, trapped with carbon electrophiles to give tandem-addition product **178**. The intermediate "ate" species, **177**, was also carbonylated to afford highly substituted cyclohexadiene **179**.[140]

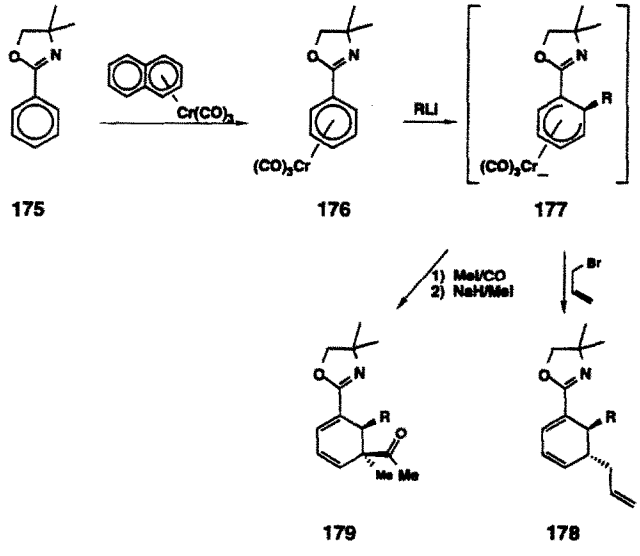
Scheme 27.



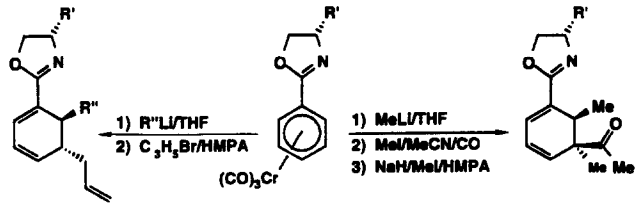
Scheme 28.



Scheme 29.



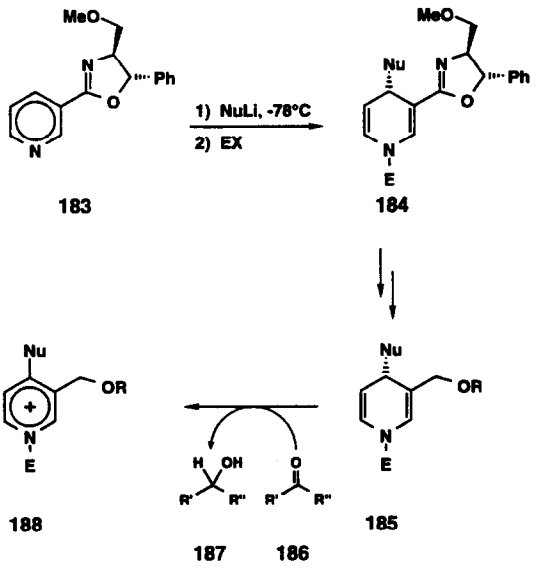
In an asymmetric variant to this very efficient process, Kundig recently achieved excellent results with the 4-isopropyl- and 4-*tert*-butyl- substituted oxazoline **180**.[141] Using conditions as described for the achiral phenyloxazoline above, reasonable yields were accompanied by diastereomeric excesses typically greater than 90%.



181 180 182

Heteroaromatic oxazolines, such as pyridyloxazolines **183**,[142] undergo addition by nucleophiles to afford dihydropyridyloxazolines **184**.[143] Other recent studies carried various examples on to nifedipine analogs **185**.[144] These dihydropyridines have, in turn, proven to be effective reducing agents through the reduction of ketones **186** to enantiomerically enriched alcohols, **187**.[145] This self-immolative process mimics the action of NADH and was performed on a variety of substrates, resulting in moderate to excellent yields and ee's in the range 72-95%.

Scheme 30.



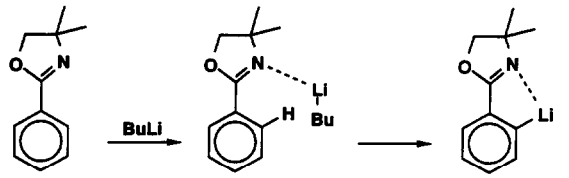
183 184 188 185 187 186

C. *Metalation and Electrophilic Substitution.*

The previous two sections detailed work employing aryloxazolines as electrophiles. These molecular building blocks also possess features allowing their ready conversion to nucleophilic species through metalation, thus allowing functionalization patterns not readily accessible by other means. Though not the only directing group used for this purpose,[146] the oxazoline has shown up in numerous syntheses owing to its reputation for ease of preparation, stability to harsh reagents, and reliability. The following examples were chosen to display the breadth of utility in this arena.

In the generic metalation (eq. 11), ready precomplexation of various reactive reagents by the oxazoline moiety provide for the proximal reactions often observed with these systems. For

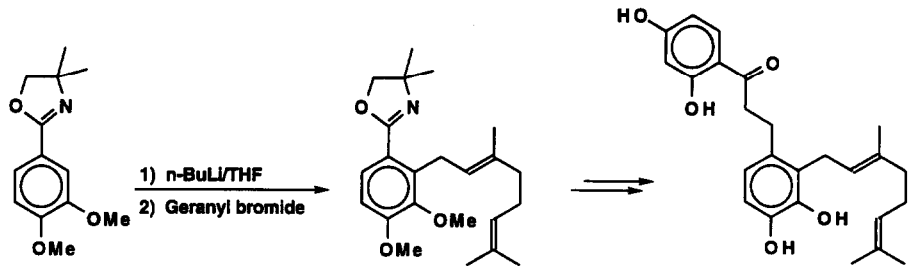
example, strong bases seldom react with the oxazoline itself though adjacent protons are rendered kinetically acidic.[147] Various alkyllithium bases serve this purpose well, though *n*-BuLi is most frequently used for *ortho*-deprotonations of aryloxazolines. Typically, *meta*- and *para*- halogens



(eq. 11)

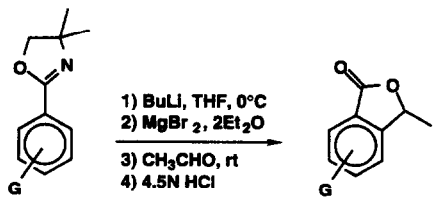
are not abstracted if an *ortho*-proton is present for reaction.[148] *Meta*- and *para*- Grignard reagents are easily prepared by treatment of the appropriate bromide with elemental magnesium.[149]

Recently, Nakano relied on the *ortho*-metalation method in his efficient synthesis of AC-5-1, a novel and potent lipoxygenase inhibitor, **191**.[150] Oxazoline **189** underwent expected lithiation followed by electrophilic trapping by geranyl bromide to afford the tetrasubstituted benzene, **190**. The lithiation took place at the most hindered site due to the double-activation of this proton by the methoxy group as well as the oxazoline, while further manipulations led to the target, **191**.[151]



189 **190** **191**

This method has been previously used in syntheses of aromatic lactones.[152] In an application to the preparation of phthlalides **193** it was necessary to trans-metalate the intermediate *ortho*-lithio species generated from oxazolines **192** to the Grignard reagent, which then allowed alkylation to afford the desired cyclization products.[153]

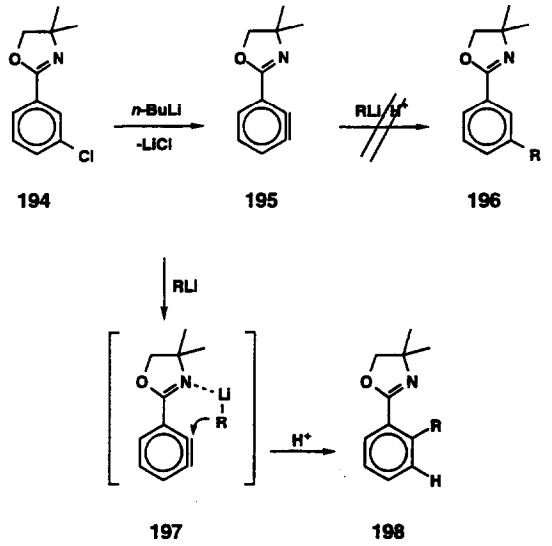


192 **193**

5 examples (47-77%)

The coordination properties of oxazolines are especially apparent in benzyne additions (Scheme 31).[154] After lithiation of phenyloxazoline **194** and elimination to afford benzyne **195**, an unusual event occurred: organolithium nucleophiles added *ortho* to the oxazoline moiety.

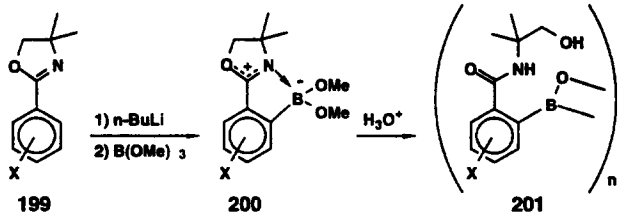
Scheme 31.



194 **195** **196** **197** **198**

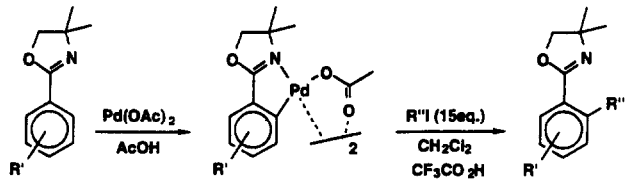
This result contrasts sharply with results obtained for other electron withdrawing groups suggesting *meta* addition should predominate giving **196** rather than the observed product, **198**. An explanation lies in the strong coordination of the oxazoline to nucleophile (as in **197**) prior to its interaction with the benzyne π-system.

A synthesis of arylboronic acid anhydrides was achieved by lithiation of a phenyloxazoline, **199**, followed by treatment with trimethyl borate or borane.[155] The resultant complex **200** was hydrolyzed leading directly to the anhydride, **201**.

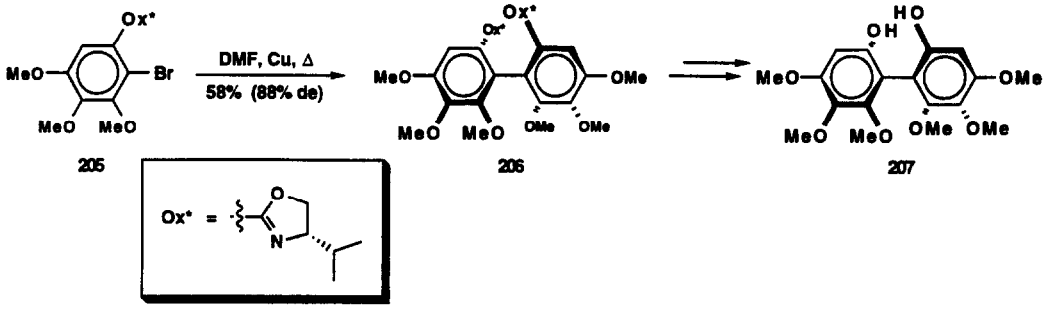


199 **200** **201**

Transition metals have been incorporated *ortho* to phenyloxazolines as well. Clinet and Balavoine carried out a cyclopalladation on oxazoline **202** to give the metallacycle, **203**.[156] Subsequent treatment with alkyl iodides gave the alkylated products **204** in good yield. This approach therefore allowed *o*-substitution without use of strong bases and was dependant on steric considerations alone, allowing substitution patterns complementary to that achieved by lithiation in some cases. This technique may find further utility in complex sensitive systems.



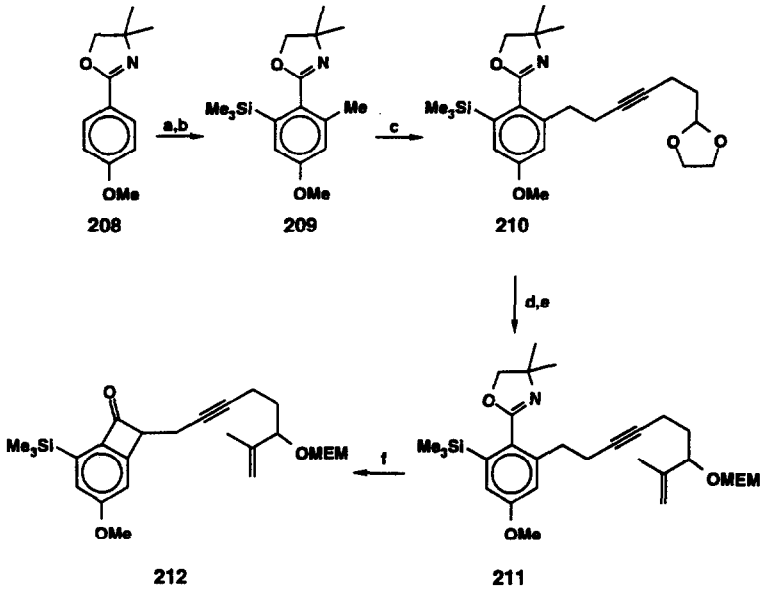
A copper-mediated reaction has recently been observed to effect a biaryl coupling of *ortho*-bromo phenyloxazolines.[157] Under standard Ullmann conditions, coupling of asymmetric starting material **205** provided axially chiral product **206** as a 94:6 ratio of separable atropisomers. The purified product was taken on to the chiral ligand, **148**, synthesized previously through a different route (Section VI A).



In the absence of *ortho*-hydrogens, a *benzylic* deprotonation may occur under the conditions described (Scheme 32). Vollhardt[158] employed this technique in the elaboration of phenyloxazoline **209**. Preparation of **209** was achieved through the typical *ortho*-deprotonation strategy from phenyloxazoline **208**. Treatment of *o,o'*-disubstituted **209** with butyllithium followed by addition of the propargyl bromide led to an excellent yield of the benzyl-homologated system, **210** (95% yield). Homologation of the masked aldehyde afforded intermediate **211**. In a related reaction, oxazoline **211** was methylated to give the oxazolinium ion and treated with methylmagnesium chloride. Rather than add to the electrophilic *N*-methyl oxazolinium species, the Grignard reagent acts as base, deprotonating the benzyl position. An acidic workup afforded a modest though still impressive 29% yield of the cyclized product, **212**.

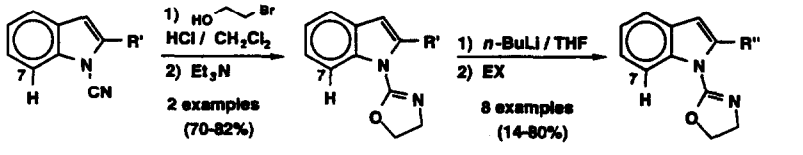
Oxazolines have also been used to direct metalation in heteroaromatic rings including furans,[159] isoxazoles,[160] thiophenes[161] and pyrroles.[162] Metalations of these systems typically give clean *ortho* lithiation followed by efficient electrophilic trapping. Terashima has investigated the lithiation of 1-(2-oxazolinyl)indoles **214** (R' = H, Me) prepared from the corresponding cyanoindole,

Scheme 32.



Key: (a) i. *n*-BuLi, 0°C, ether, ii. Me_3Cl; (b) i. *n*-BuLi, 0°C, ether, ii. MeI; (c) i. *n*-BuLi, 0°C, ether, ii. $BrCH_2CCCH_2CH(O_2C_2H_4)$, HMPA; (d) HCO_2H; (e) i. $CH_2CH(Me)MgBr$, ii. $Et_3N^+CH_2O(CH_2)_2OMeCl^-$; (f) i. MeI, ii. MeMgCl, iii. HCl, MeOH.

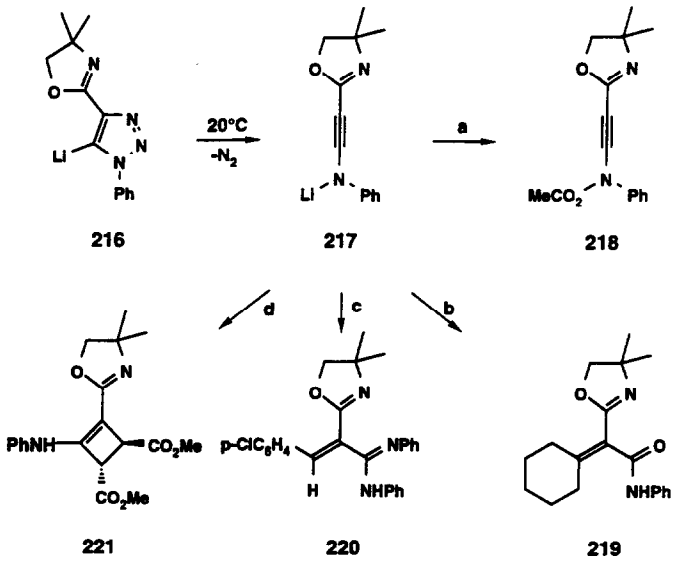
213.[163] Lithiation proved regioselective giving products **215** substituted at the 2-position only; indole metalation was observed for (a) R = H whereas benzyl metalation was observed for (b) R = Me. The phenyl proton, C-7H, was apparently not in position to react with the presumed *n*-BuLi·oxazoline coordination complex.



a) R' = H; R" = E
b) R' = Me; R" = CH_2E

Gilchrist[164] has lithiated oxazolinyltriazoles with *n*-BuLi at -78°C furnishing presumed intermediate **216**. Warming to room temperature allowed rearrangement with concomitant loss of nitrogen to afford alkynyllithium amide **217**. Subsequent reactions under a variety of conditions provided a wide array of unusual products, **218-221**.

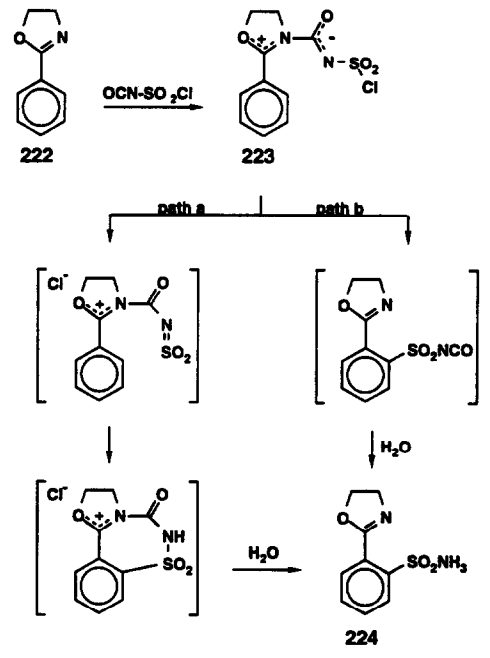
Scheme 33.



216 217 218 221 220 219

Key: (a) MeOCOCl; (b) cyclohexanone; (c) *p*-Cl-C_6H_4CHNPh; (d) (*E*)-$MeO_2CCHCHCO_2Me$.

Scheme 34.



222 223 224

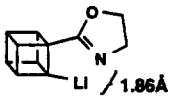
Aryloxazolines seldom suffer electrophilic attack without prior metalation except when the oxazoline nitrogen is selectively oxidized in order to facilitate reduction or hydrolysis. An unusual result appeared wherein treatment of phenyloxazoline **222** with chlorosulfonyl isocyanate (CSI) afforded a product of electrophilic aromatic substitution, **224**.[165] This reaction likely passes though an initial *N*-alkylation, giving zwitterionic species **223**. The authors gave two plausible reaction mechanisms (paths a and b) that differ primarily in the timing of bond-breaking and bond-making processes.

VII. ALIPHATIC OXAZOLINES

A. *Metalations.*

In the 1976 review of oxazoline chemistry,[1d] metalation and alkylation of aliphatic oxazolines was the prime subject surveyed. Much of the early work in the field of asymmetric C-C bond forming reactions began with these versatile substrates.[166] This area has grown in depth as well as breadth in the intervening years. Numerous papers detailed elsewhere in this review could have been placed in this category. However, only the metalations of particular import will be described here.[167]

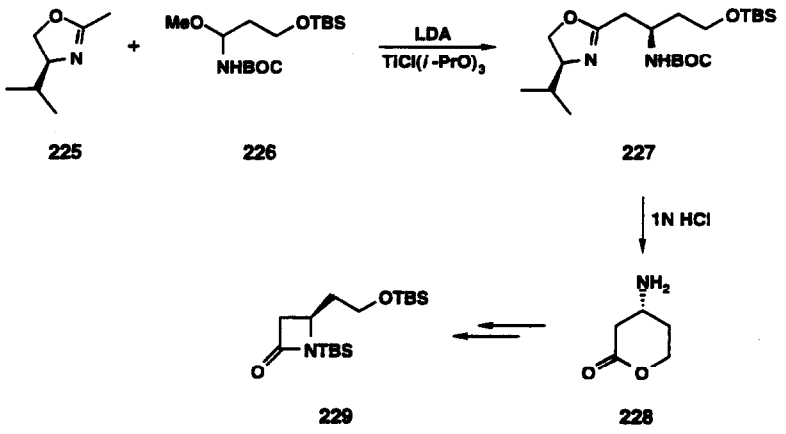
Metalation of aliphatic systems as directed by an oxazoline exhibits the same chemical features as for aryl systems (*vide infra*); proximal protons are rendered kinetically acidic. The strong coordination of the oxazoline nitrogen to lithium facilitates such transformations. Theoretical support for this assertion comes from a study of cubane lithiation by Jayasuriya showing the strong interaction between the oxazoline nitrogen and the lithium ion.[168] An unusually small calculated



distance of 1.86Å, in spite of a van der Waals radii sum of 3.4Å, provided evidence of a strong interaction. This tight coordination is a property responsible for many of the metalations and subsequent selective alkylations so often seen in this area.

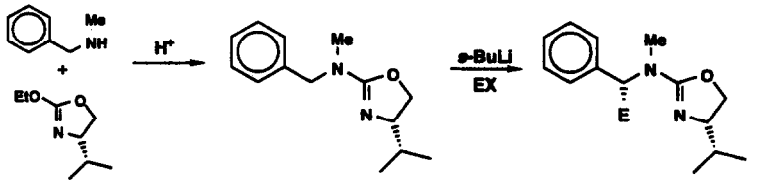
Oxazolines are commonly used for α-deprotonations and if chiral oxazolines are used, a diastereoselective alkylation is possible. Shono has extended this method in a synthesis of β-amino acids (Scheme 35).[169] An interesting feature is the racemic nature of the electrophile, an α-methoxy carbamate, **226**, which was treated with oxazoline **225** and LDA at low temperature. The mixture was then treated with $TiCl(i\text{-}PrO)_3$, presumably converting the electrophile to the achiral imine. The titanium species may also transmetalate the lithiated oxazoline though this event is not clear. The addition product, **227**, was converted to the β-amino acid, which in this instance spontaneously forms the amino lactone, **228**. Further synthetic work produced the β-lactam, **229** (80% ee).

Scheme 35.



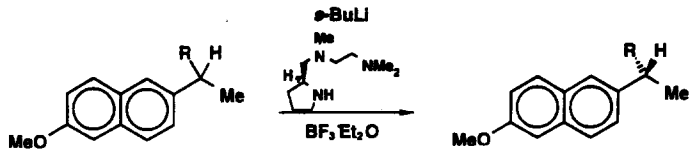
225 226 227 228 229

The oxazoline **230**, used by Gawley, lacks protons α to the oxazoline, and thus allows deprotonation α to an amine leading to alkylated products, **231**. In the example shown, an acyclic system is metalated and alkylated to give high yields (63-92%) and de's (75-96%).[170] Other alkaloids investigated by this method include piperidines,[171] isoindolines,[172] and tetrahydroisoquinolines.[173] Such α-amino anions have been used extensively with a pendant *formamidine* as the directing group.[174]



230 231

Oxazoline mediated deprotonations have also been extended to the evolving field of asymmetric internal proton return (IPR). Vedejs used an achiral Naproxen analog, oxazoline **232d**, with an enantiomerically pure diamine in a Lewis acid induced IPR.[175] Results were modest for this reaction type (50-60% ee) though better for the diisopropylamide analog, **232a** (82% ee). Although the aliphatic metalation of rac-**232d** is not the enantioselective step, the tight coordination afforded by the oxazoline likely provides a rigid intermediate upon which the enantiomerically pure proton donor attacks. The reaction was apparently not attempted with a chiral oxazoline.



rac-232 *ent*-232

a) R = C(O)N- *i*-Pr_2 (82% ee)

b) R = $C(O)NEt_2$ (50% ee)

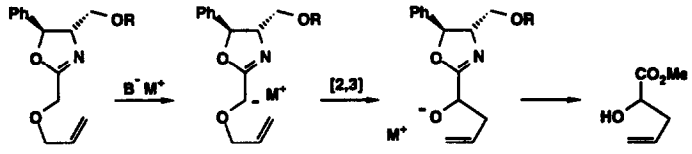
c) R = $C(O)NMe_2$ (33% ee)

d) R =  (50-60% ee)

B. *Pericyclic Reactions.*

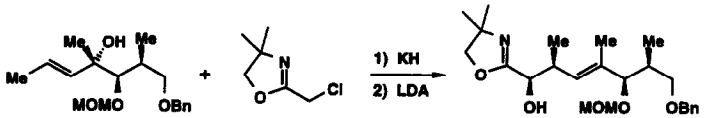
Electrocyclic rearrangements occupy a position of great importance in synthetic organic chemistry. The predictability of transition-state geometries often allows facile retrosynthetic planning. As a consequence, techniques have been designed to incorporate the advantages of oxazoline methods with the rigorous outcomes of various rearrangements. A reaction currently receiving favorable attention is the [2,3] Wittig rearrangement. This reaction has been investigated in an oxazoline-mediated setting separately by Nakai and by Kallmerten. Nakai[176] first disclosed some observations on the fundamental requirements of this application through an asymmetric synthesis of α-hydroxyesters (Scheme 36). The oxazoline **233** simultaneously facilitated formation of the necessary anion **234** and provided for diastereomeric manifolds of rearrangement to **235**. In the case R = H, treatment with two equivalents of BuLi afforded the R-isomer of **236**, whereas two equivalents of KH produced the S-isomer. Furthermore, the addition of 18-crown-6 to the KH induced rearrangement reversed the selectivity again to the R-isomer of **236**. Enantiomeric excesses ranged from 38-96% for various substrates. The lithium induced rearrangements gave *erythro*-selectivity (9:1) for terminally-substituted alkenes. *Erythro:threo* ratios were poor for the potassium induced version.

Scheme 36.



233 **234** **235** **236**

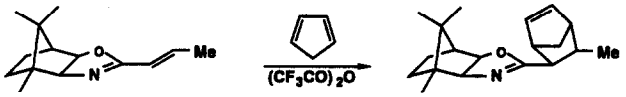
This reaction has been cleverly adapted by Kallmerten, set up by an efficient homologation step, in an approach toward an ansamycin polyketide. The potassium salt of achiral oxazoline **238** was used as the alkylating agent.[177] A tertiary ether was formed from tertiary allyl alcohol **237** and



237 238 239

underwent highly diastereoselective [2,3] rearrangement to give **239** (35:1 with an unidentified stereoisomer). High *threo* selectivity was observed here as well as in other work where *anti* alkenes were employed.[178] The high *threo* selectivity observed conflicts with the *erythro* selectivity (or lack of selectivity) observed by Nakai. The primary differences between the two approaches are the oxazoline substituents and the degree of ether substitution. A broad survey of reaction requirements has apparently not yet been disclosed.

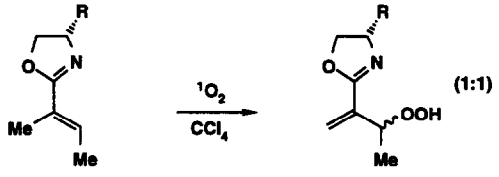
Oxazolines have also been utilized to influence stereochemistry in the Diels-Alder reaction. Langlois has used α,β-unsaturated camphor-derived oxazolines, e.g.: **240**, to effect selective asymmetric cycloadditions giving adducts **241** (for example).[179] Rather than addition of Lewis acids as is so often the case, triflic anhydride was employed, and formed an iminoether salt. This activation allowed reaction to take place at low temperature. Numerous dienes were used with diastereoselectivities typically >90%.



240 241

76% yield (100% endo, 94% ds)

Adam utilized chiral α,β-unsaturated oxazolines **242** in an electrocyclic reaction, though the singlet oxygen ene reaction afforded a 1:1 mixture of diastereomers, **243**.[180] The complete lack of selectivity may indicate that a perepoxide transition-state predominates (distant from the chiral environment), rather than a [4+2] pathway (overlapping the chiral environment).

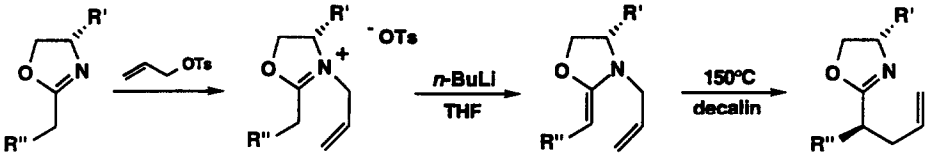


242 243

The rearrangements described above are concerned with the influence of an oxazoline on a proximal reorganization of electrons; oxazoline-*mediated* reactions. Additionally, a number of interesting and useful methods have been developed employing oxazoline-*centered* rearrangements. In the following examples, the iminoether π-electrons are involved in an electrocyclic rearrangement.

Kurth has employed chiral oxazolines in an *aza*-Claisen rearrangement (Scheme 37).[181] The oxazoline, **244**, was treated with an allyllic electrophile to give *N*-allyl iminoether **245**. Subsequent deprotonation afforded enamine **246** which on heating rearranged to **247** in high yield with high diastereoselection. This method has been applied to the synthesis of more highly substituted products[182] including the naturally-occurring sesquiterpene, (+)-dihydropallescensin.[183]

Scheme 37.

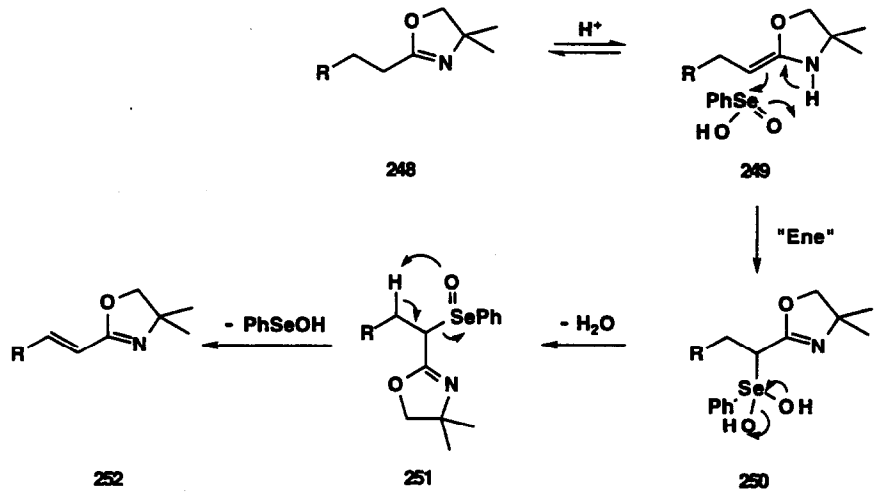


244 **245** **246** **247**

8 examples
(56-96% de)

Barton has invoked an oxazoline-based "ene" reaction as the operative mechanism in a dehydrogenation reaction (Scheme 38).[184] Various substrates **248** were treated with benzeneseleninic acid or anhydride. The tautomer **249** is envisioned to undergo the electrocyclic rearrangement to afford α-substituted oxazoline **250** followed by elimination of water (to **251**) and benzeneselenol leading to unsaturated products **252** in generally good yield.

Scheme 38.

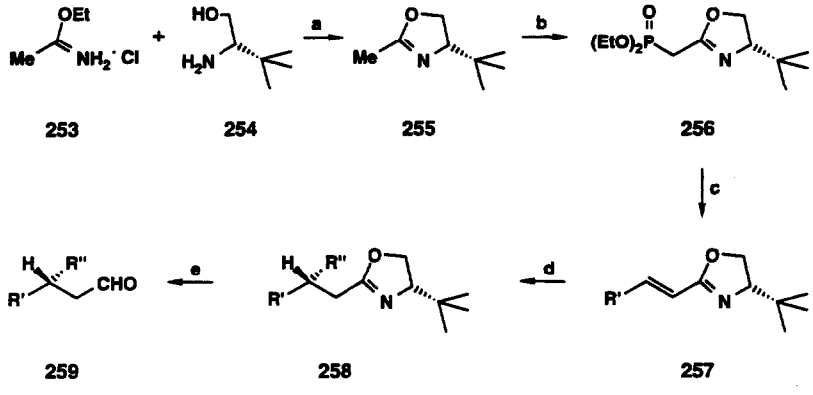


252 **251** **250**

C. *Conjugate Additions.*

Conjugate additions to non-racemic α,β-unsaturated oxazolines were first carried out in the early 1970's.[1d] In the intervening years this technique has undergone considerable improvement, though the earlier method is occasionally employed.[185] Of particular note in the recent work is the use of non-chelating auxiliaries. Just as described for naphthyl systems (Section VI B), the *tert*-leucinol-derived oxazolines were recently shown to provide excellent stereoselectivities in aliphatic systems.[186] The requisite oxazolines were prepared by condensation of ethyl acetimidate **253** with (S)-tert-leucinol, **254**, to afford the 2-methyl oxazoline, **255**. Metalation at -78°C with LDA followed by quench with diethyl chlorophosphonate gave the Horner-Wadsworth-Emmons reagent, **256**, followed by condensation with aldehydes,[187] affording α,β-unsaturated oxazolines **257** with excellent *trans* selectivity. The conjugate additions were carried out at -78°C with various alkyllithiums providing products **258**, which were carried on to the aldehydes, **260**. Overall yields

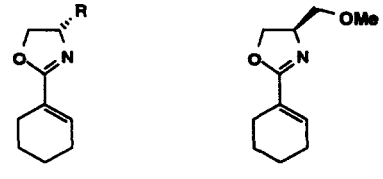
Scheme 39.



Key: (a) CH_2Cl_2; (b) LDA, $ClP(O)(OEt)_2$; (c) R'CHO; (d) R"Li; (e) MeOTf, $NaBH_4$, H_3O^+.

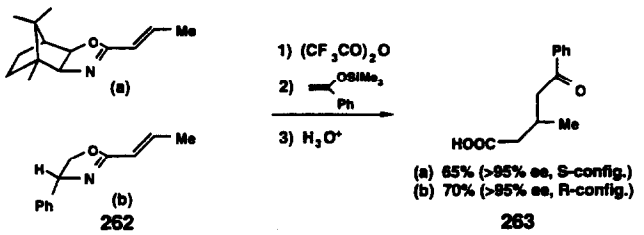
were good (~35%, 5 steps) while ee's of the aldehydes were excellent (94-97%), showing once again that alkoxy chelation is not always a necessary control element in oxazoline-mediated synthesis.

The chelating auxiliaries have, however, maintained a useful presence through their rate-enhancing properties. For example, the non-chelating (mono-coordinate) cyclohexenyloxazoline **260** failed to react appreciably with nucleophiles, whereas chelating oxazoline **261** showed high reactivity as well as moderate to high selectivity in conjugate additions with various organolithiums.[188]



260 (R = *i*-Pr, *t*-Bu) **261**

The lower reactivity of the non-chelating α,β-unsaturated oxazolines was improved by Langlois[189] through the acylation of the oxazoline nitrogen with trifluoroacetic anhydride. The increased reactivity allowed conjugate addition of silyl enol ethers at low temperature (≤ -40°C). Camphor-derived oxazoline **262a**, led to **263a** with the (S)-configuration after conjugate addition and hydrolysis.[190] The antipode **263b** was synthesized with similarly high efficiency from the phenylglycinol-derived oxazoline **262b**.

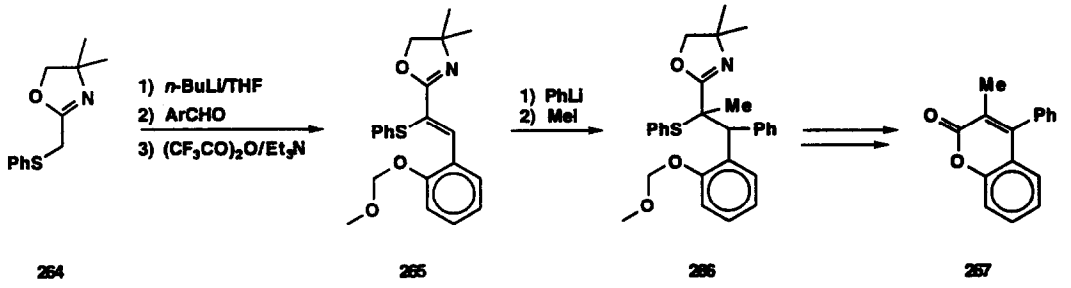


262 263

Achiral α,β-unsaturated oxazolines were effective in a synthesis of substituted coumarins.[191] Clinet utilized α-phenylthiooxazoline **264**[192] in a condensation with various acyl compounds to afford alkene **265** with good stereoselectivity. Addition of phenyllithium followed by methyl iodide quench gave the tandem-adduct **266** in 83% yield. Hydrolysis and oxidation led cleanly to the target **267** (77%).

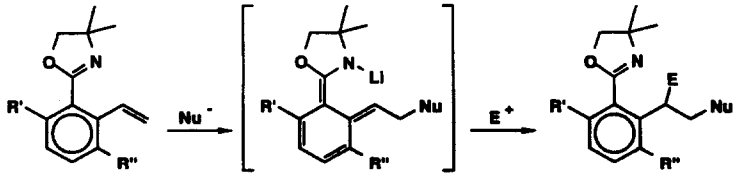
A formal 1,6-conjugate addition of alkyllithiums was described by Seijas,[193] who converted styrenyl oxazolines **268** to tandem adducts **270** presumably through **269**. Quenching with MeOH or MeI typically led to good yields of **270** for a variety of examples. The reaction proceeded readily

Scheme 40.



264 265 266 267

with alkyllithiums when R' = H and R'' = OMe, though poorer reactivity was observed when R' = R'' = H and no reaction was observed when R' = OMe and R'' = H. Treatment with Grignard reagents gave little or no reaction.

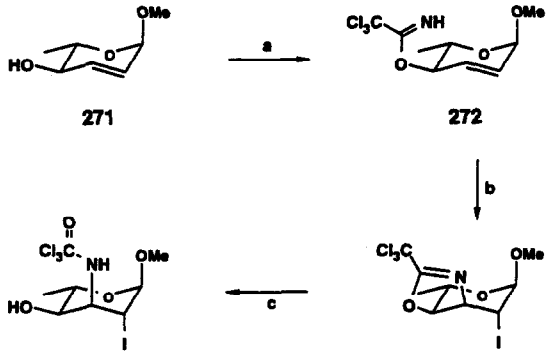


268 269 270

D. *Other Reactions of Aliphatic Oxazolines.*

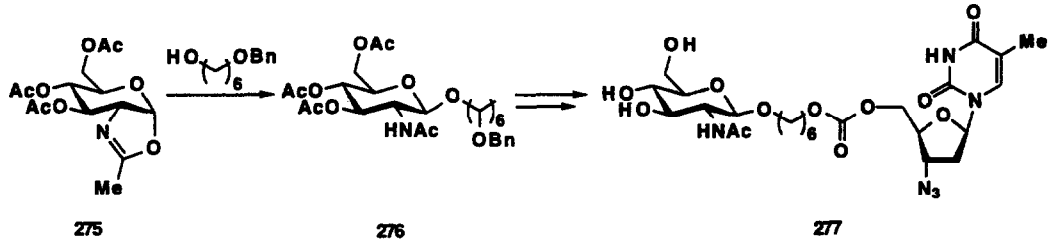
The oxazoline serves well as a masked template for the installation of amino alcohols and is used extensively to this end by carbohydrate chemists in the synthesis of amino sugars.[194] In a representative example, Sammes[195] effected the conversion of dihydropyranol **271** to trichloroacetimidate **272** following a procedure developed by Overman.[196] The cyclization[197] to **273** was induced by treatment with an electrophilic iodinating agent. Hydrolysis led to the protected amino sugar, **274** in good yield. Oxazolines have been called upon frequently in syntheses of cyclic as well as acyclic[198] sugars with either the pendant 2-methyl group[199] or the less stable 2-trichloromethyl oxazoline[200] as featured below.

Scheme 41.



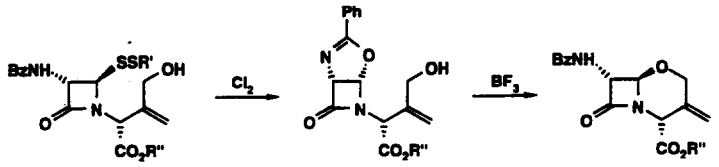
Key: (a) Cl_3CCN, NaH; (b) I^+(*s*-collidine)$_2BF_4^-$; (c) NIS, $CHCl_3$.

In fused systems where the oxazoline 4-carbon is the sugar anomeric carbon, facile nucleophilic displacement is utilized in the further functionalization of such species.[201] A route to the AZT analog **277** incorporated the aliphatic tether by displacement of the oxazolinyl moiety in **275** as outlined to yield amide **276**.[202]



275 276 277

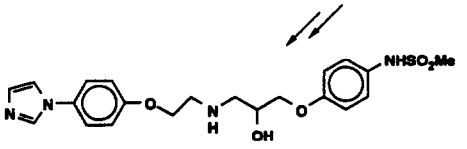
Oxazolines have been used in a similar fashion for the elaboration of β-lactams.[203] Treatment of disulfide **278** with chlorine induces cyclization of the amide moiety to afford oxazoline **279**.[204] Subsequent treatment with a Lewis acid leads to the 1-oxadethiacepham **280**, thus regenerating the amide intact.



278 279 280

Oxazolines lacking substituents at the 4- and 5- positions are useful electrophiles often employed in the synthesis of various 1,2-ethanediamines as well as (2-amino)-1-ethylethers.[205] This approach was recently used in the synthesis of antiarrhythmic agents such as **283**.[206] Treatment of the nucleophile **281** with 2-ethyloxazoline furnished, after hydrolysis, the aminoether **282**.

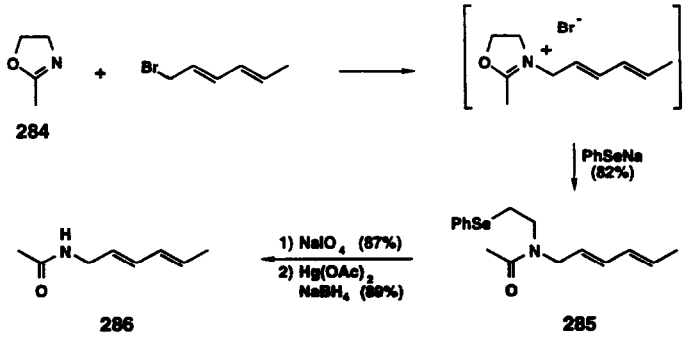
281 282



283

Moriwake[207] combined the moderate nucleophilicity of the ring nitrogen and the potential electrophilicity of the 5-position to effect an efficient synthesis of secondary carboxamides. In a representative example, this end was accomplished by quaternization of 2-methyloxazoline **284** with 2,4-hexadienyl bromide over two days followed by treatment with sodium benzeneselenolate to provide the tertiary amide, **285**. Oxidation of the selenide **285** led to an enamine that proved difficult to hydrolyze. The dealkylation procedure employed, though unusual, was effective for a number of additional substrates and reached secondary amides, **286**, in generally good yields.

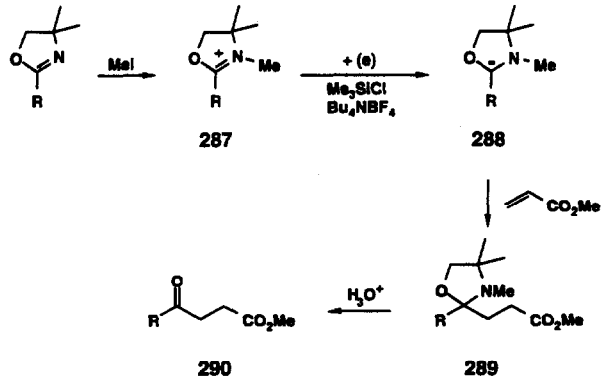
Scheme 42.



284 286 285

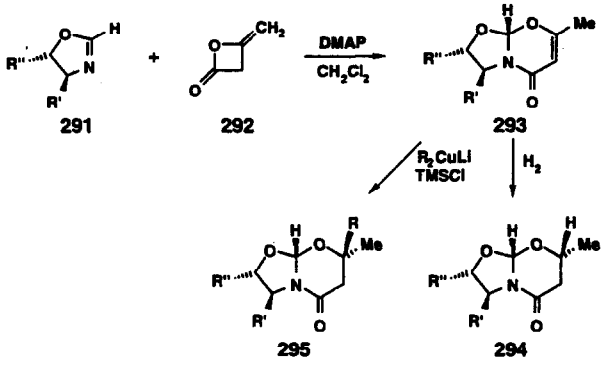
Conversion of oxazolines to acyl anion equivalents (Scheme 43) was demonstrated by Shono[208] through the electrochemical reduction of oxazolinium salts **287** to oxazolidine anions **288**.[209] Conjugate additions to methyl acrylate in the presence of TMSCl produced good yields of oxazolidines **289** and, ultimately, ketoesters **290** for numerous oxazolines. Other electrophiles used successfully included α,β-usaturated ketones (both cyclic and acyclic), benzyl bromide, and simple proton quench.

Scheme 43.

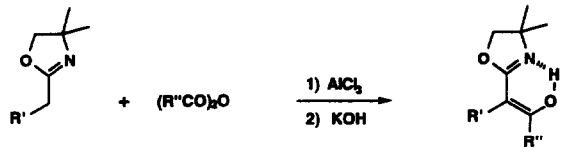


It recently was found that 2-H-oxazolines **291** undergo ready cyclocondensation with diketene, **292**.[210] Of the four chiral oxazolines employed, the *t*-leucinol-derived oxazoline (R' = t-Bu, R'' = H) afforded diastereospecific formation of bicyclic oxazinone, **293**. Subsequent hydrogenation to **294** and cuprate additions to **295** were again diastereospecific and occurred in the direction of pyramidalization of the sp^2 center in accord with the observations of Seebach.[211]

Scheme 44.

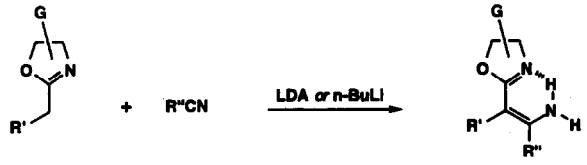


Numerous synthetic methods that allow reactivity at the 2-alkyl position without disturbing the oxazoline ring itself have been developed. Tohda[212] described a facile approach to crossed-Claisen condensations using oxazolines **296**, thus avoiding the usual self-condensation seen with other carboxylate systems. Yields of condensation products **297** were in the range 31-71% for the nine examples reported.



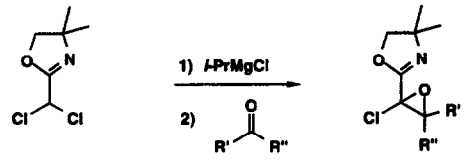
296 297

Similarly, a route to β-amino acids has been reported by Fustero and Barluenga[213] and separately by Poindexter.[214] Lithiation of the oxazolines **298** at the 2-alkyl group followed by nitrile addition afforded good yields of the masked dehydroamino acids **299** for a wide variety of oxazolines and nitriles.



298 299

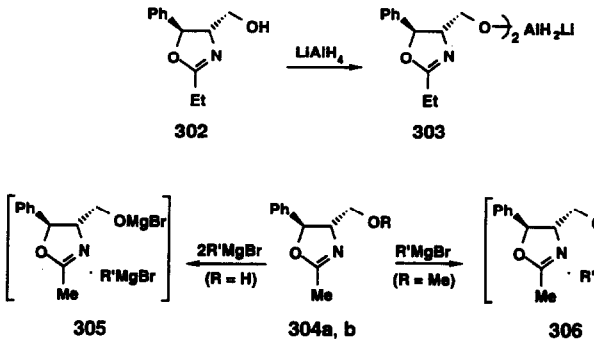
An application of the Darzens condensation was used to produce epoxyoxazolines **301** from α,α-dichlorooxazolines **300** in 60-95% yield.[215] Both aliphatic and aromatic examples were described and again showed the generalized resistence of oxazolines toward self-condensation.



300 301

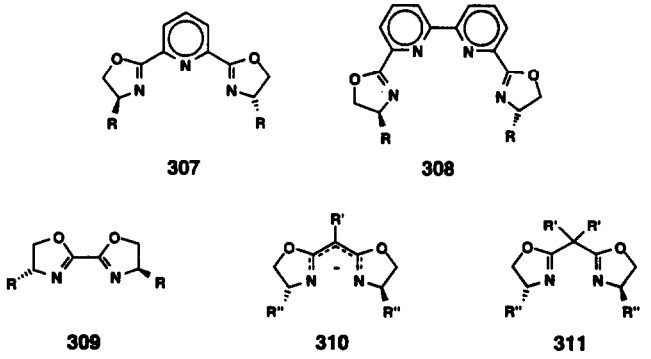
VIII. OXAZOLINES AS LIGANDS FOR CATALYSIS

Oxazolines were first used as recoverable ligands two decades ago, and facilitated both ketone reductions[119] and nucleophilic additions[216] in an asymmetric fashion. In the first instance, chiral non-racemic 4-hydroxymethyloxazoline **302** was treated with 0.5 equivalents of lithium aluminum hydride leading to presumed species, **303**. This reagent mediated the reduction of various ketones with enantiomeric excesses of 4-65% (5 examples). In a similar fashion, oxazoline **304a** (R = H) was treated with two equivalents of a Grignard reagent, the first deprotonating the hydroxy moiety to afford likely intermediate complex, **305**, whereas oxazoline **304b** (R = Me) was combined with one equivalent of Grignard reagent to give neutral-oxazoline complex, **306**.[217] Additions to various prochiral ketones yielded chiral carbinols in the range of 0-25% ee (8 examples). More recently, Williams[218] employed carbinol **304a** (R = H) and similar oxazolines as chiral ligands in the addition of diethylzinc to various aromatic aldehydes producing the secondary benzyl alcohols in moderate enantiomeric excesses (25-67% ee).

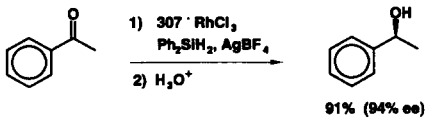


The standards for asymmetric induction have risen sharply in the intervening years since these studies were first disclosed, and ligand design in this area has met this challenge primarily through the synthesis of bis-oxazolinyl metal complexes. Bolm[219] and Pfaltz[220] have recently reviewed this aspect of oxazoline chemistry and therefore this section will be limited to a very brief overview of catalyst and reaction types explored thus far.

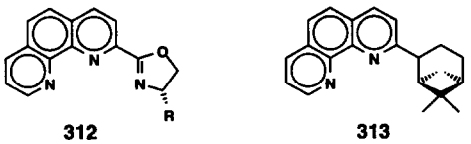
Some of the most successful systems employed include those derived from pyridine- and bipyridine-dicarboxylic acids, **307** and **308**, as well as oxalic acid, **309**, and malonic acid, anionic and neutral, **310** and **311**, respectively. Several X-ray crystal stuctures of these ligands, as their metal complexes, have been reported.[221]



The strong affinity of the oxazoline nitrogen for various metals accounts for the ready formation of bidentate coordinations complexes observed for the bis-oxazolines. Furthermore, the rigid achiral conformations imposed by various α-amino alcohol-derived oxazolines augurs well for a high degree of conformational symmetry in the catalytic cycle. A highly successful hydrosilylation of alkyl and aryl ketones was reported by Nishiyama[222] with the first-reported C_2-symmetric bis-oxazoline ligands, **307** ("pybox"), a terdentate ligand, and the related tetradentate ligand, **308** ("bipymox", R = *i*-Pr).[223] In nine of 17 examples utilizing various ligands **307**, the ee's were greater than 90%. Reductions of acetophenone showed that a combination of naked ligand *and* rhodium trichloride-complexed ligand gave the highest optical purity. Addition of a Lewis acid (silver

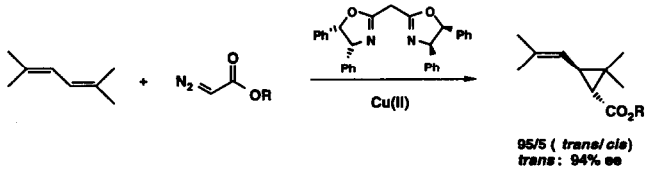


tetrafluoroborate in the example above) catalyzed the formation of the silane·ligand·rhodium complex believed responsible for the reduction. Helmchen[224] also obtained significant enantioselectivity in a rhodium-catalyzed hydrosilylation of acetophenone (up to 84% ee) utilizing ligands **309**, whereas ligands **310** and **311** gave poor results. Poor selectivity (10-20%ee) was also obtained upon use of terdentate *mono*-oxazoline **312** despite an enantioselectivity of 76% with bidentate ligand **313**.[225]



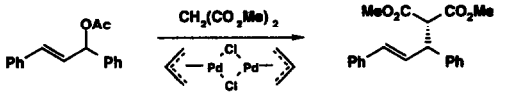
312 **313**

Asymmetric cyclopropanations have also been achieved with high enantioselectivity as well as high *trans* selectivity. Masamune[226] employed ligands of type **310** in the conversion of 2,5-dimethyl-2,4-hexadiene to the *trans* cyclopropane. Similar results were obtained by Evans[227a] with ligand **311** (R' = Me; R'' = *t*-Bu) in a study that corrected earlier stereochemical assignments in the Masamune report. A recent study by Evans[227b] has also disclosed that **311** (R'=Me, R''=Ph) is a highly effective catalyst for aziridination of olefins affording both aziridines and α-amino-β-hydroxy esters in very high enantiomeric excess.



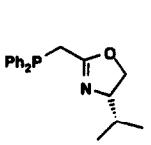
Pfaltz[228], like Masamune, has used bis-oxazolines **310** in highly stereoselective copper catalyzed cyclopropanations and has extended the use of ligands **309** to iridium catalyzed transfer hydrogenation of ketones. The valinol-derived ligand (R = *i*-Pr) was found to give excellent selectivity, while the more sterically hindered *t*-leucinol version (R = *t*-Bu) afforded <5% conversion.

Pfaltz also described palladium-catalyzed allylic substitutions (eq. 12) using ligand **311** (R' = Me; R'' = Bn) where high enantioselectivities were obtained.

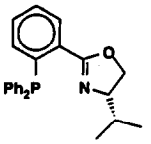


(eq. 12)

This allylic alkylation was improved separately by both Helmchen[229] and Pfaltz[230] through the use of mono-oxazoline bidentate ligands **314** (73% ee) and **315** (98.5% ee).[231]



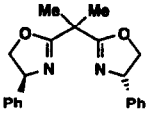
314



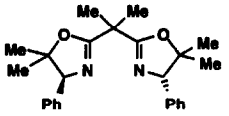
315

Corey[232] has combined ligand **311** with Lewis acid catalysts in a Diels-Alder cycloaddition between cyclopentadiene and acryloyl oxazolidinone **316** to afford adduct **317**. The choice of FeI_2 as the acid component led to enantioselectivities up to 86% and *endo* selectivity of 99:1. Use of the hexamethyl bis(oxazoline) **318** with MgI_2 as Lewis acid gave slightly better results under the same conditions.[233a] The choice of counterion was not a critical factor, though solvent selection affected both enantioselectivity and *endo* selectivity.[233b]

316 317



311
(where R = Ph)



318

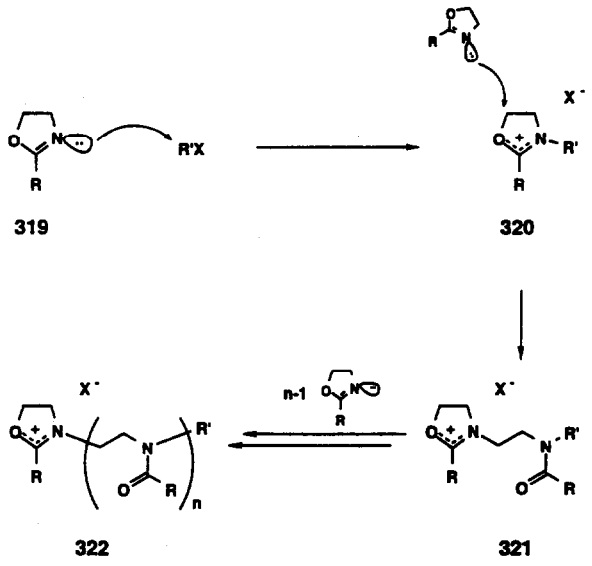
IX. MISCELLANEOUS

The synthetic utility of oxazolines has been examined in the previous sections. This final section will touch briefly on divergent areas of research including primarily polymer chemistry, oxazoline *N*-oxides, analytical probes, and finally oxazoline-containing natural products.

Oxazoline-Based Polymers:

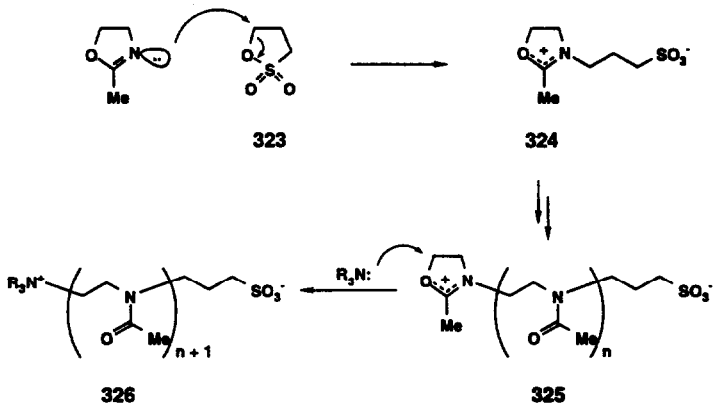
The number of publications and patents in the area of oxazoline-derived polymers exceeds the scope of a review primarily concerned with synthesis.[234] As such, we will defer to the practitioners in the polymer science field for a follow-up to their previous review[235] of this important subject. Some of the requirements for oxazoline polymerization bear mentioning if one is to *avoid* this result in *micro*molecular synthetic work. By way of illustration (Scheme 45), treatment of the generic oxazoline **319** with an electrophilic reagent may lead to nitrogen alkylation or oxidation, to afford oxazolinium species **320**. This cationic intermediate acts as an electrophile in a variety of synthetic methods. Here, in the absence of a more nucleophilic agent, unalkylated (or unoxidized) oxazoline becomes the only available nucleophile and produces ring-opened product **321**. Propagation of this sequence produces a polyamide **322** as a living polymer. Oxazolines polymerize under a wide variety of conditions[236] and have been incorporated into graft-[237] as well as block-[238] copolymers.

Scheme 45.



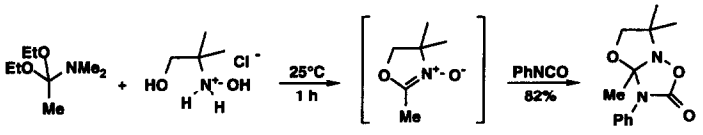
In a clever application, the use of a propylsultone **323** as electrophilic initiator polymerized 2-methyloxazoline (Scheme 45).[239] The zwitterionic oxazolinium **324** produced in the initiation step affords polyacetamide **325** after reaction with additional oxazoline. Termination to **326** occurs upon reaction with a tertiary amine to yield a surfactant possessing enhanced water solubility in comparison to related systems. This approach was also employed with related six-membered ring oxazines and butylsultones.

Scheme 46.



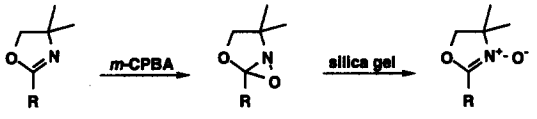
Oxazoline N-Oxides:

The oxazoline *N*-oxides are of interest to the synthetic chemist, but due to their distinctive chemistry they are discussed apart from other oxazolines. Syntheses of *N*-oxides have arisen from at least three viable procedures, including oxaziridine rearrangment, dimer dissociation, and cyclocondensation.[240] In a recent report by Coates,[240d] the hydroxylamino alcohol hydrochloride salt **328**, analogous to the most commonly used achiral amino alcohol in oxazoline synthesis, was cyclocondensed with *N,N*-dimethylacetamide diethylacetal **327** to give the unstable oxazoline *N*-oxide, **329**. Because this product could not be cleanly isolated, phenyl isocyanate was added as trapping agent to support the existence of **329**. The expected [3+2] cycloadduct **330** was obtained in good yield. Other additions gave expected cycloadducts as well.



327 **328** **329** **330**

Oxazolines **331** are also used as starting materials in the synthesis of oxazoline *N*-oxides via *m*-CPBA oxidation to give the intermediate oxaziridine, **332**.[241] The latter compounds are themselves unstable and rearrange on silica gel to give the oxazoline *N*-oxides, **333**.

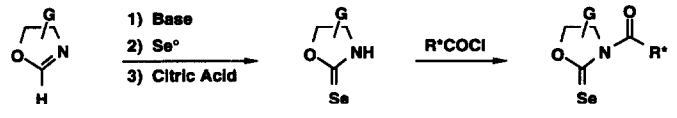


331 **332** **333**

Oxazolines as Analytical Probes:

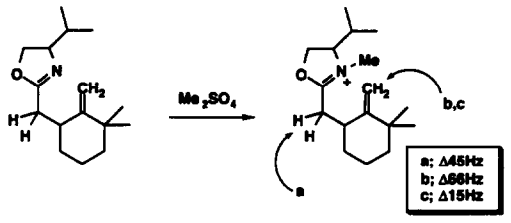
Structure elucidation of naturally-occurring fatty acids has long been carried out with heavy emphasis on mass spectral analysis of various derivatives. Huang,[242] using in-beam electron-ionization, has found that oxazoline derivatives provide highly reliable substrates for the location of hydroxy, ethylenic, acetylenic, methyl, cyclopropyl, and cyclopentyl groups on the alkyl chain with characteristic fragmentation patterns.

Another use of this heterocycle as an analytical probe started with 2-H-oxazolines in the determination of enantiomeric purity of various materials. The oxazolines were converted to oxazolidine-2-selones **334** and subsequently acylated with racemic acid chlorides affording diastereomeric mixture **335**.[243] Analysis of the ^{77}Se NMR spectra were found to provide excellent diastereomer signal resolution.



334 **335**

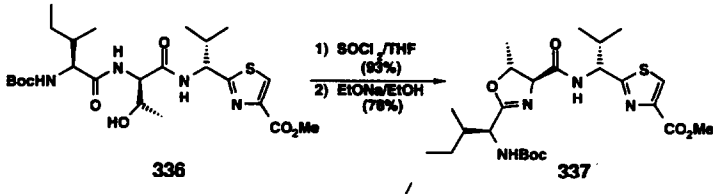
In instances where oxazoline *diastereomers* exhibit inadequate NMR diastereotopic resolution, the *N*-methyl derivatives often resolve in striking fashion as shown in a study by Kurth.[244] Treatment of numerous diastereomeric oxazoline mixtures with dimethyl sulfate yielded an oxazolinium salt that exhibited substantial ^{1}H NMR chemical shift differences as illustrated in a typical example (eq. 13).



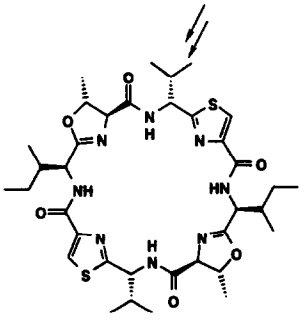
(eq. 13)

Oxazoline-Containing Natural Products:

It was mentioned earlier in this review (Section II B) that oxazolines are currently being incorporated into peptide-mimics to impart conformational rigidity to pharmacological candidates. This concept has been previously employed by nature in the form of several cyclic hepta- and octa-peptides, such as ascidiacyclamide **338**.[245] A total synthesis was reported by Hamada and Shioiri,[246] whereby the cyclization of threonine-residue precursor **336** with thionyl chloride led to a *syn*-disposed oxazoline, readily epimerized to desired *anti*-disposed oxazoline **337** in good overall yield. Subsequent protecting group removal led to dimerization to give the cyclic octapeptide **338**. Many similar compounds[247] have been reported having anti-neoplastic and other cytotoxic properties.[248]

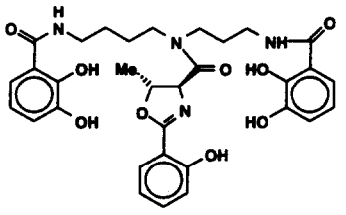


336 **337**



338

Another novel class of natural products containing the oxazoline moiety includes the iron-chelating parabactin, **339**. Total syntheses of this natural product[249] as well as various analogs[250] have been achieved.



339

X. SUMMARY

2-Oxazolines have permeated numerous sub-disciplines in synthetic organic chemistry in the 100 years since their discovery. This versatile heterocycle has served as protecting group, coordinating ligand, and activating moiety, often exhibiting all of these characteristics in a single transformation. The well-defined reactivity of *chiral* oxazolines has given rise to numerous highly efficient strategies for asymmetric synthesis including their use as ligands in asymmetric catalysis. Various unique properties have dictated their use in a multitude of dissimilar applications: as monomers in polymer production, as moderators in analytical processes, and as conformationally rigid peptide mimics in medicinal chemistry. Even natural systems have chosen to incorporate oxazolines into their chemical arsenal, as evidenced by the rapidly growing number of identified natural products and their attendant pharmacological properties.

Future studies will undoubtedly uncover unexpected properties and applications. The number of important publications detailing oxazoline-related chemistry is growing, suggesting that research in this area, as in synthetic organic chemistry in general, has yet to mature.

XI. ACKNOWLEDGEMENTS

The authors are grateful to the National Institutes of Health for supporting their studies on oxazolines and to the Proctor and Gamble Co. for a fellowship (to TGG).

XII. NOTES AND REFERENCES

1) a) Wiley, R. H.; Bennett, L. L., Jr. *Chem. Rev.* **1949**, *44*, 447 (105 references). b) Seeliger, W.; Aufderhaar, E.; Diepers, W.; Feinauer, R.; Nehring, R.; Thier, W.; Hellmann H. *Angew. Chem.* **1966**, *78*, 913; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 875 (85 references). c) Frump, J. A. *Chem. Rev.* **1971**, *71*, 483 (398 references). d) Meyers, A. I.; Mihelich, E. D. *Angew. Chem.* **1976**, *10*, 321; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 270 (83 references). e) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837 (97 references). f) Le Perchec, P. *Jansen Chim. Acta* **1986**, *4*(1), 3 (78 references). g) Maryanoff, B. E. *Heterocyclic Compounds*, Volume 45, I. Turchi, Ed., Interscience, New York, **1986**, 963 (253 references).

2) Herein referred to as simply "oxazoline." The 3- and 4-oxazolines have distinctive characteristics wholly unrelated to the 2-oxazolines as described in this article. See reference 1a for a comparison of the related heterocycles.

3) Andreasch, R. *Monatsh. Chem. 5* **1884** 33.

4) (a) Zhang, J. Y.; Yu, Q. T.; Yang, Y. M.; Huang, Z. H. *Chem. Scripta* **1988**, *28*, 357 and references cited therein. (b) See also reports cited in reference 1c.
5) Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron Lett.* **1981**, *22*, 4471.
6) For a thorough discussion of the direct synthesis of oxazolines from carboxylic acids, see: Vorbruggen, H.; Krolikiewicz, K. *Tetrahedron* **1993**, in press. For an additional analysis of the reaction mechanism, see: Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1985**, *26*, 4687.
7) Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801; *Angew. Chem.* **1975**, *87*, 863.
8) Barton, D. H. R.; Motherwell, W. B.; Wozniak, J.; Zard, S. Z. *J. Chem. Soc. Perkin Trans. I* **1985**, 1865.
9) Banerjee, S.; Desai, U. R.; Trivedi, G. K. *Synth. Commun.* **1991**, *21* (6), 757.
10) Fry, E. M. *J. Org. Chem.* **1949**, *14*, 887.
11) Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 6501. In a similar vein, β-selenamides have been oxidized at selenium to induce cyclization to the oxazoline: Toshimitsu, A.; Hirosawa, C.; Tanimoto, S.; Uemura, S. *Tetrahedron Lett.* **1992**, *33*, 4017.
12 Hydroxylamides have also been cyclized by treatment with diethylaminosulphur trifluoride (DAST). See: Burrell, G.; Evans, J. M.; Jones, G. E.; Stemp, G. *Tetrahedron Lett.* **1990**, *31*, 3649.
13) For one of numerous previous examples of Appel (Mitsunobu)-type ring-closures, see: Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026.
14) Sund, C.; Ylikoski, J.; Kwiatkowski, M. *Synthesis* **1987**, 853.
15) Galeotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807.
16) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 907.
17) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267.
18) McManus, S. P.; Carroll, J. T.; Grohse, P. M.; Pittman, C. V. *Org. Prep. Proced.*, **1969**, *1*, 183.
19) (a) Abd El Samii, Z. K. M.; Al Ashmawy, M. I.; Mellor, J. M. *Tetrahedron Lett.* **1987**, *28*, 1949. (b) Abd El Samii, Z. K. M.; Al Ashmawy, M. I.; Mellor, J. M. *J. Chem. Soc., Perkin Trans. I* **1988**, 2517.
20) Engman, L. *J. Org. Chem.* **1991**, *56*, 3425.
21) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *Tetrahedron Lett.* **1987**, *29*, 1049. (b) Hu, N. X.; Aso, Y.; Otsubo, T.; Ogura, F. *J. Chem. Soc. Perkin Trans. I* **1989**, 1775.
22) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045.
23) A similar approach using organoselenium reagents has been reported: Morella, A. M.; Ward, A. D. *Tetrahedron Lett.* **1985**, *26*, 2899.
24) (a) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc. Perkin Trans. I* **1985**, 935. (b) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Org. Chem.* **1986**, *51*, 4905. (c) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc. Perkin Trans. I* **1986**, 1339.
25) For an early example see: Oda, R.; Okano, M.; Tokiura, S.; Misumi, F. *Bull. Chem. Soc., Jpn.* **1962**, *35*, 1219.
26) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.
27) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.
28) Lindsay Smith, J. R.; Norman, R. O. C.; Stillings, M. R. *J. Chem. Soc., Perkin Trans. I* **1975**, 1200.
29) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc. Perkin Trans. I* **1986**, 1345.
30) Schmidt, U.; Zah, M.; Lieberknecht, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1002.
31) Legters, J.; van Dienst, E.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 69 and references cited therein.
32) Legraverend, M.; Huel, C.; Guilhem, J.; Bisagni, E. *Carbohydrate Res.* **1992**, *228*, 21.
33) Shimizu, M.; Yoshioka, H. *Heterocycles* **1988**, *27*, 2527.
34) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213-325.
35) Schmidt, U.; Respondek, M.; Lieberknecht, A.; Werner, J.; Fischer, P. *Synthesis* **1989**, 256.

36) Heime, H. W.; Fetter, M. E.; Nicolson, E. M. *J. Am. Chem. Soc.* **1959**, *81*, 2202.
37) Letgers, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 16.
38) Archier-Jay, D.; Besbes, N.; Laurent, A.; Laurent, E.; Stamm, H.; Tardivel, R. *Tetrahedron Lett.* **1989**, *30*, 2271.
39) Padwa, A.; Gasdaska, J. R.; Tomas, M.; Turro, N. J.; Cha, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6739.
40) (a) Tsuge, O.; Kanemasa, S.; Matsuda, K. *Chem. Lett.* **1985**, 1411. (b) Tsuge, O.; Kanemasa, S.; Matsuda, K. *J. Org. Chem.* **1986**, *51*, 1997. (c) Tsuge, O.; Kanemasa, S.; Yamada, T.; Matsuda, K. *J. Org. Chem.* **1987**, *52*, 2523.
41) Suga, H.; Shi, X.; Fujieda, H.; Ibata, T. *Tetrahedron Lett.* **1991**, *32*, 6911.
42) Dondoni, A.; Fogagnolo, M.; Mastellari, A.; Pedrini, P.; Ugozzoli, F. *Tetrahedron Lett.* **1986**, *27*, 3915.
43) Naito, T.; Yuumoto, Y.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1992**, *33*, 4033.
44) Hoppe, D.; Scholikopf, U. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 300.
45) (a) Rich, D. H.; Dhaon, M. K.; Dunlap, B.; Miller, S. P. F. *J. Med. Chem.* **1986**, *29*, 978. (b) Bosmans, J.-P.; Van der Eycken, J.; Vandewalle, M.; Hulkenberg, A.; Van Hes, R.; Veerman, W. *Tetrahedron Lett.* **1989**, *30*, 3877. (c) Rao, M. N.; Holkar, A. G.; Ayyangar, N. R. *J. Chem. Soc., Chem. Commun.* **1991**, 1007.
46) (a) Ortuno, J.-C.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1989**, *30*, 4957. (b) Katritzky, A. R.; Chen, Y.-X.; Yannakopoulou, K.; Lue, P. *Tetrahedron Lett.* **1989**, *30*, 6657. (c) van Leusen, D.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 402.
47) (a) Hundscheid, J. A.; Tandon, V. K.; Rouwette, P. H. F. M.; van Leusen, A. M. *Tetrahedron* **1987**, *43*, 5073. (b) Baggaley, K. H.; Elson, S. W.; Nicholson, N. H.; Sime, J. T. *J. Chem. Soc., Perkin Trans I* **1990**, 1521.
48) Hundscheid, F. J. A.; Tandon, V. K.; Rouwette, P. H. F. M.; van Leusen, A. M. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 159.
49) Zeiss, H.-J. *J. Org. Chem.* **1991**, *56*, 1783.
50) Ortuno, J.-C.; Langlois, Y. *Tetrahedron Lett.* **1991**, *32*, 4491.
51) Ito, Y.; Matsuura, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781.
52) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.
53) For other examples, see: (a) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 6215. (b) Ito, Y.; Sawamura, M.; Kobayashi, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 6321. (c) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253. (d) Hayashi, T. *Pure & Appl. Chem.* **1988**, *60* (1), 7. (e) Ito, Y.; Sawamura, M.; Hamashima, H.; Emura, T.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 4681. (f) Hayashi, T.; Sawamura, M.; Ito, Y. *Tetrahedron* **1992**, *48* (11), 1999.
54) Silver(I) complexes were shown to give similar results. For examples, see: (a) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935. (b) Hayashi, T.; Uozumi, Y.; Yamazaki, A.; Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron Lett.* **1991**, *32*, 2799.
55) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 239.
56) A number of elegant mechanistic as well as target-oriented studies have been carried out. See: (a) Pastor D. S.; Togni, A. *J. Am. Chem. Soc.* **1989**, *111*, 2333. (b) Togni, A.; Pastor, S. D. *Helv. Chim. Acta* **1989**, *72*, 1038. (c) Togni, A.; Pastor, S. D.; Rihs, G. *Helv. Chim. Acta* **1989**, *72*, 1471. (d) Togni, A.; Pastor, S. D. *J. Org. Chem.* **1990**, *55*, 1649. (e) Pastor, S. D.; Togni, A. *Tetrahedron Lett.* **1990**, *31*, 839. (f) Togni, A.; Pastor, S. D.; Rihs, G. *J. Organomet. Chem.* **1990**, *381*, C21. (g) Pastor, S. D.; Kesselring, R.; Togni, A. *J. Organomet. Chem.* **1992**, *429*, 415.
57) Togni, A.; Pastor, S. D. *Tetrahedron Lett.* **1989**, *30*, 1071.
58) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247.
59) Solladie-Cavallo, A.; Quazzotti, S.; Colonna, S.; Manfredi, A.; Fischer, J.; DeCian, A. *Tetrahedron: Asymm.* **1992**, *3*, 287.
60) (a) Solladie-Cavallo, A.; Quazzotti, S.; Colonna, S.; Manfredi, A. *Tetrahedron Lett.* **1989**, *30*, 2933. (b) Colonna, S.; Manfredi, A.; Solladie-Cavallo, A.; Quazzotti, S. *Tetrahedron Lett.* **1990**, *31*, 6185.

61) Kim, U. T.; Bhatia, S. K.; Hajdu, J. *Tetrahedron Lett.* **1991**, *32*, 6521.
62) (a) Jones, R. C. F.; Ward, G. J. *Tetrahedron Lett.* **1988**, *29*, 3853. (b) Breton, P.; Andre-Barres, C.; Langlois, Y. *Synth. Commun.* **1992**, *22*, 2543.
63) Michelin, R. A.; Bertani, R.; Mozzon, M.; Bombieri, G.; Benetollo, F.; Angelici, R. J. *Organometallics* **1991**, *10*, 1751.
64) Hegedus, L. S.; Mulhern, T. A.; Asada, H. *J. Am. Chem. Soc.* **1986**, *108*, 6224.
65) Meyers, A. I.; Robichaud, A. J.; McKennon, M. J. *Tetrahedron Lett.* **1992**, *33*, 1181.
66) Stille, J. K.; Crisp, G. T.; Scott, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 7500.
67) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
68) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085.
69) (a) Dondoni, A.; Fogagnolo, M.; Fantin, G.; Medici, A.; Pedrini, P. *Tetrahedron Lett.* **1986**, *27*, 5269. (b) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 693. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Mastellari, A.; Medici, A.; Negrini, E.; Pedrini, P. *Gazz. Chim. Ital.* **1988**, *118*, 211. (d) Kosugi, M.; Fukiage, A.; Takayanagi, M.; Sano, H.; Migita, T.; Satoh, M. *Chem. Lett.* **1988**, 1351. (e) Dondoni, A. *Pure & Appl. Chem.* **1990**, *62*, 643.
70) Leonard, W. R.; Romine, J. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 1961.
71) Teng, M.; Lauher, J. W.; Fowler, F. W. *J. Org. Chem.* **1991**, *56*, 6840.
72) Meyers, A. I.; Wallace, R. H.; Harre, M.; Garland, R. *J. Org. Chem.* **1990**, *55*, 3137.
73) Meyers, A. I.; Temple, D. L. *J. Am. Chem. Soc.* **1970**, *92*, 6646.
74) Feuer, H.; Bevinakatti, H. S.; Luo, X.-G. *J. Heterocyclic Chem.* **1987**, *24*, 9.
75) Meyers, A. I.; Bamer, B. A. *J. Org. Chem.* **1986**, *51*, 120.
76) Levin, J. I.; Weinreb, S. M. *Tetrahedron Lett.* **1982**, *23*, 2347.
77) Phillion, D. P.; Pratt, J. K. *Synth. Commun.* **1992**, *22*, 13.
78) Kouklovsky, C.; Pouilhes, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672.
79) Gonda, J.; Kristian, P.; Mikler, L. *Collect. Czech. Chem. Commun.* **1986**, *51*, 112.
80) Dordor, I. M.; Mellor, J. M.; Kennewell, P. D. *Tetrahedron Lett.* **1983**, *24*, 1437.
81) Castedo, L.; Castro, J. L.; Riguera, R. *Tetrahedron Lett.* **1984**, *25*, 1205.
82) Overly, K. R.; Williams, J. M.; McGarvey, G. J. *Tetrahedron Lett.* **1990**, *31*, 4573.
83) Hardinger, S. A.; Jakubowski, J. A.; Fuchs, P. L. *Biorganic & Med. Chem. Lett.* **1991**, *1*, 79.
84) Ryan, C. M.; Kariv-Miller, E. *Tetrahedron* **1988**, *44*, 6807.
85) Meyers, A. I.; Shimano, M. *Tetrahedron Lett.* **1993**, *34*, in press.
86) White, J. D.; Butlin, R. J.; Hahn, H.-G.; Johnson, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 8595.
87) Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. H.; Mazzu, A. L.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497.
88) Knight, D. W,; Pattenden, G.; Rippon, D. E. *SynLett* **1990**, 36.
89) The thionyl chloride-induced cyclization has been applied to similar systems previously: Hamada, Y.; Shibata, M.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 6501.
90) (a) Yokokawa, F.; Hamada, Y.; Shioiri, T. *SynLett* **1992**, 149. (b) Yokokawa, F.; Hamada, Y.; Shioiri, T. *SynLett* **1992**, 151. (c) Yokokawa, F.; Hamada, Y.; Shioiri, T. *SynLett* **1992**, 153.
91) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961.
92) McGarvey, G. J.; Wilson, K. J.; Shanholtz, C. E. *Tetrahedron Lett.* **1992**, *33*, 2641. See also: Padwa, A.; Rasmussen, J. K.; Tremper, A. *J. Am. Chem. Soc.* **1976**, *98*, 2605.
93) A. I. Meyers and F. Tevaras -- studies are in progress to utilize photochemical oxidative routes to accomplish this transformation.
94) Meguro, K.; Tawada, H.; Sugiyama, Y.; Fujita, T.; Kawamatsu, Y. *Chem. Pharm. Bull.* **1986**, *34*, 2840.
95) (a) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 530. (b) Toshimitsu, A.; Terao, K.; Uemura, S. *J. Org. Chem.* **1987**, *52*, 2018.
96) Kurth, M. J.; Bloom, S. H. *J. Org. Chem.* **1989**, *54*, 411.
97) Atmani, A.; El Hallaoui, A.; El Hajji, S. *Synth. Commun.* **1991**, *21*, 2383.
98) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; second edition; John Wiley & Sons: New York, **1991**, pp. 265-266, 433-436.

99) For a brief discussion of this observation, see: Avila, W. B.; Crow, J. L.; Utermoehlen, C. M. *J. Chem. Ed.* **1990**, *67*, 350.

100) For example: (a) Hindered esters have been used for this purpose, though subsequent hydrolysis is difficult except in intramolecular lactonizations, thus limiting the generality of this approach - Hattori, T.; Suzuki, T.; Miyano, S. *J. Chem. Soc., Chem. Commun.* **1991**, 1375. (b) Oxazoles have also been used with a measure of success: Cram, D. J.; Bryant, J. A.; Doxsee, K. M. *Chem. Lett.* **1987**,19.

101) The methoxide displacement is observed more frequently in the literature most certainly due to the greater availability of the appropriate starting materials. The fluoride group often allows coupling at more sterically-conjested sites. For example, see: Cram, D. J.; Katz, H. E.; Dicker, I. B. *J. Am. Chem. Soc.* **1984**, *106*, 4987.

102) (a) Pridgen, L. N.; Snyder, L.; Prol, J., Jr. *J. Org. Chem.* **1989**, *54*, 1523. (b) Lipschutz, B. H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* **1991**, *113*, 8161. (c) For an excellent review of biaryl coupling reactions, see: Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (d) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201.

103) Findlay, J. A.; Daljeet, A.; Murray, P. J.; Rej, R. N. *Can. J. Chem.* **1987**, *65*, 427.

104) Patten, A. D.; Nguyen, N. H.; Danishefsky, S. J. *J. Org. Chem.* **1988**, *53*, 1003.

105) Comber, M. F.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1991**, 190.

106) Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 841.

107) Saha, A.; Nasipuri, D. *Tetrahedron Lett.* **1991**, *32*, 3213.

108) See, for example: Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.

109) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090.

110) Meyers, A. I.; Knaus, G.; Kamata, K. *J. Am. Chem. Soc.* **1974**, *96*, 268.

111) (a) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879. (b) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682. (c) This approach has previously been employed in the synthesis of (-)-steganone: Meyers, A. I.; Flisak, J. R.; Aitken, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 5446.

112) Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Chem. Commun.* **1991**, 278.

113) Rizzacasa, M. A.; Sargent, M. V. *J. Chem. Soc., Perkin Trans 1* **1991**, 845.

114) Castedo, L.; Cid, M. M.; Seijas, J. A.; Villaverde, M. C. *Tetrahedron Lett.* **1991**, *32*, 3871.

115) O'Malley, S.; Kodadek, T. *J. Am. Chem. Soc.* **1989**, *111*, 9116.

116) Perchonock, C. D.; Uzinskas, I.; McCarthy, M. E.; Erhard, K. F.; Gleason, J. G.; Wasserman, M. A.; Muccitelli, R. M.; Devan, J. F.; Tucker, S. S.; Vickery, L. M.; Kirchner, T.; Weichman, B. M.; Mong, S.; Scott, M. O.; Chi-Rosso, G.; Wu, H.-L.; Crooke, S. T.; Newton, J. F. *J. Med. Chem.* **1986**, *29*, 1442. Oxazolines have themselves proven to be effective leukotriene antagonists: Musser, J. H.; Kubrak, D. M.; Bender, R. H. W.; Kreft, A. F.; Nielson, S. T.; Lefer, A. M.; Chang, J.; Lewis, A. J.; Hand, J. M. *J. Med. Chem.* **1987**, *30*, 2087.

117) Anderson, P. L. (Sandoz, A.-G.) PCT Int. Appl. WO 84 02,903 (Cl. C07C59/56), 02 Aug 1984, US Appl. 460,600, 24 Jan 1983: *Chem. Abstr.* **1985**, *102*, 61957p.

118) (a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, III, J. B.; Wells, G. J.; Wexler, R. B.; Wong, P. C.; Yoo, S.-E.; Timmermans, P. B. *J. Med. Chem.* **1991**, *34*, 2525. (b) Murray, W. V. *Chemtracts* **1992**, *5*, 52.

119) Meyers, A. I.; Kendall, P. M. Tetrahedron Lett. 1974, 15, 1337.

120) (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

121) Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853.

122) Rawson, D.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1992**, 494.

123) Additions have also been achieved in: (a) tricarbonylchromium-complexed naphthalenes: Kundig, E. P.; Simmons, D. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1320; (b) Naphthylimines: Meyers, A. I.; Brown, J. D.; Laucher, D. *Tetrahedron Lett.* **1987**, *28*, 5279; (c) Hindered esters: i. Tomioka, K.; Shindo, M.; Koga, K. *J. Org. Chem.* **1990**, *55*, 2276. ii. Tomioka, K.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 681; and (d) oxazolidines: Pridgen, L. N.; Mokhallalati, M. K.; Wu, M.-J. *J. Org. Chem.* **1992**, *57*, 1237.

124) It has been observed that organolithium reagents behave quite differently when freshly generated for immediate use. Many mixtures that failed to react were found to react quite well if the lithium reagent was formed *in situ*. This behavior suggests changes in aggregation of the reagent over time affording a complex with typically lower reactivity. This problem has been circumvented through the use of vinyltin reagents as precursors to vinyllithiums: Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107. An increase in reactivity of other organolithium reagents was also observed when generated from "Freeman's reagent" (LiDBB): Rawson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **1991**, *32*, 2095.
125) Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865.
126) Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1984**, *25*, 3667.
127) (a) See reference 75. (b) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.
128) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854.
129) Meyers, A. I.; Higashiyama, K. *J. Org. Chem.* **1987**, *52*, 4592.
130) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949.
131) Robichaud, A. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607.
132) Meyers, A. I.; Licini, G. *Tetrahedron Lett.* **1989**, *30*, 4049.
133) Rawson, D. J.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2292.
134) Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010.
135) Meyers, A. I.; Gant, T. G. *J. Org. Chem.* **1992**, *57*, 4225.
136) Gant, T. G.; Meyers, A. I. *Tetrahedron Lett.* **1993**, in press.
137) Alam, M.; Bechtold, C.; Skoog, M. S.; Gant, T. G.; Patrick, A.; Colonno, R. J.; Meyers, A. I.; Li, H.; Trimble, J.; Lin, P.-F. *Antiviral Res.* **1993**.
138) Kundig, E. P.; Cunningham, A. F., Jr.; Paglia, P.; Simmons, D. P.; Bernardinelli, G. *Helv. Chim. Acta* **1990**, *73*, 386.
139) Kundig, E. P.; Amurrio, D.; Liu, R.; Ripa, A. *Synlett* **1991**, 657.
140) Kundig, E. P.; Bernardinelli, G.; Liu, R.; Ripa, A. *J. Am. Chem. Soc.* **1991**, *113*, 9676.
141) Kundig, E. P.; Ripa, A.; Bernardinelli, G. *Angew. Chem.* **1992**, *104*, 1115; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1071.
142) (a) Hauck, A. E.; Giam, C.-S. *J. Chem. Soc., Perkin Trans 1* **1980**, 2070. (b) Meyers, A. I.; Natale, N. R.; Wettlaufer, D. G.; Rafii, S.; Clardy, J. *Tetrahedron Lett.* **1981**, *22*, 5123. (c) Meyers, A. I.; Natale, N. R. *Heterocycles* **1982**, *18*, 13. (d) Binay, P.; Dupas, G.; Bourguignon, J.; Queguiner, G. *Can. J. Chem.* **1987**, *65*, 648.
143) In a related approach, an achiral oxazoline was used in addition to a chiral nitrogen-alkylating moiety. Low enantiomeric enrichment was obtained: Gosmini, R.; Mangeney, P.; Alexakis, A.; Commercon, M.; Normant, J.-F. *Synlett* **1991**, 111.
144) Meyers, A. I.; Oppenlaender, T. *J. Chem. Soc., Chem. Commun.* **1986**, 920.
145) (a) Meyers, A. I.; Oppenlaender, T. *J. Am. Chem. Soc.* **1986**, *108*, 1989. (b) The first example of a non-enzymic stereospecific intramolecular reduction by an NADH mimic containing a covalently bound carbonyl moiety was accomplished through this method: Meyers, A. I.; Brown, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 3155. (c) Meyers, A. I.; Brown, J. D. *Tetrahedron Lett.* **1988**, *29*, 5617.
146) An excellent review covering primarily the tertiary amide and carbamate metalation directors has appeared with introductory remarks referencing similar directing groups: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. See also: de Silva, S. O.; Reed, J. N.; Billedeau, R. J.; Wang, X.; Norris, D. J.; Snieckus, V. *Tetrahedron* **1992**, *48*, 4863.
147) For a more detailed discussion of the concept of complex-induced proximity effects, see: Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.
148) Hagen, S. E.; Domaglia, J. M. *J. Heterocyclic Chem.* **1990**, *27*, 1609.
149) Gildea, B. D.; Coull, J. M.; Koster, H. *Tetrahedron Lett.* **1990**, *31*, 7095.
150) Nakano, J.; Uchida, K.; Fujimoto, Y. *Heterocycles* **1989**, *29* (3), 427.
151) (a) Meyers, A. I.; Avila, W. B. *Tetrahedron Lett.* **1980**, *21*, 3335. (b) Mori, S.; Ohno, T.; Harada, H.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1991**, *47*, 5051.

152) (a) Meyers, A. I.; Avila, W. B. *J. Org. Chem.* **1981**, *46*, 3881. (b) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *52*, 713.
153) Boulet, C. A.; Poulton, G. A. *Heterocycles* **1989**, *28* (1), 405.
154) (a) Meyers, A. I.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690. (b) Pansegrau, P. D.; Rieker, W. F.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7178.
155) Altman, J.; Bohnke, H.; Steigel, A.; Wulff, G. *J. Organomet. Chem.* **1986**, *309*, 241.
156) Clinet, J. C.; Balavoine, G. *J. Organomet. Chem.* **1991**, *405*, C29. See also: (a) Izumi, T.; Watabe, H.; Kasahara, A. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1711. (b) Balavoine, G.; Clinet, J. C.; Zerbib, P.; Boubekeur, K. *J. Organomet. Chem.* **1990**, *389*, 259. (c) Balavoine, G.; Clinet, J. C. *J. Organomet. Chem.* **1990**, *390*, C84. (d) Doisneau, G.; Balavoine, G.; Fillebeen-Khan, T.; Clinet, J. C.; Delaire, J.; Ledoux, I.; Loucif, R.; Puccetti, G. *J. Organomet. Chem.* **1991**, *421*, 299.
157) Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061. For a prior example of an intermolecular asymmetric Ullmann reaction (2-13% de), see: Miyano, S.; Tobita, M.; Suzuki, S.; Nishikawa, Y.; Hashimoto, H. *Chem. Lett.* **1980**, 1027. For prior examples of intramolecular asymmetric Ullmann reactions (>99% ee), see: (a) Miyano, S.; Fukushima, H.; Handa, S.; Ito, H.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3249. (b) Takahashi, M.; Kuroda, T.; Ogiku, T.; Ohmizu, H.; Kondo, K.; Iwasaki, T. *Tetrahedron Lett.* **1991**, *32*, 6919.
158) Butenschon, H.; Winkler, M.; Vollhardt, K. P. C. *J. Chem. Soc., Chem. Commun.* **1986**, 388.
159) Dominguez, C.; Csaky, A. G.; Plumet, J. *Tetrahedron* **1992**, *48*, 149.
160) Balasubramaniam, T. N.; Mirzaei, Y. R.; Natale, N. R. *Synthesis* **1990**, 1076.
161) Della Vecchia, L.; Vlattas, I. *J. Org. Chem.* **1977**, *42*, 2649.
162) (a) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1343. (b) Cartoon, M. E. K.; Cheeseman, G. W. H. *J. Organomet. Chem.* **1982**, *234*, 123.
163) Takeda, Y.; Nishiyama, H.; Ishikura, M.; Kamata, K.; Terashima, M. *Heterocycles* **1992**, *33*(1), 173.
164) Ghose, S.; Gilchrist, T. L. *J. Chem. Soc., Perkin Trans. 1* **1991**, 775.
165) Daniel, J.; Dhar, D. N. *Synth. Commun.* **1993**, *23* (1), 121.
166) (a) For the first report on this subject, see: reference 110. (b) For a review, see: Meyers, A. I.; Lutomski, K. A. in "*Asymmetric Synthesis*" Vol. 3, pp. 213-274, J. D. Morrison, Ed., Academic Press, Inc., New York, **1984**.
167) The standard 2-alkyloxazoline metalation is still used extensively, for example: (a) Feuer, H.; Bevinkatti, H. S.; Luo, X.-G. *J. Heterocyclic Chem.* **1986**, *23*, 825. (b) English, R. B.; Liddell, R. J.; Whiteley, C. G. *S. Afr. J. Chem.* **1987**, *40* (1), 39. (c) Liddell, J. R.; Whiteley, C. G. *S. Afr. J. Chem.* **1991**, *44* (2), 35. (d)
168) Jayasuriya, K.; Alster, J.; Politzer, P. *J. Org. Chem.* **1988**, *53*, 677.
169) Shono, T.; Kise, N.; Sanda, F.; Ohi, S.; Tsubata, K. *Tetrahedron Lett.* **1988**, *29*, 231.
170) Gawley, R. E.; Rein, K.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002.
171) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175.
172) Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381.
173) (a) Gawley, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1265. (b) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211. (c) Rein, K. S.; Gawley, R. E. *Tetrahedron Lett.* **1990**, *31*, 3711. (d) Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 1564. (e) Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 839.
174) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589 and references cited therein.
175) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483.
176) (a) Mikami, K.; Fujimoto, K.; Kusaga, T.; Nakai, T. *Tetrahedron Lett.* **1984**, *25*, 6011. (b) Mikami, K.; Kasuga, T.; Fujimoto, K.; Nakai, T. *Tetrahedron Lett.* **1986**, *27*, 4185.
177) Coutts, S. J.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1990**, *31*, 4301.
178) (a) Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 4631. (b) Rossano, L. T.; Plata, D. J.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 5189. (c) Balestra, M.; Wittman, M. D.;

Kallmerten, J. *Tetrahedron Lett.* **1988**, *29*, 6905. (d) Cywin, C. L.; Webster, F. X.; Kallmerten, J. *J. Org. Chem.* **1991**, *56*, 2953. (e) Sin, N.; Kallmerten, J. Tetrahedron Lett. 1993, 34, 753.

179) For racemic series, see: Pouilhes, A; Kouklovsky, C.; Langlois, N.; Langlois, Y. Tetrahedron Lett. 1987, 28, 6183. For aracemic series, see: (a) Pouilhes, A.; Uriarte, E.; Kouklovsky, C.; Langlois, N.; Langlois, Y. *Tetrahedron Lett.* **1989**, *30*, 1395. (b) Kouklovsky, C.; Pouilhes, A.; Langlois, Y. *J. Am. Chem. Soc.* **1990**, *112*, 6672. (c) Langlois, Y.; Pouilhes, A. *Tetrahedron: Asymm.* **1991**, *2*, 1223.

180) (a) Adam, W.; Griesbeck, A. *Synthesis* **1986**, 1050. (b) Adam, W.; Brunker, H.-G.; Nestler, B. *Tetrahedron Lett.* **1991**, *32*, 1957.

181) (a) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443.

182) (a) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769. (b) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377.

183) Kurth, M. J.; Soares, C. J. *Tetrahedron Lett.* **1987**, *28*, 1031.

184) (a) See reference 8. (b) Zhou, W.-S.; Huang, L.-F. *Tetrahedron* **1992**, *48*, 1837.

185) See, for example: Whittaker, M.; McArthur, C. R.; Leznoff, C. *C. Can. J. Chem.* **1985**, *63*, 2844.

186) Meyers, A. I.; Shipman, M. *J. Org. Chem.* **1991**, *56*, 7098.

187) According to the procedure of: Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

188) Meyers, A. I.; Schmidt, W.; McKennon, M. J. *Synthesis* **1993**, 250.

189) Langlois, N.; Dahuron, N. *Tetrahedron Lett.* **1990**, *31*, 7433.

190) Michelon, F.; Pouilhes, A.; Van Bac, N.; Langlois, N. *Tetrahedron Lett.* **1992**, *33*, 1743.

191) Clinet, J. C. *Tetrahedron Lett.* **1988**, *29*, 5901.

192) Clinet, J. C.; Balavoine, G. *Tetrahedron Lett.* **1987**, *28*, 5509.

193) Seijas, J. A.; Vazquez-Tato, M. P.; Castedo, L.; Estevez, R. J.; Ruiz, M. *J. Org. Chem.* **1992**, *57*, 5283.

194) (a) Tronchet, J. M. J.; Massoud, M. A. M. *Heterocycles* **1989**, *29* (3), 419. (b) Vasella, A.; Witzig, C.; Husi, R. *Helv. Chim. Acta* **1991**, *74*, 1362. (c) Colon, M.; Staveski, M. M.; Davis, J. T. *Tetrahedron Lett.* **1991**, *32*, 4447. (d) Fraser-Reid, B.; Alonso, R. A.; McDevitt, R. E.; Rao, B. V.; Vite, G. D.; Zottola, M. A. *Bull. Soc. Chim. Belg.* **1992**, *101*, 617.

195) Sammes, P. G.; Thetford, D. *J. Chem. Soc. Perkin Trans. 1* **1988**, 111.

196) (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901. (b) Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247.

197) See also: (a) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190. (b) Vankar, Y. D.; Kumaravel, G. *Tetrahedron Lett.* **1984**, *25*, 233.

198) (a) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127. (b) Csuk, R.; Hugener, M.; Vasella, A. *Helv. Chim. Acta* **1988**, *71*, 609. (c) Mack, H.; Brossmer, R. *Tetrahedron Lett.* **1992**, *33*, 1867.

199) (a) Hohgardt, H.; Dietrich, W.; Kuhne, H.; Muller, D.; Grzelak, D.; Welzel, P. *Tetrahedron* **1988**, *44*, 5771. (b) Abdel-Malik, M. M.; Perlin, A. S. *Carbohydr. Res.* **1989**, *189*, 123. (c) Nishimura, S.-I.; Kuzuhara, H.; Takiguchi, Y.; Shimahara, K. *Carbohydr. Res.* **1989**, *194*, 223. (d) Sarfati, S. R.; Pochet, S.; Neumann, J.-M.; Igolen, J. *J. Chem. Soc. Perkin Trans. 1* **1990**, 1065. (e) Magnusson, G.; Ahlfors, S.; Dahmen, J.; Jansson, K.; Nilsson, U.; Noori, G.; Stenvall, K.; Tjomebo, A. *J. Org. Chem.* **1990**, *55*, 3932. (f) Schreiner, E.; Zbiral, E.; Kleineidam, R. G.; Schauer, R. *Liebigs Ann. Chem.* **1991**, 129. (g) Roy, R.; Tropper, F. D.; Grand-Maitre, C. *Can. J. Chem.* **1991**, *69*, 1462. (h) Gordon, D. M.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 3713. (i) Lee, J.; Coward, J. K. *J. Org. Chem.* **1992**, *57*, 4126.

200) (a) Jacobsen, S. *Acta Chem. Scand.* **1986**, *B 40*, 493. (b) Jacobsen, S. *Acta Chem. Scand.* **1986**, *B 40*, 498. (c) Jacobsen, S. *Acta Chem. Scand.* **1988**, *B 42*, 605. (d) Beier, B.; Schurrle, K.; Werbitzky, O.; Piepersberg, W. *J. Chem. Soc. Perkin Trans. 1* **1990**, 2255.

201) (a) Diolez, C.; Sarfati, S. R.; Szabo, L. *J. Chem. Soc. Perkin Trans. 1* **1985**, 57. (b) Boldt, P.-C.; Schumacher-Wandersleb, M. H. M. G.; Peter, M. G. *Tetrahedron Lett.* **1991**, *32*,

1413. (c) Hollosi, M.; Kollat, E.; Laczko, I.; Medzihradszky, K. F.; Thurin, J.; Otvos, L. Jr. *Tetrahedron Lett.* **1991**, *32*, 1531.
202) Pochet, S.; Kansal, V.; Destouesse, F.; Sarfati, S. R. *Tetrahedron Lett.* **1990**, *31*, 6021.
203) (a) Crackett, P. H.; Greengrass, C. W.; Stoodley, R. J. *Tetrahedron Lett.* **1986**, *27*, 1301. (b) Banville, J.; Lapointe, P.; Belleau, B.; Menard, M. *Can. J. Chem.* **1988**, *66*, 1390. (c) Hoppe, D.; Schmincke, H.; Kleemann, H.-W. *Tetrahedron* **1989**, *45*, 695. (d) Edmunds, J. J.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1348. (e) Guest, A. W.; Milner, P. H.; Southgate, R. *Tetrahedron Lett.* **1989**, *30*, 5791. (f) Blaszczak, L. C.; Armour, H. K.; Halligan, N. G. *Tetrahedron Lett.* **1990**, *31*, 5693.
204) Cooper, R. D. G; Kinnik, M. D.; Peters, L. R.; Morin, J. M. Jr. *Synth. Commun.* **1988**, *18*, 763.
205) (a) Poindexter, G. S. *Synthesis* **1981**, 541. (b) Fazio, M. J. *J. Org. Chem.* **1984**, *49*, 4889. (c) Herman, H. H.; Husain, P. A.; Colbert, J. E.; Schweri, M. M.; Pollock, S. H.; Fowler, L. C.; May, S. W. *J. Med. Chem.* **1991**, *34*, 1082.
206) (a) Morgan, T. K., Jr.; Lis, R.; Lumma, W. C., Jr.; Wohl, R. A.; Nickisch, K.; Phillips, G. B.; Lind, J. M.; Lampe, J. W.; Di Meo, S. V.; Reiser, H. J.; Argentieri, T. M.; Sullivan, M. E.; Cantor, E. *J. Med. Chem.* **1990**, *33*, 1087. (b) Lis, R.; Morgan, T. K., Jr.; Marisca, A. J.; Gomez, R. P.; Lind, J. M.; Davey, D. D.; Phillips, G. B.; Sullivan, M. E. *J. Med. Chem.* **1990**, *33*, 2883.
207) Inaba, M.; Moriwake, T.; Saito, S. *Tetrahedron Lett.* **1985**, *26*, 3235.
208) (a) Shono, T.; Kashimura, S.; Yamaguchi, Y.; Kuwata, F. *Tetrahedron Lett.* **1987**, *28*, 4411. (b) Shono, T.; Kashimura, S.; Yamaguchi, Y.; Ishige, O.; Uyama, H.; Kuwata, F. *Chem. Lett.* **1987**, 1511.
209) Similarly, a reductive homocoupling of aryloxazolinium salts has been recently reported: Shono, T.; Kise, N.; Nomura, R.; Yamanami, A. *Tetrahedron Lett.* **1993**, *34*, 3577.
210) Meyers, A. I.; Leonard, W. R., Jr.; Romine, J. L. *Tetrahedron Lett.* **1991**, *32*, 597. An interesting double-addition of mono-ketene to 2-H-oxazolines has been reported: Nyce, P.; Puar, M. S.; Gala, D.; Jaret, R. S. *J. Heterocyclic Chem.* **1987**, *24*, 505.
211) Seebach, D.; Zimmerman, J.; Gysel, U.; Ziegler, R.; Ha, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4763.
212) Tohda, Y.; Morikawa, M.; Kawashima, T.; Ariga, M.; Mori, Y. *Chem. Lett.* **1986**, 273.
213) Fustero, S.; Diaz, M. D.; Barluenga, J.; Aguilar, E. *Tetrahedron Lett.* **1992**, *33*, 3801.
214) Poindexter, G. S.; Catt, J. D.; Sasse, P. A.; Kercher, M. A. *Heterocycles* **1993**, *36* (2), 295.
215) Combret, J. C.; Meghni, A.; Postaire, D.; Tekin, J. *Tetrahedron Lett.* **1991**, *32*, 87.
216) Meyers, A. I.; Ford, M. E. *Tetrahedron Lett.* **1974**, *15*, 1341.
217) These oxazolines were subsequently employed as ligands in cuprate additions to cyclohexenone with similarly low enantiomeric excesses (10-20%): Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* **1986**, *51*, 4953. Ordinary, achiral, 2,4,4-trimethyl-2-oxazoline has been used as ligand in cuprate additions as well: Jalander, L.; Oksanen, L.; Rosling, A. *Acta Chem. Scand.* **1990**, *44*, 842.
218) Allen, J. V.; Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymm.* **1993**, *4*, 649.
219) Bolm, C. *Angew. Chem.* **1991**, *103*, 556; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 542.
220) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
221) (a) Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1. (b) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500. (c) Bolm, C.; Weickhardt, K.; Zehnder, M.; Glasmacher, D. *Helv. Chim. Acta* **1991**, *74*, 717. (d) Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173. (e) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 430.
222) (a) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846. (b) See reference 221b. (c) Nishiyama, H.; Yamaguchi, S.; Kondo, M.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 4306.
223) Nishiyama, H.; Yamaguchi, S.; Park, S.-B.; Itoh, K. *Tetrahedron: Asymm.* **1993**, *4*, 143.
224) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257.
225) Gladiali, S.; Pinna, L.; Delogu, G.; Graf, E.; Brunner, H. *Tetrahedron: Asymm.* **1990**, *1*, 937.

226) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005. (b) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373.
227) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
228) (a) Muller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232. (b) Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143.
229) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769.
230) von Matt, P.; Pfaltz, A. *Angew. Chem.* **1993**, *105*, 614; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566.
231) For a mechanistic analysis, see: Reiser, O. *Angew. Chem.* **1993**, *105*, 576; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 547.
232) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.
233) (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (b) See also Evans, D. A.; Miller, S. J.; Leckta, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460.
234) A brief sampling of reports in this area include: (a) Kobayashi, S.; Miyamoto, M.; Saegusa, T. *Macromolecules* **1981**, *14*, 1582. (b) Kobayashi, S.; Isobe, M.; Saegusa, T. *Macromolecules* **1982**, *15*, 703. (c) Kobayashi, S.; Tokuzawa, T.; Saegusa, T. *Macromolecules* **1982**, *15*, 707. (d) Kobayashi, S.; Kaku, M.; Mizutani, T.; Saegusa, T. *Polym. Bull. (Berlin)* **1983**, *9*, 169. (e) Kobayashi, S.; Mizutani, T.; Saegusa, T. *Makromol. Chem.* **1984**, *185*, 441. (f) Kobayashi, S.; Morikawa, K.; Shimizu, N.; Saegusa, T. *Polym. Bull. (Berlin)* **1984**, *11*, 253. (g) Kobayashi, S.; Saegusa, T. *Makromol. Chem. Suppl.* **1985**, *12*, 11. (h) Kobayashi, S.; Saegusa, T. *Makromol. Chem., Macromol. Symp.* **1986**, *1*, 23. (i) Litt, M. H.; Hsieh, B. R.; Krieger, I. M.; Chen, T. T.; Lu, H. L. *J. Colloid Interface Sci.* **1987**, *115*, 312. (j) Rivas, B. L.; Ananias, S. I. *Polym. Bull.* **1987**, *18*, 189. (k) Simionescu, C. I.; David, G.; Grigoras, M. *Eur. Polym. J.* **1987**, *23*, 689. (l) Rodriguez-Parada, J. M.; Percec, V. *J. Polym. Sci., Polym. Chem. Ed.* **1987**, *25*, 2269. (m) Gunatillake, P. A.; Odian, G.; Tomalia, D. A. *Macromolecules* **1988**, *21*, 1556. (n) Kobayashi, S.; Kaku, M.; Saegusa, T. *Macromolecules* **1988**, *21*, 334. (o) Schulz, R. C.; Schwarzenbach, E. *Makromol. Chem., Macromol. Symp.* **1988**, *13/14*, 495. (p) Cheradame, H.; Tadjang, A. U.; Gandini, A. *Makromol. Chem., Rapid Commun.* **1988**, *9*, 255. (q) Hirao, A.; Ishino, Y.; Nakahama, S. *Macromolecules* **1988**, *21*, 561. (r) Kobayashi, S.; Masuda, E.; Shoda, S.; Shimano, Y. *Macromolecules* **1989**, *22*, 2878. (s) Kobayashi, S.; Uyama, H.; Narita, Y. *Polym. J.* **1990**, *22*, 175. (t) Kobayashi, S.; Uyama, H.; Narita, Y. *Macromolecules* **1990**, *23*, 353. (u) Kobayashi, S.; Tsukamoto, Y.; Saegusa, T. *Macromolecules* **1990**, *23*, 2609. (v) Kobayashi, S.; Uyama, H.; Shirasaka, H. *Makromol. Chem., Rapid Commun.* **1990**, *11*, 11. (w) Kobayashi, S.; Uyama, H.; Higuchi, N.; Saegusa, T. *Macromolecules* **1990**, *23*, 54.
235) Kobayashi, S.; Saegusa, T. *Ring-Opening Polymerization*; Elsevier Applied Science: Essex, England, **1984**; Vol. 2, pp 761-807.
236) Hrkach, J. S.; Matyjaszewski, K. *Macromolecules* **1992**, *25*, 2070 and references cited therein.
237) For example, see: Kobayashi, S.; Kaku, M.; Saegusa, T. *Macromolecules* **1988**, *21*, 1921.
238) For example, see: Kobayashi, S.; Uyama, H.; Ihara, E.; Saegusa, T. *Macromolecules* **1990**, *23*, 1586.
239) Brunel, S.; Chevalier, Y.; Le Perchec, P. *Tetrahedron* **1989**, *45*, 3363.
240) Also see: (a) Keana, J. F. W.; Lee, T. D. *J. Am. Chem. Soc.* **1975**, *97*, 1273. (b) Lee, T. D.; Keana, J. F. W. *J. Org. Chem.* **1976**, *41*, 3237. (c) Hendrickson, J. B.; Pearson, D. A. *Tetrahedron Lett.* **1983**, *24*, 4657. (d) Ashburn, S. P.; Coates, R. M. *J. Org. Chem.* **1984**, *49*, 3127. (e) Hisano, T.; Harano, K.; Matsuoka, T.; Watanabe, S.; Matsuzaki, T. *Chem. Pharm. Bull.* **1989**, *37*(4), 907.
241) Recent contributions include: (a) Abramovitch, D. A.; Abramovitch, R. A.; Benecke, H. *Heterocycles* **1985**, *23* (1), 25. (b) Banerjee, S.; Desai, U. R.; Trivedi, G. K. *Tetrahedron* **1992**, *48*, 133. (c) Kobayakawa, M.; Langlois, Y. *Tetrahedron Lett.* **1992**, *33*, 2353.

242) Zhang, J. Y.; Yu, Q. T.; Yang, Y. M.; Huang, Z. H. *Chem. Scripta* **1988**, *28*, 357 and references cited therein.
243) Silks, L. A.; Peng, J.; Odom, J. D.; Dunlap, R. B. *J. Org. Chem.* **1991**, *56*, 6733.
244) Kurth, M. J.; Brown, E. G.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 4984.
245) For crystal structure data, see: Ishida, T.; Inoue, M.; Hamada, Y.; Kato, S.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1987**, *5*, 370.
246) Hamada, Y.; Kato, S.; Shioiri, T. *Tetrahedron Lett.* **1985**, *26*, 3223.
247) A review of oxazole-containing natural products has appeared, covering many species possessing oxazoline moieties as well: Pattenden, G. *J. Heterocyclic Chem.* **1992**, *29*, 607. Similarly, a review of marine metabolites has indirectly addressed this topic: Michael, J. P.; Pattenden, G. *Angew. Chem.* **1993**, *105*, 1; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1.
248) (a) Ireland, C.; Scheuer, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 5688. (b) Ireland, C.; Durso, A. R., Jr.; Newman, R. A.; Hacker, M. P. *J. Org. Chem.* **1982**, *47*, 1807. (d) Biskupiak, J. E.; Ireland, C. *J. Org. Chem.* **1983**, *48*, 2302. (e) Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. *J. Org. Chem.* **1983**, *48*, 4445. (f) Hamamoto, Y.; Endo, M.; Nakagawa, M.; Nakanishi, T.; Mikuzawa, K. *J. Chem. Soc., Chem. Commun.* **1983**, 323. (g) Schmidt, U.; Griesser, H. *Tetrahedron Lett.* **1986**, *27*, 163. (h) Sugiura, T.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1987**, *28*, 2251. (i) Ishida, T.; Tanaka, M.; Nabae, M.; Inoue, M.; Kato, S.; Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1988**, *53*, 107. (j) Ishida, T.; Ohishi, H.; Inoue, M.; Kamigauchi, M.; Sugiura, M.; Takao, N.; Kato, S.; Hamada, Y.; Shioiri, T. *J. Org. Chem.* **1989**, *54*, 5337. (k) Williams, D. E.; Moore, R. E.; Paul, V. J. *J. Nat. Prod.* **1989**, *52*, 732. (l) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; van den Brenk, A. L.; Walters, D. J. *J. Med. Chem.* **1989**, *32*, pp 1349-1354, 1354-1359. (m) Schmitz, F. J.; Ksebati, M. B.; Chang, J. S.; Wang, J. L.; Hossain, M. B.; van der Helm, D. *J. Org. Chem.* **1989**, *54*, 3463. (n) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; van den Brenk, A.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634. (o) Wipf, P.; Miller, C. P. *J. Am. Chem. Soc.* **1992**, *114*, 10975. (p) McDonald, L. A.; Ireland, C. M. *J. Nat. Prod.* **1992**, *55*, 376. (q) Foster, M. P.; Concepcion, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671.
249) (a) Bergeron, R. J.; Kline, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 4489. (b) Nagao, Y.; Miyasaka, T.; Hagiwara, Y.; Fujita, E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 183.
250) Miyasaka, T.; Nagao, Y.; Fujita, E.; Sakurai, H.; Ishizu, K. *J. Chem. Soc. Perkin Trans. II* **1987**, 1543.

(*Received* 2 *August* 1993)