1,2-Amino Alcohols and Their Heterocyclic Derivatives as Chiral Auxiliaries in Asymmetric Synthesis

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A. Introduction

Amino acids have not only been used as chiral building blocks in organic synthesis, they have also been used as chiral auxiliaries and the source of a stereogenic center. Simple transformations, such as α-amino acid reductions, allow entry to other classes of compounds that are also useful as the source of chiral centers, as with α-amino aldehydes, that, in turn, can be used in a plethora of transformations.[1,2] This review covers the use of completely reduced derivatives, α-amino alcohols. Although a wide range of these 1,2-amino alcohols have been incorporated into target molecule synthesis, we will limit the coverage to the use of these molecules as chiral auxiliaries or ligands—that is the use of the amino alcohol to generate another stereogenic center, while that of the original molecule is not incorporated into the final product.

Chiral auxiliaries represent the vast majority of examples for the usage of amino alcohols with many as part of a cyclic system, especially five-membered rings (Figure 1). However, other systems, including acyclic ones, have been used in asymmetric synthesis.

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David Ager was born in Northampton, England, in 1953. He received a B.Sc. from Imperial College, London, and a Ph.D. from the University of Cambridge, working with Dr. Ian Fleming on organosilicon chemistry. In 1977 he was awarded a Science Research Council Postdoctoral Fellowship that allowed him to collaborate with Professor Richard Cookson FRS at the University of Southampton. In 1979 he joined the faculty of the University of Liverpool as a Senior Demonstrator. This was followed by an assistant professor position at the University of Toledo in Ohio. In 1986, he joined the NutraSweet Company's Research and Development group, that has now become NSC Technologies, part of Monsanto Growth Enterprises. Dr. Ager is responsible for the chemical development of new products, for the fine chemical intermediates business.

Indra Prakash was born in Muzaffarnagar, India, in 1956. Receiving an M.Sc. degree from the University of Roorkee, India, in 1977, he was awarded the Gold Medal for academic distinction. In 1982, he received a Ph.D. degree from Kurukshetra University, India, under the direction of Professor S. P. Singh. He also worked at Union Carbide at Bhopal, India. After coming to the United States, he joined Professor Kagan at the University of Illinois at Chicago and worked on the preparation of phototoxic photoantibiotic agents. Later, he collaborated with Professor Moriarity to study the utility of hypervalent iodine reagents in organic synthesis and then with Professor Sosnovsky at University of Wisconsin—Milwaukee on the synthesis of anticancer and NMR contrast agents. Joining Aldrich Chemical Company in 1987 as a Senior Chemist, he then became a Principal Investigator for a National Cancer Institute contract at Aldrich. In addition to his administrative and technical responsibilities with the NCI contract, he developed several new product lines (preparing chiral products using enzymes, NMR contrast agents, compounds used in PET and radiation tomography) and wrote technical bulletins. Currently, Dr. Prakash is a project leader developing processes for new sweetener candidates for NutraSweet Kelco, a business unit of Monsanto.

This review discusses each of these systems and is further subdivided into the major examples of each ring system. Each auxiliary system is covered with regard to its preparation, transformations that are available with it, and methods that can be used to remove it.

David Schaad was born in Fond du Lac, WI, in 1964. He obtained his B.S. degree from the University of Wisconsin—Madison, and Ph.D. from the University of Colorado at Boulder, 1992, under the direction of Professor Clark Landis. He continued at this institute as a postdoctoral associate with Professor Tarek Sammakia. In 1994, Dr. Schaad joined NutraSweet Research and Development, and has now progressed to NSC Technologies, where he works on the development of new processes to chiral intermediates.

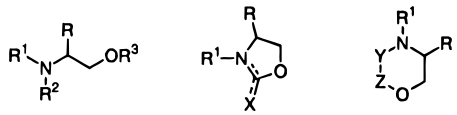


Figure 1. Auxiliary systems based on amino alcohols.

The 1,2-amino alcohols can be ligands, of both the acyclic and cyclic varieties, where the heteroatoms can be used to form a complex with the metal reaction center.

In addition to being useful compounds to effect a wide variety of transformations, especially when modified to cyclic derivatives or complexed to a metal center, a relatively large number of natural products contain the amino alcohol functionality. (Examples of derivatives are discussed in the appropriate section.) Not only can amino sugars be considered as members of this class of compounds, but nucleosides and nucleotides also fall within the definition. In many examples, the amino alcohol functionality is embedded deep within the molecule, and the synthesis of these derivatives is beyond the scope of this review. (For a discussion of these complex molecules see ref 3.) In most cases, the stereogenic centers are derived either from a carbohydrate,[4,5] or an amino acid (*vide infra*).[3,6]

In addition to natural products, many amino alcohol derivatives have chemotherapeutic properties. The approaches to these compounds have again relied heavily upon manipulations of carbohydrate derivatives or amino acids.[7−12]

B. Acyclic 1,2-Amino Alcohol Derivatives

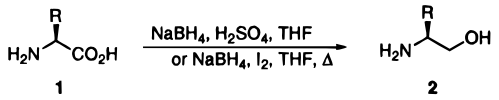
1. Preparations of 1,2-Amino Alcohols

1,2-Amino alcohols can either be prepared so that a chiral center is created in the reaction, or derived from a compound that already contains a stereogenic center. In the latter case, amino acids are natural compounds that are also readily available. The method of choice is often reduction of the parent amino acid.

a. From Amino Acids

Efficient reductions of amino acids **1** to form amino alcohols **2** have been reported recently: One approach uses a sodium borohydride ($NaBH_4$)−sulfuric acid system,[13] while another employs $NaBH_4$−iodine (Scheme 1).[14]

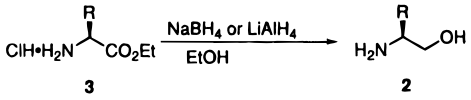
Scheme 1



Other reagents have also been used for the reduction of amino acids, such as lithium aluminum hydride ($LiAlH_4$),[15−20] borane−methyl sulfide in the presence of boron trifluoride etherate,[16,21−25] and lithium borohydride in the presence of trimethylsilyl chloride.[26]

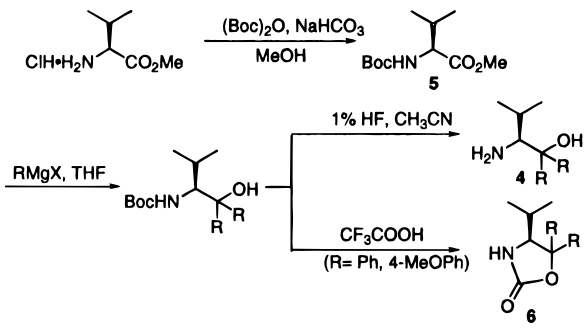
Amino ester hydrochlorides **3** can be reduced to the corresponding amino alcohols **2** with $LiAlH_4$[27,28] or $NaBH_4$ (Scheme 2).[29]

Scheme 2



The synthesis of uncommon β-amino alcohols **4** in high yields from *N*-Boc-L-valinate **5** and Grignard reagents has also been described (Scheme 3).[30] No

Scheme 3

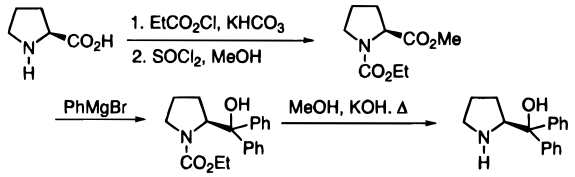


racemization was observed under these conditions. Attempted deprotection of the *N*-Boc amino alcohol with common reagents (e.g. aqueous HCl, HBr in acetic acid) lead to degradation, but trifluoroacetic acid treatment resulted in quantitative formation of an oxazolidinone chiral auxiliary **6** (section D.1).[31] Cleavage with 1% hydrogen fluoride in acetonitrile ultimately proved successful for the formation of **4**. The resultant amino alcohols **4** were then employed in enantioselective reactions that included reductions of and nucleophilic additions to carbonyl compounds.[32]

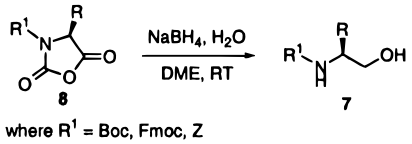
The Grignard reaction with amino acid derivatives to afford α,α-disubstituted β-amino alcohols has proven efficient with many examples (Scheme 4).[33−35]

The synthesis of β-amino alcohols **7** can be achieved by $NaBH_4$ reduction of *N*-protected *N*-carboxyanhydrides **8** (Scheme 5).[36,37] In addition, *N*-protected mixed anhydrides can be reduced with this reagent to provide 1,2-amino alcohols.[38,39]

Scheme 4



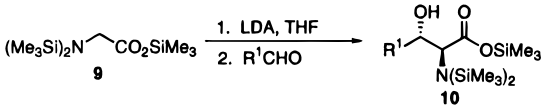
Scheme 5



where R^1 = Boc, Fmoc, Z

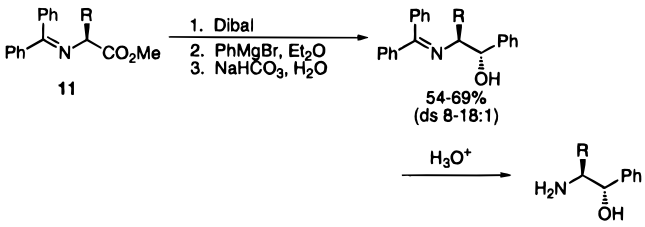
Amino esters can be deprotonated to provide the ester enolate that, in turn, can be treated with aldehydes. A 1,2-amino alcohol results. The selectivity is not high when *tert*-butyl *N*,*N*-dimethylglycinate is the ester substrate. In contrast, trimethylsilyl *N*,*N*-bis(trimethylsilyl)glycinate (**9**) exclusively gave the *ancat* product **10** (Scheme 6).[40,41] (*Ancat* and *syncat* have been used as defined by Carey.[42])

Scheme 6



α-Amino esters can be converted to the corresponding imines; a popular choice is the imine **11** derived from benzophenone. Reactions can then be performed at the ester group, such as reduction to the aldehyde and subsequent reaction with an organometallic reagent (Scheme 7).[43]

Scheme 7



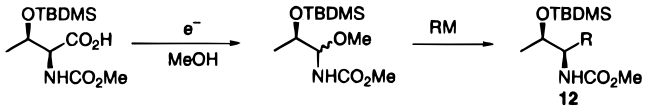
In addition, imines derived from amino acids can be alkylated; this also provides methodology to modify the stereogenic center of α-amino acids. For the benzophenone-derived imines, asymmetric induction has been observed through the use of an ester derived from a chiral alcohol, to form the chiral ester,[44] or a chiral phase transfer catalyst.[45,46] This imine approach also allows other anion reactions, such as arylations[47,48] and Michael additions.[49]

The condensation of the amino acid derivative can be performed with an acylating agent to afford α-amino-β-oxo esters, that, in turn, can be reduced to β-hydroxy derivatives with high diastereoselection.[50]

Electrolytic decarboxylation of threonine allows preparation of 1,2-amino alcohol derivatives **12**, but the stereogenic center bearing the amino group can be compromised (Scheme 8).[51]

The presence of other functional groups within the substrate molecule allows for a wider variety of

Scheme 8

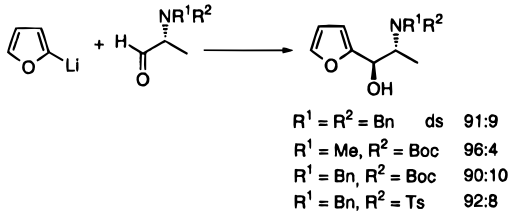


approaches to establish the two stereogenic centers of 1,2-amino alcohols.[52,53]

b. From α-Amino Carbonyl Compounds

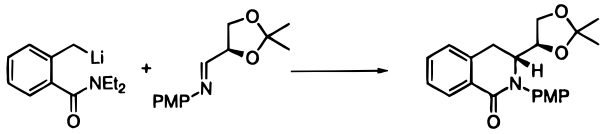
α-Amino aldehydes can undergo highly selective additions (Scheme 9),[1,2,54−61] as can α-amino ketones.[62]

Scheme 9



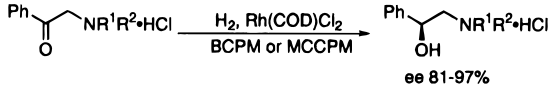
Like carbonyl compounds, imines can react with organometallic reagents and, if the appropriate α-substituent is present, with chelation control (Scheme 10).[63−66]

Scheme 10



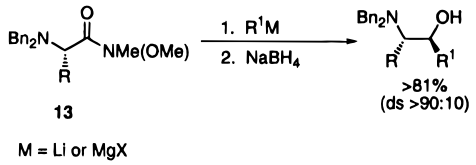
α-Amino carbonyl compounds can be reduced to α-amino alcohols (Scheme 11).[1,2,67−72]

Scheme 11



Reduction of α-amino ketones and amides **13** with sodium borohydride proceeds with good face selectivity and no chelation control (Scheme 12).[73]

Scheme 12

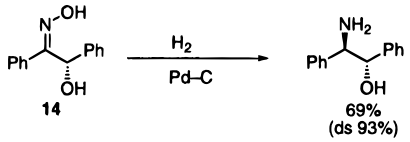


This face selectivity allows for product control depending on whether a carbonyl reduction—for example, of an α-amino ketone—or nucleophilic addition—as with an α-amino aldehyde—is the chosen method; the two approaches often provide complementary product stereochemistry.[69] An alternative is to use a different counterion; *syncat* selectivity is observed for lithium aluminum hydride,[74,75] especially in the presence of lithium iodide,[76,77] but is reversed in the presence of titanium.[78]

c. From Alkoxy Carbonyl Compounds

α-Hydroxy carbonyl compounds can also be used to access 1,2-amino alcohols through reduction of an oxime derivative **14** (Scheme 13).[79]

Scheme 13



Nucleophilic additions to an imine can also be used to provide amino alcohols.[80] Reaction of (cyclohexylmethyl)magnesium bromide with the imine **15** gave no addition products **16** unless the Grignard reagent was first treated with cerium(III), and then only one amine **16a** resulted; the selectivity could be reversed by use of a copper reagent or a Lewis acid (Scheme 14), thus providing compound **16b**.[81]

Oxime chemistry can be used to prepare 1,2-amino alcohols and the oxazinone ring system (Scheme 15).[82,83]

d. From Epoxides

If the 1,2-functionality is prepared by a construction method, then the most common approach is to use an epoxide, or equivalent, with a nitrogen nucleophile.[4,5] In turn, this also demands a stereoselective method to the epoxide. There are a number of means to achieve this with simple alkenes, but the one with most promise is that based on the use of manganese−salen.[84−91] With unsymmetrical epoxides, the regioselectivity can be controlled through reagent choice.[92] Nucleophilic attack tends to prefer reaction at the least hindered center with concurrent inversion, as observed with primary and secondary amines (Scheme 16),[93−103] and their group I or II metal salts,[95,104−107] while group IV and V amine compounds tend to provide reaction of the nitrogen nucleophile at the more hindered center.[108−112]

Azides can also be used as the nucleophilic species and a similar regiochemical trend is observed.[113−117] Reaction of an epoxide with a nitrile in the presence of perchloric acid results in formation of the 2,3-hydroxy *N*-acyl amine through a Ritter reaction.[118]

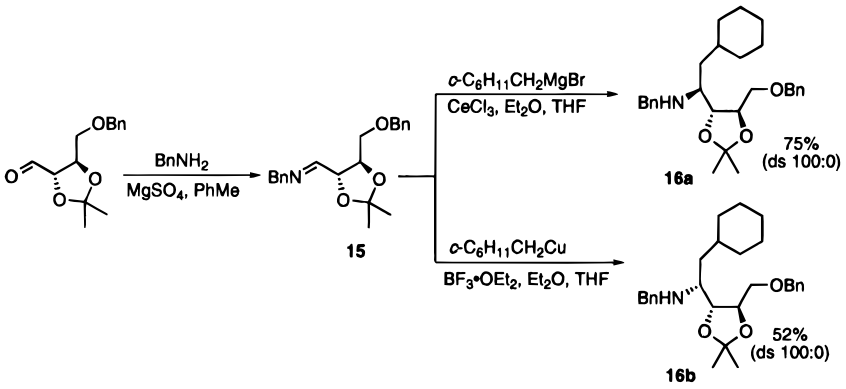
These epoxide-opening reactions are also available with more complex systems, such as 2,3-epoxy alcohols derived from allyl alcohols.[4,5,119] 2,3-Epoxy alcohols react cleanly with isocyanates to provide the corresponding urethanes **17** that can then cyclize under acidic or basic conditions (Scheme 17).[120−123] The same transformation could also be achieved as a one-pot reaction. The resultant oxazolidinones **18** and **19** are cleanly opened by lithium hydroxide to afford 2-amino 1,3-diols **20** (Scheme 18).[120,124]

This methodology has been used for the preparation of β-hydroxy-α-*N*-methylamino acids.[125−127]

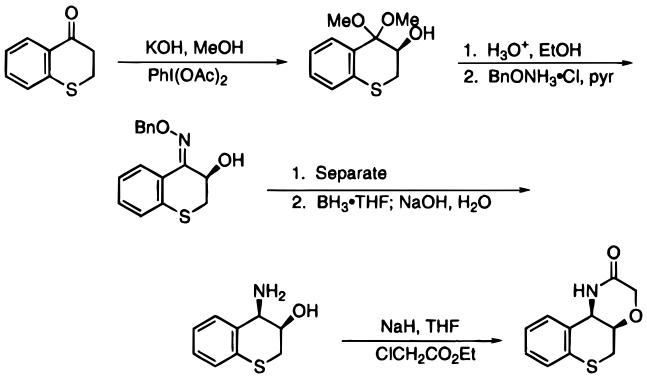
e. From Cyclic Sulfates

1,2-Cyclic sulfates are an alternative to epoxides. They are readily available from 1,2-dihydroxy com-

Scheme 14

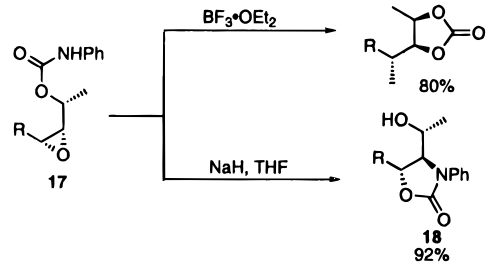


Scheme 15

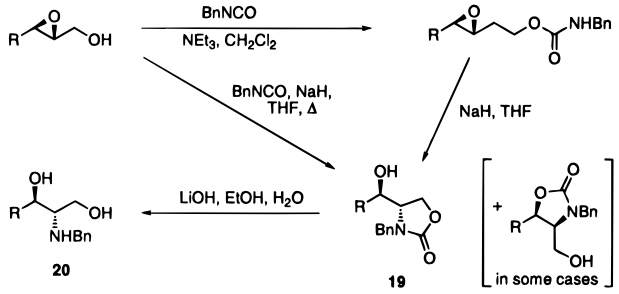


Scheme 16

Scheme 17

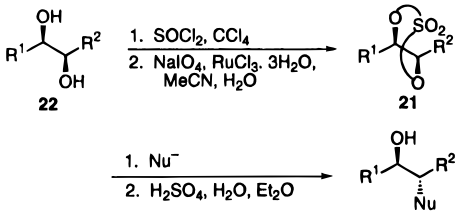


Scheme 18



pounds, in turn accessible from the Sharpless asymmetric dihydroxylation methodology.[128−140] The sulfates **21** are prepared by reaction of the 1,2-diol **22** with thionyl chloride followed by ruthenium oxidation of the sulfur (Scheme 19).[141] This oxidation has the advantage over previous procedures, as it only uses

Scheme 19



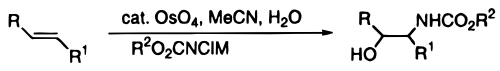
a small amount of the transition metal catalyst.[142,143] The cyclic sulfates undergo ring opening with a wide variety of nucleophiles, such as hydride, azide, fluoride, benzoate, amines, and Grignard reagents.[144]

The nucleophilic displacement by azide can be accomplished at the sulfite oxidation level when R^2 is an amide.[145]

f. Other Methods

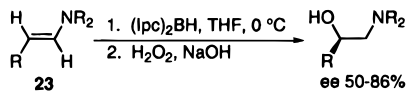
1,2-Amino alcohols are accessible from alkenes by oxyamination and oxymercuration processes (Scheme 20).[146−148]

Scheme 20



The asymmetric synthesis of β-amino alcohols of moderate enantiomeric purity has been achieved through hydroboration of aldehyde enamines **23** (Scheme 21).[149]

Scheme 21

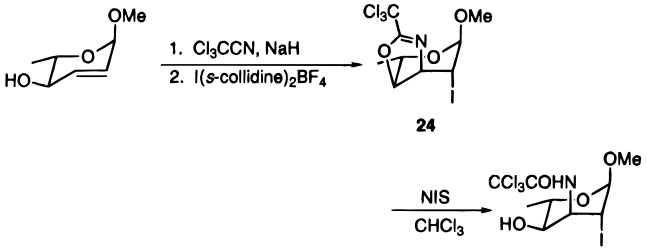


A useful variant of an intramolecular platinum-catalyzed hydrosilylation reaction provides an entry to *syncat*-1,2-amino alcohols.[150] While reduction of an oxime derived from an α-hydroxy ketone can provide a diastereoselective entry to 1,2-amino alcohols.[83,151]

Reaction of an allyl alcohol with trichloroacetonitrile provides a useful method for the preparation of amino alcohols that has been exploited in the synthesis of amino sugars;[5] the reaction proceeds through an oxazoline **24** (Scheme 22).[152−178]

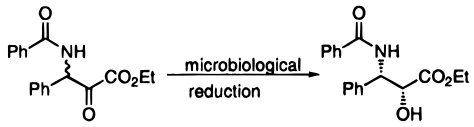
Epoxides can also be used as the electrophilic moiety (see section B.1.d),[179] as well as allowing access to six-membered heterocycles.[180]

Scheme 22



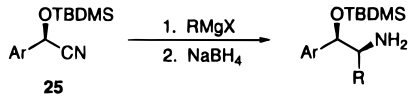
Under certain circumstances, 1,2-amino alcohols are available by biological reduction of a carbonyl precursor (Scheme 23).[181]

Scheme 23



Cyanohydrins **25** react with nucleophiles, such as Grignard reagents, to form imines that can be reduced to provide 1,2-amino alcohols (Scheme 24).[80,182−184]

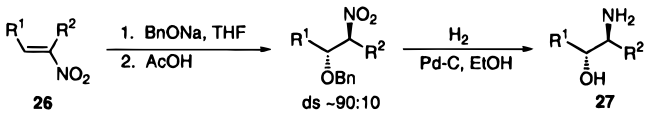
Scheme 24



Lithium aluminum hydride reduction of *O*-silyl cyanohydrins also results in the formation of 1,2-amino alcohols.[183]

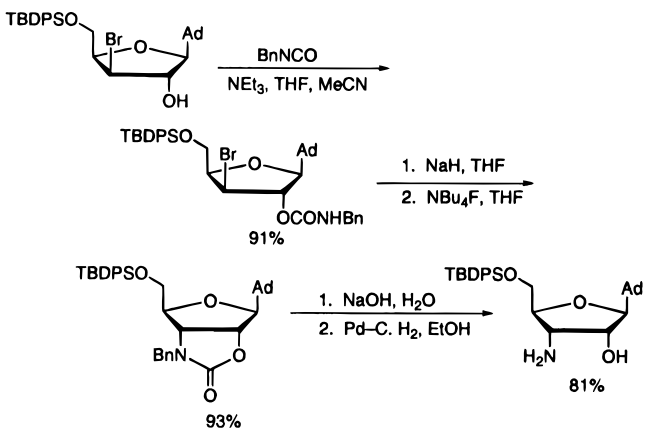
Michael addition of an alkoxide to nitroolefin **26** provides, after reduction, the *ancat*-1,2-amino alcohol **27**, selectively (Scheme 25).[185]

Scheme 25



Even a substitution reaction, such as formation of an oxazolidinone ring from a carbamate, can provide 1,2-amino alcohols (Scheme 26).[186] However, the system has to be amenable so that other, unwanted reactions do not compete.

Scheme 26



A wide variety of other synthetic methods have been investigated for the formation of 1,2-amino alcohols, but the stereochemical consequences, or control, have not been sufficiently advanced to allow them to make significant contributions to the preparation of this class of compounds, although advances continue to be made. An example is provided by the reaction of an anion generated from a nitro compound with an aldehyde,[187] where some selectivity has now been achieved.[188]

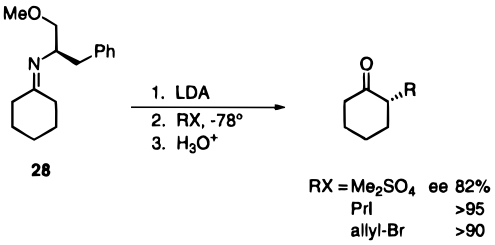
2. Reactions as Chiral Auxiliaries

Amino alcohols can be used for a wide range of synthetic transformations. This section is limited to their usage as auxiliaries to influence the stereochemistry at a new stereogenic center.

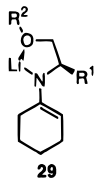
a. Alkylations

The use of acyclic chiral auxiliaries often raises problems associated with the control of chelate formation. The use of heteroatoms to force formation of an intramolecular chelate has been exploited for the alkylations of cyclohexanone derivatives **28** (Scheme 27).[189,190] The presence of the oxygen moiety

Scheme 27



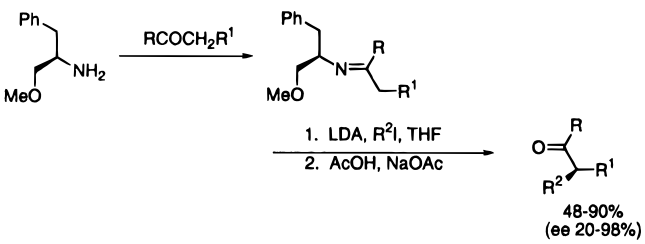
provides for good diastereoselectivity as its absence provides poor facial bias (~3:1).[191−193] With evidence derived from simple imine alkylations,[194,195] a hypothesis advanced for one of the original systems seems to provide the best rationalization for the observed induction. The metalloenamine undergoes kinetic *syn*-selective reactions with electrophiles, in a 1,4-sense. This maximizes the effect of the stereogenic center in the chelate **29** with regard to the incoming electrophile.[196]



29

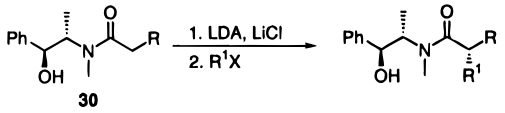
The methodology has also been used with acyclic carbonyl compounds (Scheme 28).[197,198]

Scheme 28



Pseudoephedrine has been found to be a practical acyclic chiral auxiliary. Treatment of either isomer with an acid chloride or anhydride leads to the amide derivatives **30**, that can be alkylated (de 96−99%) (Scheme 29). Hydrolysis of the amide products that

Scheme 29

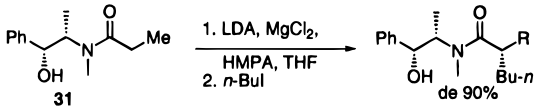


30

are not acid sensitive can be accomplished with heat and strong acid, and results in highly enantiomerically enriched carboxylic acids (ee 95−97%). Base hydrolysis of the amides results in slight epimerization. Chiral alcohols (ee 88−99%) are obtained when borane−lithium pyrrolidide is employed as the reductant. Chiral aldehydes and ketones can also be prepared from the pseudoephedrine amides.[199]

This work extends the use of ephedrine as a chiral auxiliary. Alkylations of up to 90% de were observed when the deprotonation reactions **31** (**30**; R = Me) were conducted in the presence of magnesium chloride and hexamethylphosphoric triamide (HMPA) (Scheme 30).[200,201] The addition of salts, such as

Scheme 30

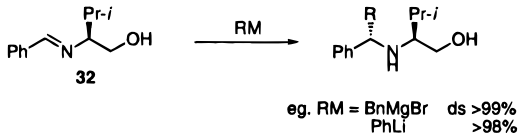


31

lithium chloride, can eliminate the need for HMPA to achieve high selectivity in the reactions of enolates.[202]

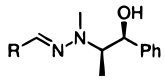
Reaction of a 1,2-amino alcohol, or an ether derivative, with a carbonyl compound can provide the imine **32**. In turn, this imine **32** can undergo addition reactions with Grignard or organolithium reagents (Scheme 31).[203−205] The degree of induction can be

Scheme 31



32

high. However, the auxiliary is not trivial to remove. This problem has been circumvented by use of a variation where the hydrazone **33** derived from ephedrine is used; reduction of the N−N bond then removes the auxiliary.[206,207]

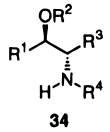


33

Amino esters have been used as chiral auxiliaries for the asymmetric synthesis of nitrogen heterocycles.[208]

b. Aldol

A number of amino ethers **34** have been investigated as potential sources of chiral bases for an aldol reaction. Both the lithium and magnesium amides gave very low levels of asymmetric induction (<12%).[209]

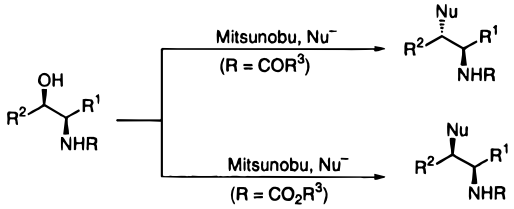


34

3. Reactions of Amino Alcohols

1,2-Amino alcohols provide for nucleophilic substitution under Mitsunobu conditions with the stereochemistry controlled by the nitrogen protection. Use of an amide provides retention of configuration through formation of an intermediate oxazoline; this results in two substitutions with inversion to give overall retention. In contrast, use of a carbamate to protect the nitrogen provides overall inversion at the reaction center as no intramolecular reaction is involved (Scheme 32).[210]

Scheme 32



Aziridines are also available from amino alcohols through treatment with triphenylphosphine dibromide.[211]

Reaction of an amino alcohol with nitrous acid results in the semipinacol rearrangement, a reaction analogous to the pinacol rearrangement.[212] As a carbocation is formed, other reactions of these reactive species are also available under favorable circumstances, such as the Tiffeneau−Demyanov ring expansion.[213]

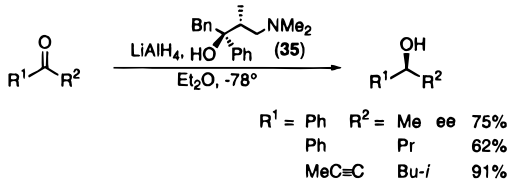
4. Ligands

In this review we discuss the use of compounds derived from 1,2-amino alcohols. With regard to their usage as ligands, we have defined this to mean 1,2-amino alcohols where the chirality is derived from this moiety. Thus, ligands that contain a 1,2-amino alkoxy function that complexes to the metal center, but with the stereogenic center elsewhere within the molecule, are not included.

1,2-Amino alcohols have been used to modify lithium aluminum hydride and can provide for the reduction of aryl alkyl ketones and propargylic ketones with reasonable selectivities.[214−223] With other carbonyl compounds, the selectivity can be very low. In the early systems, a third component was added to the reaction system to enhance the selectivity. These reactions have a number of components that can cause reduction of the substrate with different selectivities. The effects of temperature can, therefore, be significant if the optimum temperature is not employed. Examples of the additives are 3,5-dimethylphenol,[217,220−223] and *N*-ethylaniline.[218,219] Darvon alcohol (**35**) was the first amino alcohol,

although it is 1,3 in construction, that did not require the use of additional additives to provide useful levels of induction (Scheme 33).[215,216,224,225] Care still has

Scheme 33

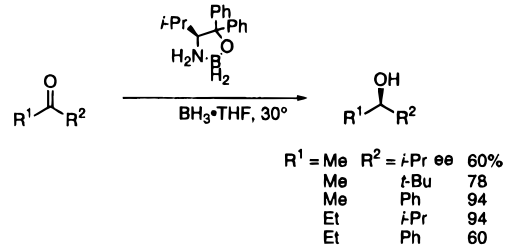


to be exercised with the darvon alcohol−lithium aluminum hydride system, as not only the degree of induction may be affected by the age of the reagent, but its sense as well.[224] Other naturally occurring amino alcohols had been investigated, such as quinine, and a camphor derivative but the levels of induction were not high enough to be synthetically useful.[226,227]

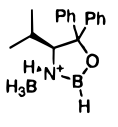
The use of amino alcohols that contain additional functional groups, on the whole, does not improve on the stereoselection of the reductions, and can even be considered to be detrimental.[228−232] With cyclic examples, as for oxazolines, only moderate degrees of induction were observed, (see section E.7.c).[233,234] In the related reaction, complex formation of chiral oxazolines with Grignard reagents does allow some enantioselectivity in the subsequent reaction with carbonyl compounds, but, again, the ee's are low.[235]

Little success has been achieved with the use of amino alcohols as chiral ligands for borohydride reductions. In contrast, this class of ligand with boranes does provide for reasonable stereoselection with ketones where the two groups have reasonable differences in size (Scheme 34).[236−239]

Scheme 34



Although not derived from an acyclic amino alcohol, the system derived from proline has found widespread usage for the reduction of carbonyl compounds (see section C.3.b). The monocyclic oxazaborolidine **36** has been found to provide the highest degree of asymmetric induction for the reduction of imines to amines.[240,241]



36

The amino alcohol derived from 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid by reaction with phenyl Grignard does provide for moderate asymmetric induction for the borane reduction of aromatic ketones.[35]

Amino alcohols have been employed as ligands for early transition metals to provide complexes where the metal is in a highly asymmetric environment.[242] A zirconium catalyst of this type has provided 93% ee for the opening of cyclohexene oxide with isopropyldimethylsilyl azide.[243,244]

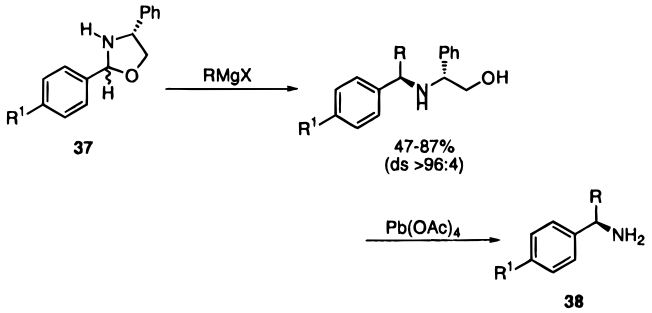
C. Cyclic Derivatives

This section discusses the reactions of cyclic amino alcohol derivatives with the exceptions of oxazolidinones and oxazolines. These latter classes of compounds have been treated separately.

1. Oxazolidines

Oxazolidines **37** are useful substrates for nucleophilic additions as they act as acetal equivalents (Scheme 35); the addition is thought to occur through

Scheme 35

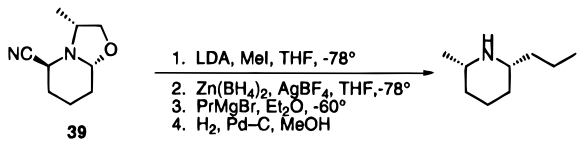


37 **38**

ring opening and subsequent reaction of the resultant imine.[245,246] Although 2 equiv of Grignard reagent are required, the first equivalent can be derived from a cheap source as this does not participate in the addition itself; it simply deprotonates the nitrogen. The asymmetric induction in the resultant amine **38** can be high (>92% ee).[246]

Oxazolidines have been employed as imine equivalents, including bicyclic systems, such as **39** (Scheme 36).[247−251]

Scheme 36



39

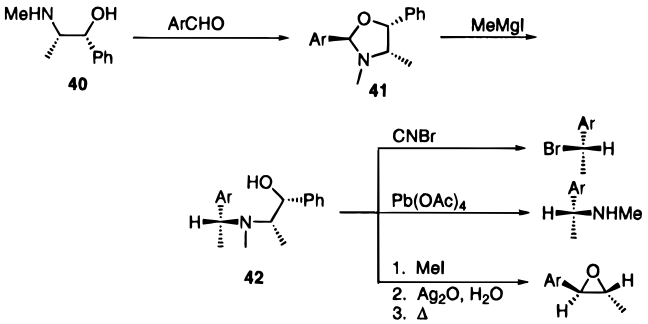
Reaction of ephedrine (**40**) with an aromatic aldehyde forms an oxazoline **41** that can be cleaved by Grignard reagents to give a tertiary amino alcohol **42**; other 1,2-amino alcohols can be used in place of ephedrine to provide a general approach to analogs of the alcohol **42** (Scheme 37),[252−256] and has been extended to nonaromatic aldehydes.[257−259]

If the initial condensation is performed with the aldehyde bisulfite, followed by treatment with cyanide and acid, the morpholone **43** results (Scheme 38).[253]

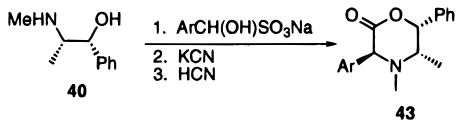
An alternative methodology is described in Scheme 39.[260]

A variant is the use of 2-methoxyoxazolidines **44** where the choice of Lewis acid employed can control the stereochemical outcome of the reaction (Scheme

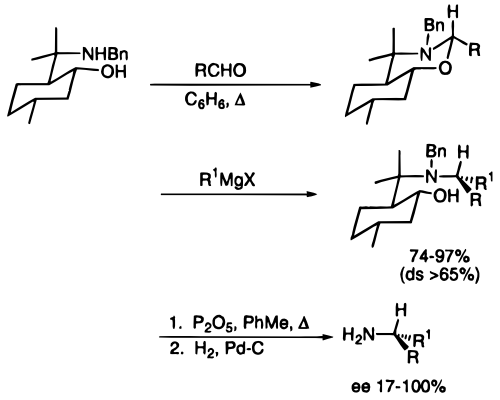
Scheme 37



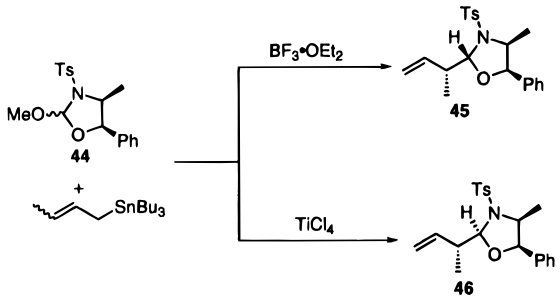
Scheme 38



Scheme 39



Scheme 40

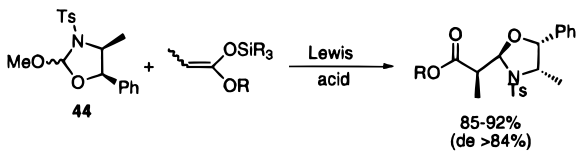


40). In this case, the addition could be selective, while the Lewis acid promotes an equilibration; treatment of **45** with titanium tetrachloride provided exclusively **46**.[261,262]

The borohydride reduction of 2-acetyl-1,3-oxazolines can be directed by use of chelation or Anh−Felkin addition.[263] Oxazolidinium salts can be used as acetal equivalents to provide stereoselection.[264]

In aldol-type reactions, oxazolidines (e.g. **44**) provide an alternative to acetals (Scheme 41).[265−267] The

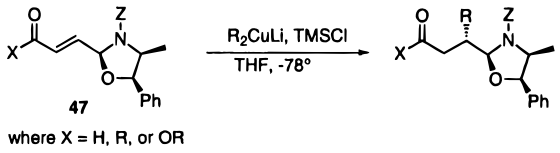
Scheme 41



stereoselection is, however, not high across a broad range of substrates. The silyl enol ether approach can be extended to silyl ketene acetals where the additional alkoxy moiety is a useful handle for the incorporation of a chiral unit.[268]

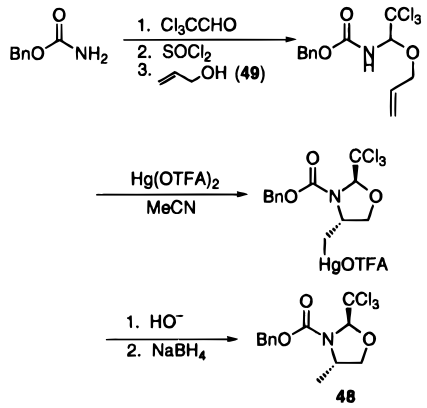
The use of an oxazolidine as a chiral auxiliary is exemplified by the 1,4-addition of a cuprate to an α,β-unsaturated carbonyl systems **47** (Scheme 42).[269−271]

Scheme 42

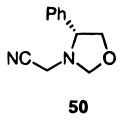


N-Acyloxazolidines, such as **48**, are available from allyl alcohols **49** by an amido mercuration reaction (Scheme 43).[272]

Scheme 43



The oxazolidine **50**, derived from phenylglycine, has been used to access α-amino nitriles[273] and cyclopropane derivatives.[274,275]



2. Oxazinones

Reaction of an oxazoline (e.g. **51**) with diketene (**52**) results in a bicyclic oxazinone **53**; the *tert*-leucinol-derived oxazoline gave the highest degree of diastereoselectivity (Scheme 44).[276−278]

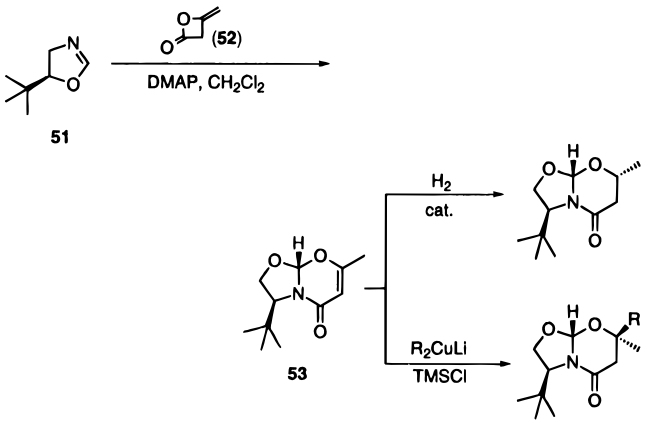
Diphenyloxazinones **54** have been used as chiral systems for the preparation of arylglycines (**55**) (Scheme 45).[66]

The halo compounds **56** can be reacted with a variety of nucleophiles.[279−283] The nucleophile approaches from the least hindered face (Scheme 46); this includes silyl enol ethers in the presence of a Lewis acid.[281]

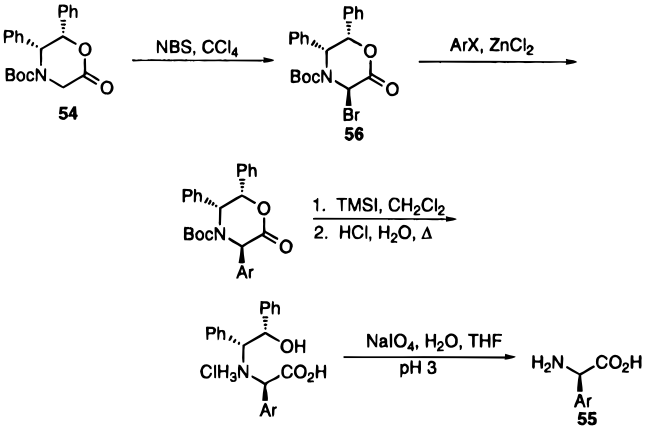
The system has been used to control the face selectivity in an approach to α-amino acid derivatives (Scheme 47).[284]

The diphenyloxazinone system **54** has also been used to prepare α,α-disubstituted amino acids[285,286] and 2,6-diaminopimelic acid derivatives.[286−288]

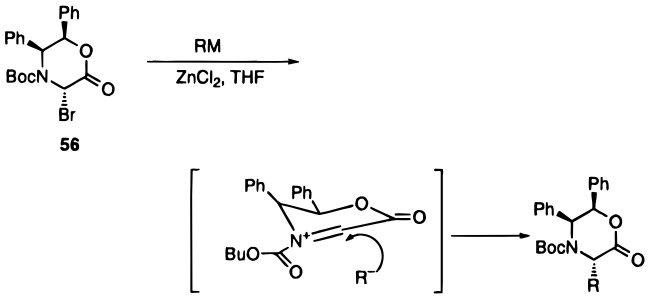
Scheme 44



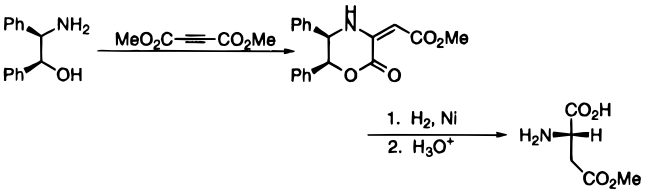
Scheme 45



Scheme 46



Scheme 47



There are variations on this auxiliary system including the use of D-phenylglycinol as the amino alcohol.[289]

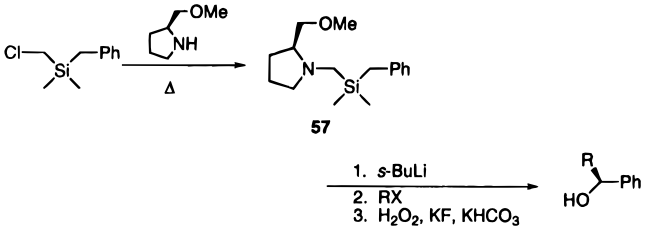
3. Proline Derivatives

Proline derivatives have been used as ligands to effect reductions. In addition, they provide stereogenic moieties for other systems. The other two major uses can be encompassed through the use of the amino alcohol as a ligand for a metal ion and the hydrazone derivatives as chiral auxiliaries, RAMP and SAMP.

a. As Auxiliaries

The proline system has been used as a chiral auxiliary with a silicon-based reaction that provides a benzyl alcohol anion equivalent **57** (Scheme 48). In

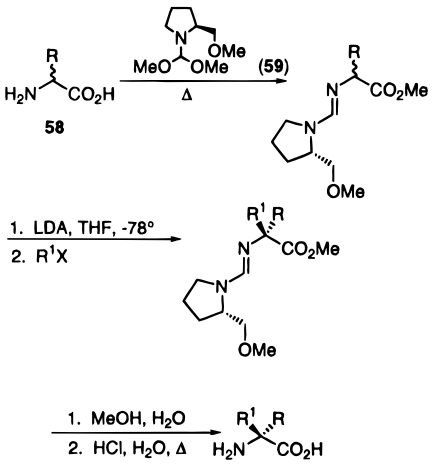
Scheme 48



addition, the use of a functionalized alkyl halide allows for the preparation of oxygen heterocycles.[290,291]

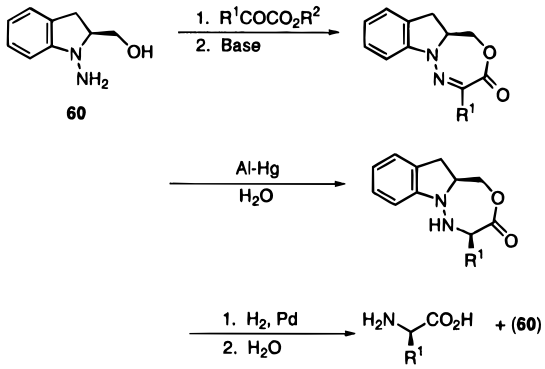
Racemic amino acids **58** can be alkylated with some enantioselectivity through the use of a proline-derived acetal **59** (Scheme 49).[292]

Scheme 49



A variation that has been used for the preparation of amino acid derivatives is based on the bicyclic 2-(hydroxymethyl)indolines **60** (Scheme 50).[293,294]

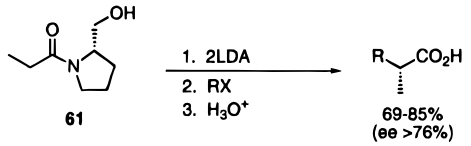
Scheme 50



Proline-derived amides **61** do provide for reasonable degrees of diastereoselection in alkylation reactions (Scheme 51).[17]

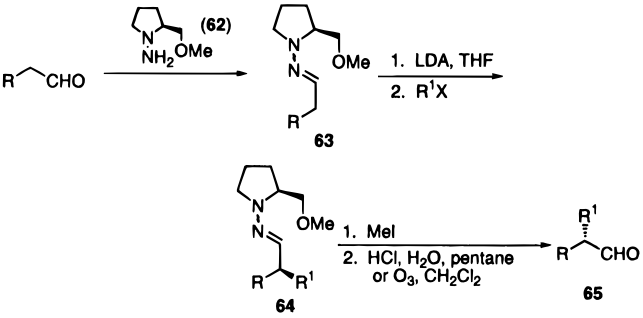
I. Hydrazones. Many of the reactions are based on the RAMP/SAMP (**62**) system.[295] The initial work was performed with aldehydes, where a regiochemical problem did not occur. Subsequent deprotonation of the hydrazone **63** and alkylation provides the

Scheme 51



substituted hydrazone **64** that can be converted to the aldehyde **65** by ozonolysis or hydrolysis of the methiodide (Scheme 52).[296,297] An alternative hydra-

Scheme 52

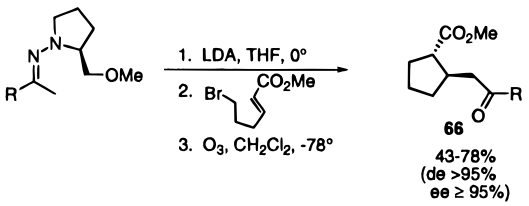


zone cleavage is available through the use of magnesium monoperoxyphthalate as oxidant.[298]

For ketones, deprotonation, and reaction with the electrophile, occur at the least hindered center, unless an additional anion stabilizing group is present.[295,299,300] As with other auxiliaries, a wide range of electrophiles can be used with this system, including carbonyl compounds[295,301,302]—although the stereoselectivity can be low—and oxidants.[303]

The resultant anion from an alkylation reaction can be used for additional transformations, as illustrated by the Michael addition to form the cyclopentane compounds **66** (Scheme 53).[304]

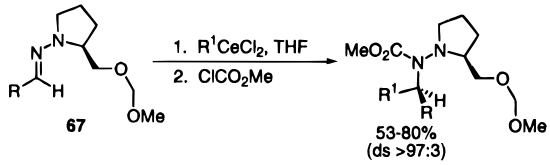
Scheme 53



Carbonyl compounds can be used as the electrophilic agents to provide β-hydroxy ketones. However, the ee's are only moderate (<78%).[301]

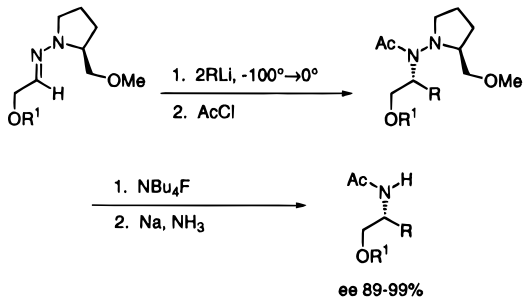
Additions of organocerium reagents to proline-derived hydrazones provide the highest diastereoselectivity when the 1-amino-2-[(2-methoxyethoxy)-methyl]pyrrolidine (SAMEMP) (**67**) system is used (Scheme 54).[305]

Scheme 54



This approach has been extended to provide 1,2-amino alcohols through the RAMP/SAMP auxiliaries.[306]

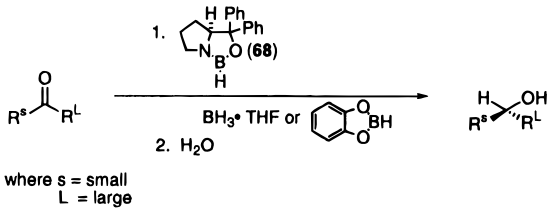
Scheme 55



b. As Ligands

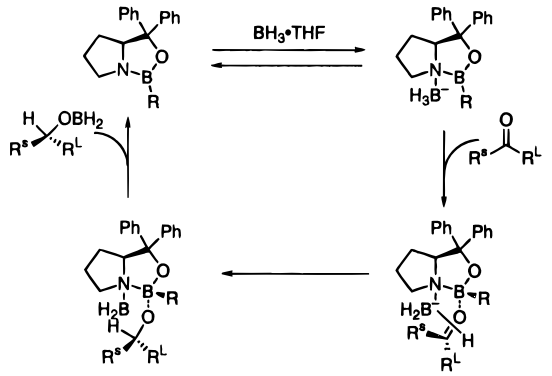
Proline-derived ligands have been investigated for a number of transformations. The reduction of carbonyl compounds has been the most successful for this class of ligands. To date, the system that can provide high selectivity, even in alkyl cases, is based on oxazaborolidines **68** (Scheme 56).[33,236,307−318]

Scheme 56

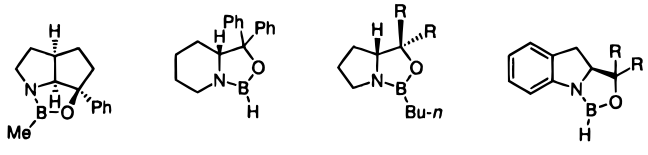


The proposed mechanism for the reduction is summarized in Scheme 57.[308,309,319−325]

Scheme 57



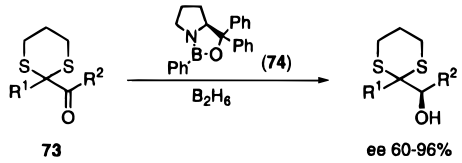
Other oxazaborolidines, such as **69**−**72**, are also



excellent catalysts for the asymmetric reduction of ketones to secondary alcohols.[307−309,313,314,317,326−338] Oxazaborole−boranes give high degrees of asymmetric reduction with dialkyl ketones and are stable and amenable to scale up,[333] as do terpene-based oxazaborolidines, although enantioselectivity is not as high with the latter.[339] The addition of triethylamine to oxazaborolidine-catalyzed reactions has been shown to increase enantioselectivity, especially in dialkyl ketones.[340]

A group that allows for the choice between chelation or Anh−Felkin addition can also be incorporated into the substrate. The use of a dithiane-protected α-dicarbonyl system **73** provides such a system and allows for good induction with an oxazaborolidine catalyst **74** (Scheme 58).[310]

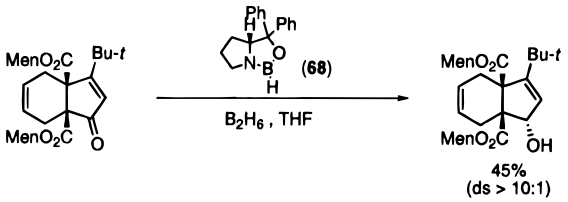
Scheme 58



73

Oxazaborolidines are also useful for the 1,2-reduction of enones; this methodology was paramount in a synthesis of ginkgolide.[319,320,341] It proceeds in high yield and follows the same model as for "simple" carbonyl compounds (Scheme 59).[309,319−325]

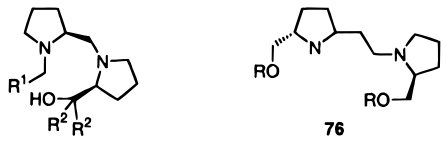
Scheme 59



Other functionalized carbonyl compounds, such as α-chloro ketones, including trihalo ketones, are also effectively reduced by this system.[307−309,342,343] Reductions of α-keto oxime derivatives provide an entry to 1,2-amino alcohols.[83]

The use of oxaborolidines is discussed in the general ligand section (section B.4). Other proline-based amino alcohol ligands have been used for organometallic reactions.

The dimeric ligands **75** and **76** provide for moderate degrees of induction for the addition of an alkyl lithium reagent to an aldehyde.[344−347]



75

76

where R = Li or Me

D. Oxazolidinones

Despite the widespread usage of oxazolidin-2-ones as chiral auxiliaries since the first report in 1981,[18] the topic has not been recently reviewed.[17,31,348]

The majority of reactions are performed on *N*-acyloxazolidinones in the presence of a metal atom; Figures 2 and 3 show a typical complex. The two separate views show how the side chain masks one face of the molecule.

1. Preparations of Oxazolidinones

Reaction between amino alcohols and either phosgene or diethyl carbonate have proved to yield the most direct route to oxazolidinones. However, other amino acid-derived starting materials can be employed in addition to amino alcohols (*vide infra*).

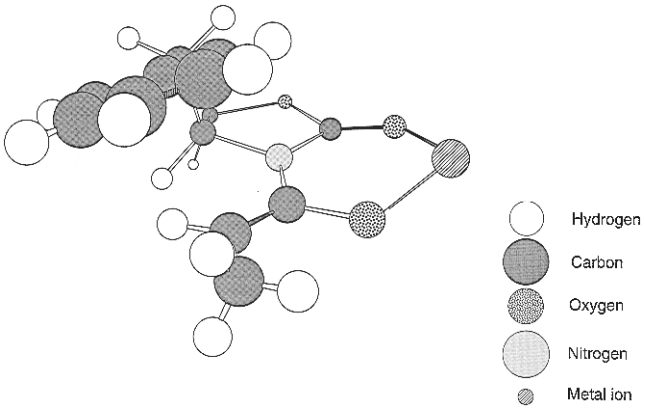


Figure 2. View of *N*-acetyl-4-benzyl-2-oxazolidinone metal complex.[4] (The structure was minimized as the enol with MM2 parameters.)

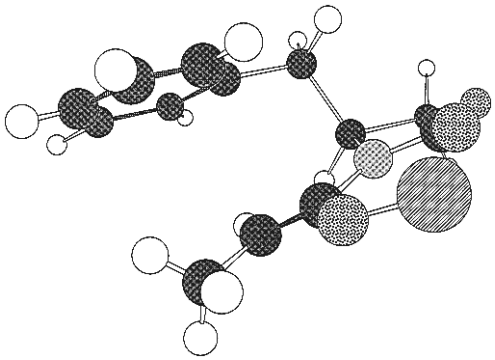
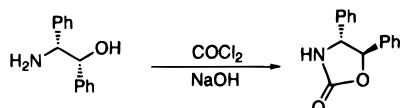


Figure 3. Side view of *N*-acetyl-4-benzyl-2-oxazolidinone metal complex.

The amino alcohols, in general, are readily available by reduction of the appropriate amino acid (section B.1.a). Oxazolidinones derived from the amino alcohols of phenylalanine, phenylglycine, valine, norephedrine, and *tert*-leucine are commercially important (Table 1); other derivatives that have been employed as chiral agents can also be found in this table.

A number of reagents have been employed with amino alcohols to form oxazolidinones. Early methods tended to employ phosgene in reactions with amino alcohols (Scheme 60).[18,351−354] In this case, the amine cannot be tertiary.

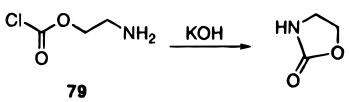
Scheme 60



77 **78**

Oxazolidinones also result from base-catalyzed cyclization of β-amino chloroformates **79** (Scheme 61).[355,356]

Scheme 61



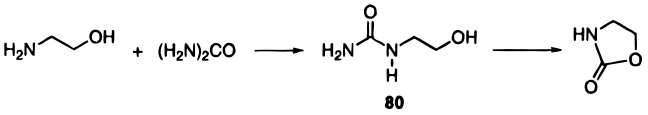
79

Table 1. Common Oxazolidinones Derivatives

oxazolidinone precursor	ref	oxazolidinone precursor	ref
L-phenylalanine	349	D-phenylalanine	349
L-phenylglycine	349	D-phenylglycine	349
L-valine	18	L-*tert*-leucine	350
(1*S*,2*R*)-norephedrine	18	L-alanine	350
L-cyclohexylalanine	350	(*R*)-cyclohexylglycine	349
L-*p*-methoxyphenylalanine	350	L-*p*-chlorophenylalanine	350
L-*p*-(trifluoromethyl)phenylalanine	350	L-2-aminobutyric acid	350

Other early efforts toward oxazolidinones focused on the fusion of urea with the amino alcohols above their melting points (Scheme 62).[357−360] It has been

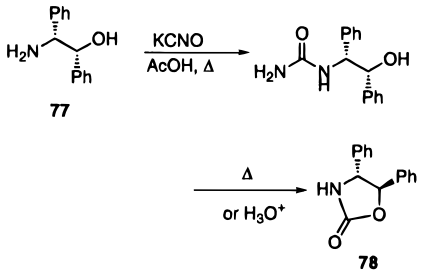
Scheme 62



proposed that the reaction proceeds through the intermediate *β*-hydroxyethyl urea **80**, followed by loss of ammonia to yield the 2-oxazolidinone.

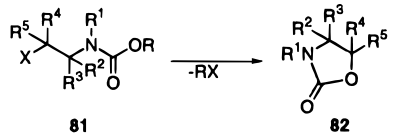
Reaction of *β*-amino alcohols with isocyanates followed by cyclization of the substituted urea by heat or acid results in oxazolidinone formation (Scheme 63).[361,362]

Scheme 63



Oxazolidinones can be formed through urethanes **81**, as they are set up for cyclization (Scheme 64).

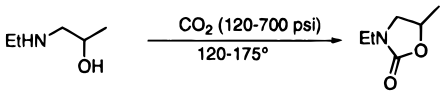
Scheme 64



This can be accomplished pyrolitically, with base, or acid; the former two are more common than acid.[363]

The heterocyclic system can be obtained from the innocuous reagent, carbon dioxide, in a limited number of cases, but with elevated temperatures and pressures (Scheme 65). The starting amino alcohols

Scheme 65

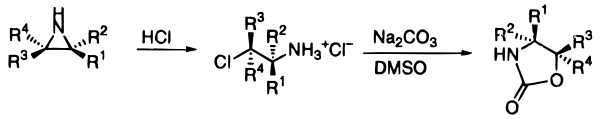


can be *N*-substituted, with or without substitution on the carbon bearing the alcohol functional group.[364,365]

Milder reaction conditions can be used with an intramolecular cyclization based on the Mitsunobu reaction.[366]

Aziridine ring expansion may be employed in oxazolidinone formations (Scheme 66).[367−369] Chlo-

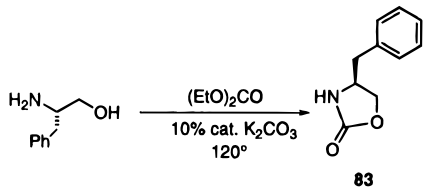
Scheme 66



roamines, formed regio- and stereospecifically from aziridine and hydrogen chloride, can be condensed with sodium carbonate to yield isomerically pure oxazolidinones.

More recently, with the decreased use of phosgene, efficient, high-yielding syntheses of oxazolidinones, e.g. **83**, from dialkyl carbonates have become prevalent (Scheme 67).[25] The parent 2-oxazolidinone may

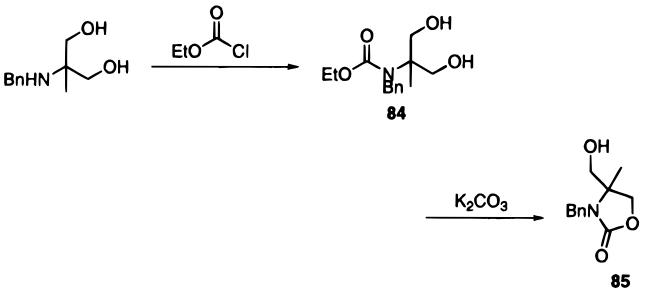
Scheme 67



be synthesized from 2-aminoethanol, diethyl carbonate, and sodium methoxide.[370]

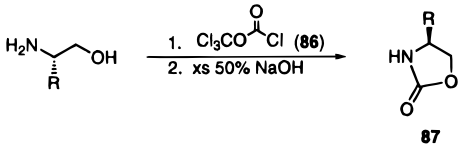
Ethyl chloroformate can also be employed; it first reacts with the amine of amino alcohols. The resultant carbamate **84** can then be cyclized in the presence of base to give the desired oxazolidinone **85** (Scheme 68).[371]

Scheme 68



Trichloromethyl chloroformate (**86**) provides a simple entry into oxazolidinones **87**, without the need for isolation of the intermediate *β*-amino alcohol (Scheme 69).[372] Trichloromethyl acetic anhydride has

Scheme 69

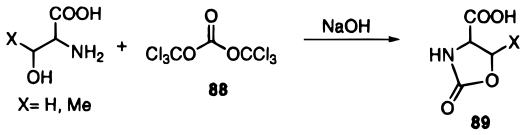


been employed in a similar manner,[373] as have esters.[374] In this latter case, it is proposed that attack

of the alcohol on the ester occurs first, followed by intramolecular attack of nitrogen to eliminate chloroform.

Triphosgene (**88**) has been substituted for phosgene, yielding a relatively mild route to oxazolidinones **89** (Scheme 70). The methyl esters can be

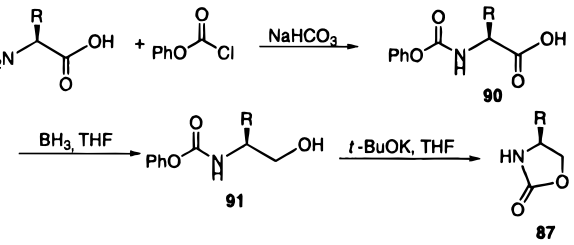
Scheme 70



obtained in the 4-position by the addition of methanol to the resultant oxazolidinone.[375]

Schotten−Baumann conditions have been performed on a number of amino acids with phenyl chloroformate as reagent (Scheme 71).[376] The iso-

Scheme 71

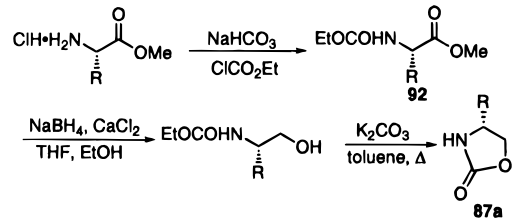


lated *N*-protected amino acid derivative was reduced with borane, followed by cyclization with a catalytic amount of potassium *tert*-butoxide to form the desired oxazolidinone **87**. Crystalline material is not obtained unless the carbamate **90** is isolated prior to the cyclization step. It is not necessary, however, to isolate the intermediate *N*-protected *β*-amino alcohol **91**. Heat is required to accomplish the cyclization when isobutyl chloroformate is used in place of phenyl chloroformate, presumably because phenol is a better leaving group than isobutyl alcohol.[376]

Cyclization with tosyl chloride can be achieved with amino alcohol derivatives if the amino group is protected as the *N*-methylated Boc derivative.[377] Trichloroacetate esters and carbonyl diimidazole provide alternative activation methods to achieve cyclization.[356,378,379] Some of these methods can be coupled to the reduction and provide a "one-pot" procedure from an amino acid to oxazolidinone.[372,373]

N-(Ethoxycarbonyl)amino esters **92** can be reduced efficiently with sodium borohydride−calcium chloride and then cyclized in the presence of potassium carbonate in toluene under reflux to the corresponding oxazolidinone (Scheme 72).[380]

Scheme 72

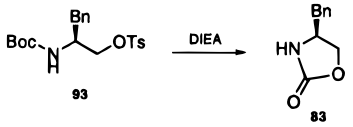


Mono- and dichloromethyl chloroformates react with 1,2-amino alcohols to form carbamates that, under mild conditions, provide the oxazolidinone derivatives directly.[381]

Treatment of a *β*-hydroxy amide with lead tetraacetate in pyridine results in a Hoffmann-like rearrangement to form a 2-oxazolidinone.[382]

When *N*-Boc-*O*-tosyl amino alcohols **93** are reacted in the presence of diisopropylethylamine (DIEA), with or without heat, oxazolidinones result (Scheme 73).[377,383]

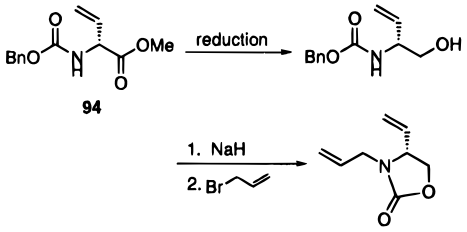
Scheme 73



The heterocycle is formed from *N*-Boc amino alcohols by reaction with thionyl chloride.[384]

N-Derivatized oxazolidinones derived from "unusual" amino acids can be produced by reduction and then cyclization of the amino ester carbamate **94**, itself obtained by enzymatic resolution (Scheme 74).[385] The cyclization and derivatization can be

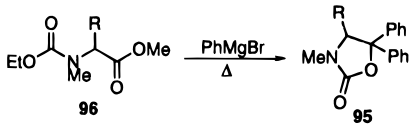
Scheme 74



carried out in one pot.

A new route to oxazolidinones **95** has been achieved by coupling Grignard reagents with *N*-(alkoxycarbonyl)-α-amino esters **96**, followed by heating under reflux in THF (Scheme 75). The reaction may

Scheme 75

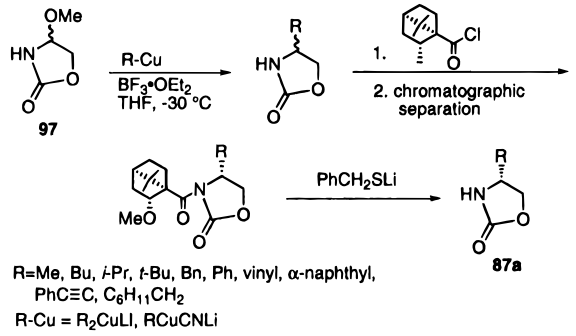


also be accomplished in two steps through isolation of the alcohol and then cyclization in the presence of potassium hydroxide.[34]

Oxazolidinones can also be synthesized by many nonconventional routes. A versatile and efficient approach to both *R*- and *S*-enantiomers of oxazolidinones has been reported and uses a preformed ring as a building block (Scheme 76).[386] All of the products were formed by substitution at the 4-position, followed by chromatographic separation. Valuable access to alkenyl- and alkynyl-substituted derivatives can be realized. The starting 4-methoxy-2-oxazolidinone (**97**) is available from simple anodic oxidation of 2-oxazolidinone in methanol.[386,387] The approach can be used to prepare 5-methyl-4-substituted oxazolidinones starting from L-threonine.[388,389]

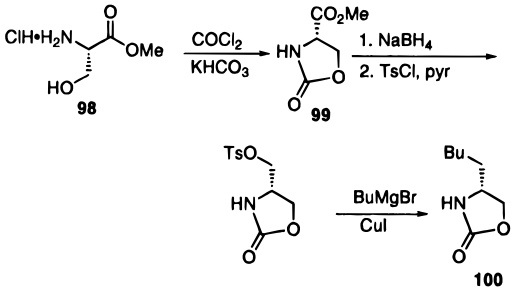
The use of a sulfide group as a handle for the modification of oxazolidinones by photoinitiated radical alkylations has been effected in a synthesis of statine.[390,391]

Scheme 76



Reaction of L-serine methyl ester hydrochloride (**98**) with phosgene and base results in an oxazolidinone **99** that, after reduction and tosylation, can undergo nucleophilic displacements to provide (*R*)-4-substituted oxazolidinones **100** (Scheme 77).[392] The alcohol

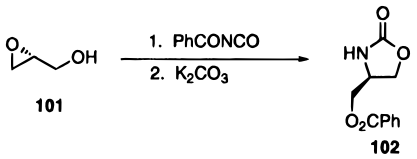
Scheme 77



derived from the reduction of ester **99** is also available from other chiral starting materials, such as D-mannitol, L-ascorbic acid, and (*R*)- or (*S*)-malic acid.[393]

2,3-Epoxy alcohols **101** can be used as the source of the stereogenic center in an oxazolidinone **102** synthesis (Scheme 78).[394] Manipulation of the oxygen

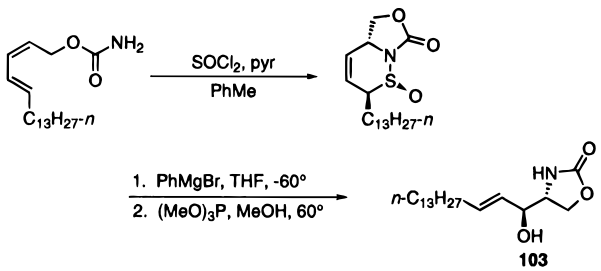
Scheme 78



group in the side chain provides an alternative to the use of serine as a starting material.

An alternative strategy to more complex oxazolidinone derivatives, such as **103**, relies on a cycloaddition (Scheme 79)[395] or cyclization reaction (see

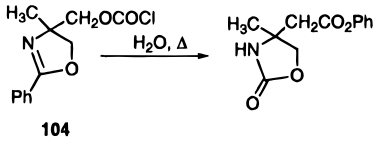
Scheme 79



section B.1.f) to establish stereochemistry.

An unusual route to oxazolidinones has been reported from oxazolines (Scheme 80). The original

Scheme 80



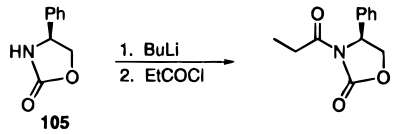
oxazoline **104** can be readily synthesized from the starting amino alcohol. (For oxazoline syntheses see section E.1 and ref 396.) Oxazolines with amino or alkyl groups at the 2-position can be converted to 2-oxazolidinones.[397]

Other methods starting from β-amino alcohols, that include carbon monoxide and sulfur or selenium, carbon tetrachloride, cyanogen bromide with potassium hydroxide, carbon disulfide followed by methyl chloroformate, *N*,*N*′-carbonyldiimidazole, β-aminosulfuric acids, and β-halo amines and alcohols, all result in 2-oxazolidinones.[348,398−400]

a. Formation of N-Acyloxazolidinone Derivatives

N-Acyloxazolidinones are readily accessible from the reaction of *n*-butyl lithium with the auxiliary followed by the addition of acid chlorides (Scheme 81).[18,401,402] Lithiated oxazolidinones also react with

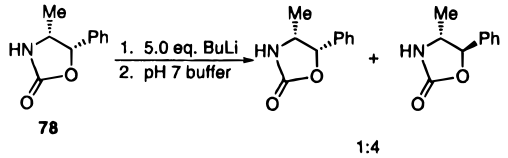
Scheme 81



mixed anhydrides to form *N*-acyl imides.[403,404]

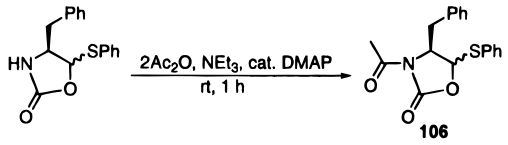
The use of excess butyllithium for this acylation should be avoided with ephedrine derivatives as epimerization can occur at the benzylic C-5 position through a dianion intermediate (Scheme 82).[405]

Scheme 82



An alternate approach for *N*-acylation that employs mild reaction conditions has been reported for the preparation of 3-acetyl-5-(phenylthio)oxazolidinones (**106**) (Scheme 83).[406]

Scheme 83



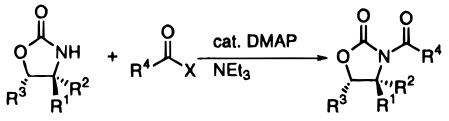
N-Acylation has been carried out on the parent 2-oxazolidinone with sodium acetate in refluxing acetic anhydride.[370,407]

The methods described above tend to cause polymerization with acryloyl substrates; the use of the appropriate acid chloride with the magnesium salt

of the oxazolidinone[408,409] or the *N*-trimethylsilyl derivative in the presence of copper(II) chloride and copper powder alleviates the occurrence of this unwanted side reaction.[410,411]

Recently, two new procedures for the *N*-acylation of chiral oxazolidinone auxiliaries have been put forward that eliminate the use of *n*-BuLi. In the first case, a large variety of oxazolidinones have been acylated with triethylamine and catalytic quantities of DMAP at room temperature (Scheme 84).[412] The acylation source can be either anhydrides (mixed or symmetrical) or acid chlorides.

Scheme 84



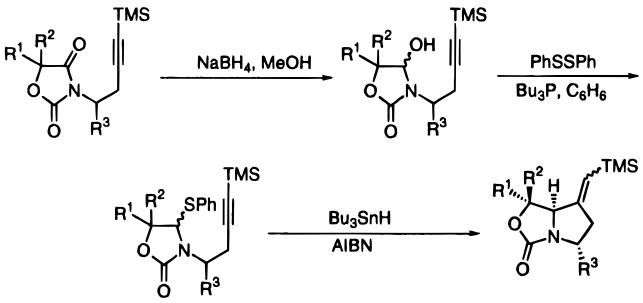
X = Cl, OC(O)R4, or OC(O)Bu-*t*

In an alternate procedure, the oxazolidinone may be efficiently acylated with mixed anhydrides using triethylamine and a slight molar excess of lithium chloride.[413] The oxazolidinone chiral auxiliaries employed ranged from the parent 2-oxazolidinone to the (*S*)-phenylalaninol, (1*S*,2*R*)-norephedrine and (1*S*,2*R*)-1-amino-2-hydroxyindan-derived systems.

Alkylations can be performed with the lithium oxazolidinone derivative in an analogous manner to acylations.[414−416]

A cyclization method allows for the concurrent formation of oxazolidinones (Scheme 85).[417]

Scheme 85

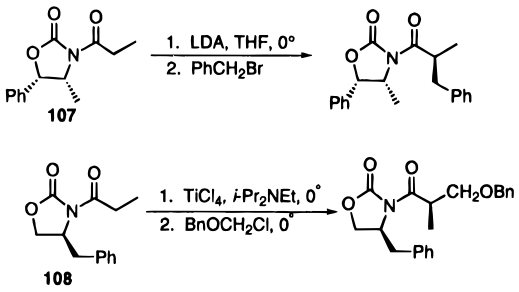


2. Alkylations

One of the major objectives in organic synthesis has been the development of general strategies for the stereoselective bond construction.[418,419] Nonetheless, the goal to develop carbon−carbon bond construction reactions, wherein chiral molecules are produced in high enantiomeric purity, has been a challenging as well as elusive endeavor. With the development of chiral enolate systems, it has been found that amide and imide enolates of **107** and **108** exhibit excellent levels of asymmetric induction for alkylation reactions (Scheme 86).[19]

Part of the high selectivity observed for reactions, such as alkylations, of *N*-acyloxazolidinones can be attributed to the high degree of stereoselectivity observed during enolate formation. *Z*-Enolates with high diastereoselectivity (typically >100:1) are obtained by reaction of the parent acyloxazolidinone with LDA,[19] sodium hexamethyldisilazide,[19] dibutylboron triflate in the presence of a tertiary amine,[18,20,420]

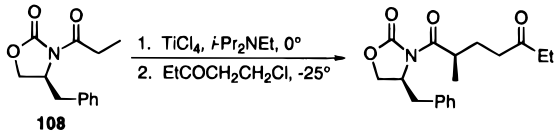
Scheme 86



or titanium(IV) chloride with a tertiary amine and Lewis acid.[421,422] Although the selectivity need not be as high, aluminum chloride, magnesium bromide etherate, and tin(II) triflate all result in enolate formation,[423] but tin(IV) chloride, dimethylaluminum chloride, and zirconium(IV) chloride do not.[424]

Along with the highly versatile reaction, enolates derived from chiral *N*-acyloxazolidinones were quenched with a variety of carbon electrophiles in a highly stereoregulated manner (Scheme 87).[19,421,425−427]

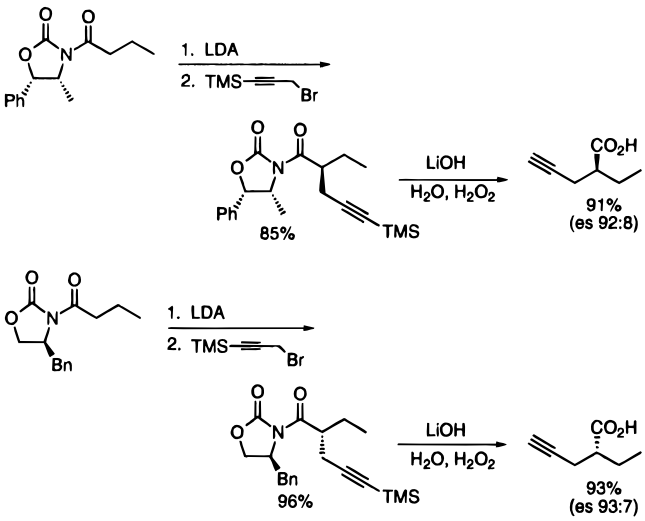
Scheme 87



The highest yields are usually seen with triflates (*vide infra*).[19,401]

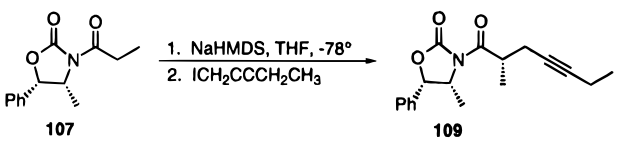
Complementary selectivity is available, as illustrated in Scheme 88.[19,428]

Scheme 88



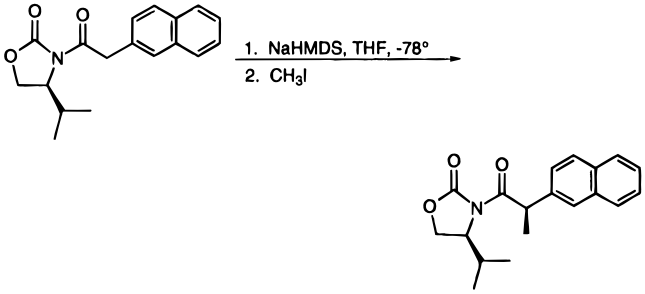
The diastereoselective alkylation of the chiral oxazolidinone **107**, with 1-iodo-2-pentyne gave the alkylated product **109**, an intermediate used in the synthesis of prostacyclin analogs (Scheme 89).[429]

Scheme 89



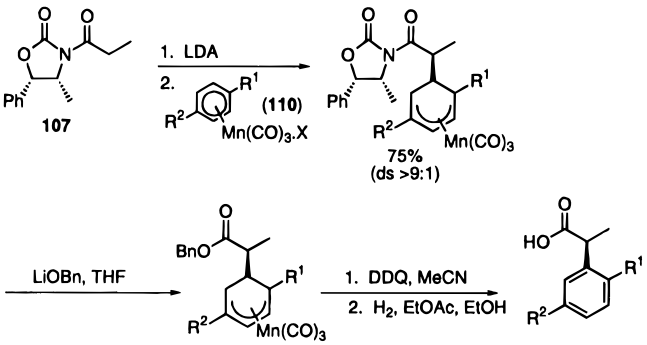
The methodology has been applied in the synthesis of optically active arylpropionic acids from the stereoselective alkylation of chiral imide enolates (Scheme 90).[430]

Scheme 90



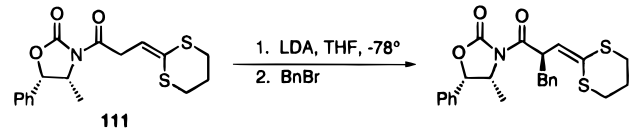
Organometallic reagents can also provide useful electrophiles as the functionality can be masked, or one face can be made extremely bulky.[431−434] This is illustrated by the use of the manganese arene complex **110** in the preparation of 2-arylpropionic acids (Scheme 91).[433]

Scheme 91



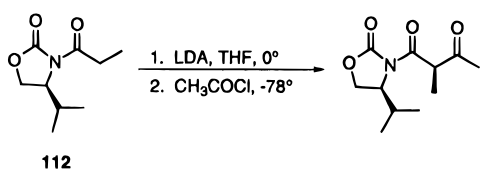
The methodology can be extended to delocalized systems. This approach has been utilized in the enantioselective preparation of β-alkyl-γ-butyrolactones. The key step in this procedure is an oxazolidinone **111**-directed alkylation of a lithiated ketene dithioacetal that proceeds with excellent regiochemical and high diastereofacial selectivity (Scheme 92).[401]

Scheme 92



These chiral enolates also undergo highly diastereoselective acylation reactions that give rise to chiral β-dicarbonyl synthons (Scheme 93).[421,435]

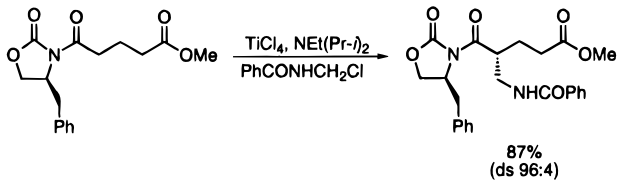
Scheme 93



The alkylation approach has been utilized in the synthesis of "unusual" amino acids, such as β-methyltryptophan,[436,437] β-methyltyrosine,[438] and homophenylalanine derivatives.[439]

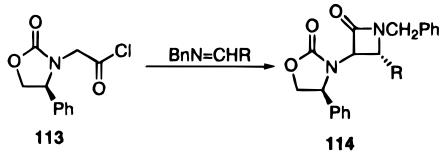
Overall, titanium has given the best results for alkylation reactions; the imide can be selectively enolized in the presence of another carbonyl group (Scheme 94).[421]

Scheme 94



Another application of carbon−carbon bond formation is in the synthesis of β-lactams. The reactions of oxazolidinone **113** with *N*-benzylimines proceed with an exceptional level of asymmetric induction to form the cycloadduct **114** (Scheme 95). Subsequent

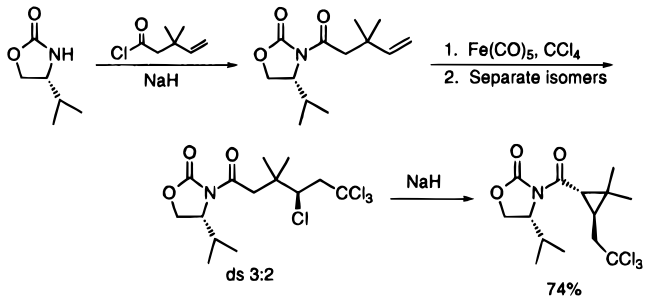
Scheme 95



dissolving metal reduction affords the β-lactam derivatives in good yield.[414]

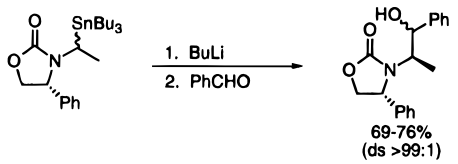
Cyclopropanes can be formed by an intramolecular reaction (Scheme 96); double diastereoselection can be observed.[440]

Scheme 96



The α position can be nucleophilic (Scheme 97).[416,441,442]

Scheme 97



3. α-Substitution Reactions

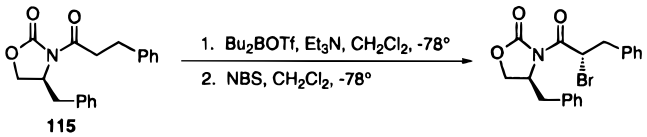
a. α-Halogenation

Chiral imide enolates have been demonstrated to undergo diastereoselective halogenation with a variety of agents in high yield. α-Iodo carboximides are not configurationally stable at room temperature, thus eliminating diastereoselective iodination as a viable option. A survey of both bromination and

chlorination agents reveals that bromination, in general, provides the higher diastereoselection, presumably because of the greater steric requirements of the larger halogen atom.[443] The asymmetric induction is derived from simple face selectivity [*cf.* Figures 2 and 3].

The chiral *N*-acyloxazolidinone **115**, as the derived dibutylboron enolate, undergoes diastereoselective bromination with *N*-bromosuccinimide (NBS) (Scheme 98). A change in the base from triethylamine to

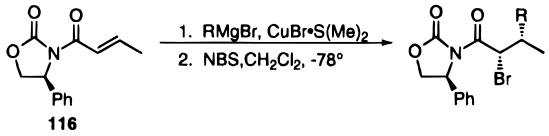
Scheme 98



diisopropylethylamine resulted in an increase in diastereoselectivity.[443−445]

The approach has been extended to allow for the preparation of β-amino acids through the Michael addition of a Grignard−copper reagent to a crotyloxazolidinone **116** followed by bromination of the resultant enolate (Scheme 99).[446,447]

Scheme 99



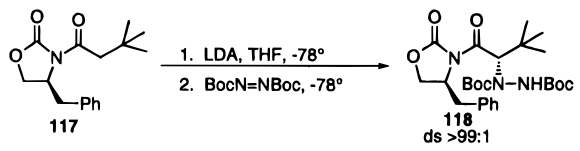
The Evans approach to unusual amino acids (see section D.3.b) has involved the bromination of a side chain that was fluorinated.[448] A lithium *N*-acyloxazolidinone enolate reacts successfully with *N*-fluoro-*o*-benzodisulfonimide.[449]

b. α-Amination

Nonproteinogenic and unnatural amino acids are important constituents in peptide-derived chemotherapeutics. The application of amination reactions of the chiral enolates derived from oxazolidinones has been used to provide α-amino acids.

Di-*tert*-butyl azodicarboxylate (DBAD) reacts readily with the lithium enolates of **117** to provide hydrazides **118** in excellent yield and high diastereomeric ratio (Scheme 100); these adducts can be

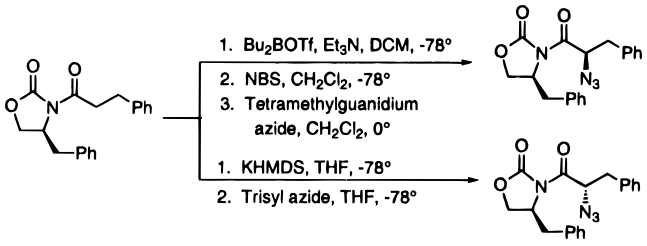
Scheme 100



converted to amino acids.[450,451] This methodology complements the chiral glycinate approaches.[279,452]

The electrophilic introduction of azide with chiral imide enolates has also been used to prepare α-amino acids with high diastereoselection (Scheme 101). The reaction can be performed with either the enolate directly,[443,453−456] or through a halo intermediate (*vide infra*).[444] The resultant azide can be reduced to an amine.[457]

Scheme 101



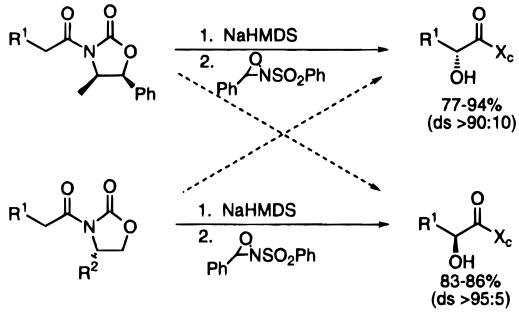
Other nitrogen nucleophiles, such as thiocyanate, can be used to displace halogens.[425]

The methods outlined above have been used to prepare a wide variety of amino acid derivatives.[458−464]

c. Oxygenation

α-Hydroxy acids, and simple derivatives thereof, have proven to be a versatile class of molecules that have been extensively exploited in asymmetric synthesis.[6] It has been demonstrated that diastereoselective hydroxylation of chiral imide enolates with oxaziridine oxidants provides a convenient method for the preparation of α-hydroxy acid synthons (Scheme 102).[403,465−473] Peroxydicarbonate can also be used as the oxidant.[474]

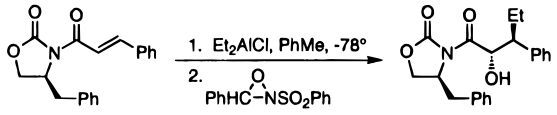
Scheme 102



The Michael addition of a carbon nucleophile followed by oxidation of the resultant enolate allows for the diastereoselective introduction of two groups.[475]

Diastereoselection through 1,4-addition of dialkylaluminum chlorides to α,β-unsaturated *N*-acyl urethanes followed by oxidation, has provided an elegant method for the preparation of β-alkyl-α-hydroxy acids (Scheme 103).[475]

Scheme 103

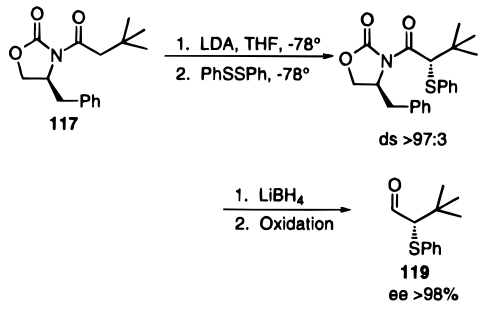


d. Sulfenylation

The use of racemic 2-phenylthio aldehydes to achieve high Anh−Felkin selectivity have been well demonstrated in Mukiyama-type aldol reactions of both stereogenic and nonstereogenic silyl ketene acetals.[476] Employment of the chiral derivatives, however, has been limited because of their difficult syntheses. The synthesis of highly enantiomerically enriched linear and branched-chain 2-phenylthio aldehydes **119** was achieved by diastereoselective

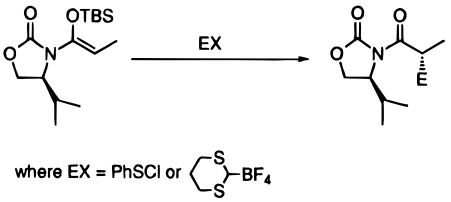
sulfenylation of chiral enolates derived from *N*-acyloxazolidinone **117** (Scheme 104).[477]

Scheme 104



For sulfenylation reactions, silyl enol ethers do not require Lewis activation with the oxazolidinone present (Scheme 105).[478]

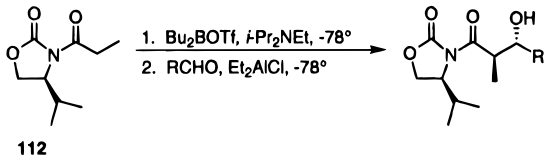
Scheme 105



4. Aldol Reaction

The development of chiral enolates that participate in stereoregulated aldol condensations has been a challenging undertaking. Oxazolidinones have been able to fulfill most of the requirements. The utility of *Z*-enolates (see section D.2), derived from *N*-acyl imides of chiral oxazolidinones **107** and **112**, has been shown through the aldol condensation reaction with aldehydes to give α-substituted-*β*-hydroxy imides in high yields (Scheme 106). Table 2 illustrates the

Scheme 106



variety of structural forms this process can tolerate.[18]

Sterically demanding metal centers play an important role in the enhancement of aldol stereoregulation. For dialkylboron enolates, kinetic aldol product stereochemistry has been shown to be strongly coupled to enolate geometry, while for dicyclopentadienylchlorozirconium enolates kinetic *erythro*-selective condensations have been observed from either enolate geometry.[479] Titanium enolates have shown to be highly selective under chelation-controlled aldol reactions. On the other hand, chelation control has been postulated for other metals such as lithium, zinc, and tin, although levels are rarely high. The most efficient processes utilize boron enolates. These provide well-ordered transition states that lead to predictably high levels of stereoselection.[480] As the *Z*-enolate is usually formed for boron enolates, the *syncat* adducts result.[17,18,20,31,420,445,481,482] This is a general observation and includes reactions with

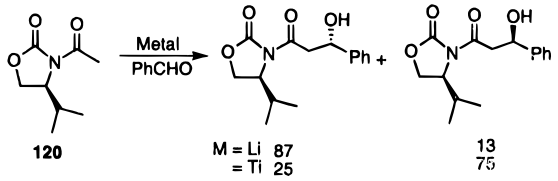
Table 2. Reactions of Aldehydes with Oxazolidinones 107 and 112

imide	aldehyde	*erythro* selection	yield (%)
107	*t*-BuCHO	497:1	78
107	*n*-BuCHO	141:1	75
107	PhCHO	500:1	88
112	*t*-BuCHO	1:500	91
112	*n*-BuCHO	1:500	95
112	PhCHO	1:500	89

imines as well as aldehydes, but the effect of enolate geometry (*vide supra*) does override the inherent induction from an asymmetric center within the electrophilic moiety.[404,483−487] A boron enolate, in the presence of a Lewis acid such as diethylaluminum chloride, can give the *ancat* adduct as the major product, while titanium(IV) or tin(IV) chlorides provide access to the "non-Evans" *syncat* product.[426] The *anti*-aldol approach has been used to resolve 2-phenylthio aldehydes.[488]

Solvent also plays an important role in aldol reactions, including those of an acyloxazolidinone-derived titanium enolate. It has been observed, for this latter case, that diethyl ether produces nearly a 5-fold increase in the diastereofacial selectivity compared to THF. This strong solvent effect arises from stoichiometric binding, most probably to the titanium, of THF in the transition structure, whereas ether is not bound.[489−491] It has also been demonstrated that aldol reactions of the titanium enolate of **120** with aldehydes gave high diastereofacial selectivities for the *syn* aldol adducts derived from chelation control (Scheme 107). This reversal in

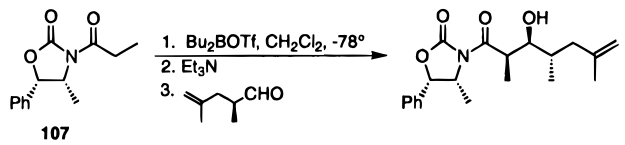
Scheme 107



reactivity, compared with boron enolate, permits the preparation of either enantiomeric aldol product from a single oxazolidinone.

The use of oxazolidinone **107** is illustrated as part of a synthesis of (+)-Prelog−Djerassi lactonic acid, where the aldol reaction is used to set up two stereogenic centers (Scheme 108).[492] This aldol meth-

Scheme 108

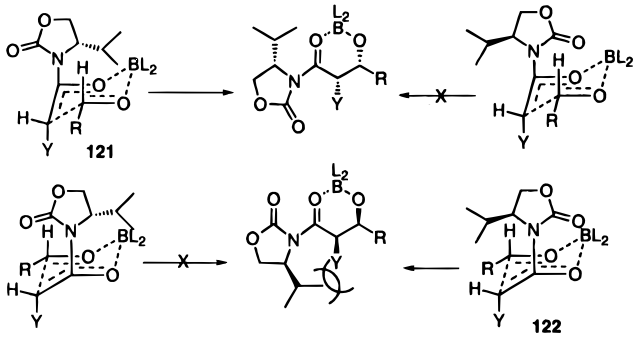


odology has been employed in approaches to the synthesis of a wide range of natural products.[31,403,404,423,485,493−500]

To observe high selectivity with oxazolidinone auxiliaries, an α-substituent should be present. This observation has been rationalized in terms of the Zimmerman−Traxler model where the interactions between the α-substituent (Y) and the control group drive the two possible reaction pathways (Scheme

109). The approach of the aldehyde is away from the bulky control group to favor intermediate **121**, although the alternative, **122**, is still viable when Y = H.[17,20,501]

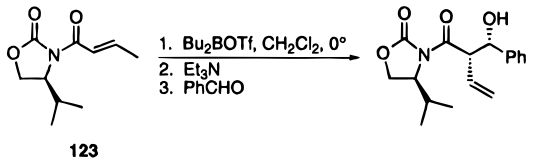
Scheme 109



For boron enolates based on Evans oxazolidinone chemistry, the use of triethylamine, rather than Hunig base, has been advocated as the former provides higher diastereoselection. This infers that the resultant ammonium salt plays a role in the transition state for the reaction with aldehydes.[502,503]

These aldol reactions based on the usage of oxazolidinones have been extended to the crotonate imides, such as **123**. The reaction of the derived dibutylboron enolates proceeds with complete α-regioselectivity, and the diastereoselection of the aldol products is good (>98%) (Scheme 110).[504,505] Self-condensation

Scheme 110

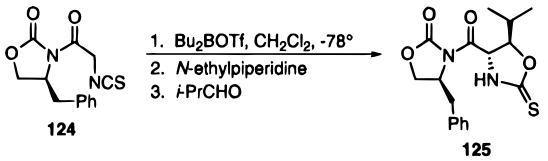


problems can be reduced through the use of triethylamine.

With *N*-acetyloxazolidinones, the boron enolate gives rise to a statistical mixture of products in aldol reactions. The work round is to use a removable group, such as methylthio or halogen.[17,506]

The chiral glycine synthon **124** has been demonstrated to undergo highly *syn* diastereoselective aldol addition reactions with aldehydes to give the aldol adduct **125** (Scheme 111).[425] This adduct can then

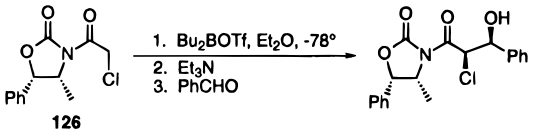
Scheme 111



be converted to the unusual C_9 amino acid, MeBmt, found in the immunosuppressive peptide, cyclosporin.[507]

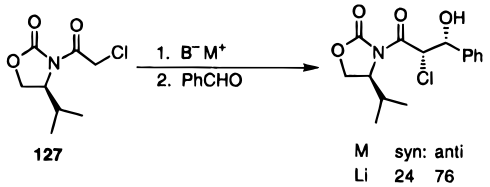
The diastereoselective aldol reaction of **124,** an isothiocyano derivative, with aldehydes gives high enantioselectivity for the *syn*-*β*-hydroxy-α-amino acids products, whereas **126**, a chloro derivative, provides *anti*-*β*-hydroxy-α-amino acids (Scheme 112).[506]

Scheme 112



Chiral haloacetyl oxazolidinones on reaction with aldehydes show a strong dependence on the metal counterion for the determination of the stereochemical outcome (Scheme 113).[508,509] The "non-Evans"

Scheme 113

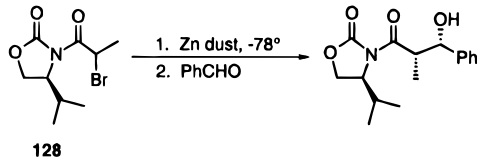


M	syn:	anti
Li	24	76
Sn^{IV}	22	78
Sn^{II}	96	4
B	99	0
Zn	33	67

syncat product is obtained with $TiCl(Oi\text{-}Pr)_3$.[489,491] The halogen in the product can be used for further reactions.[506,510]

The bromo compound, **128**, has been used in the Reformatsky reaction to afford *β*-hydroxy carboxylic acid equivalents (Scheme 114).[511−515]

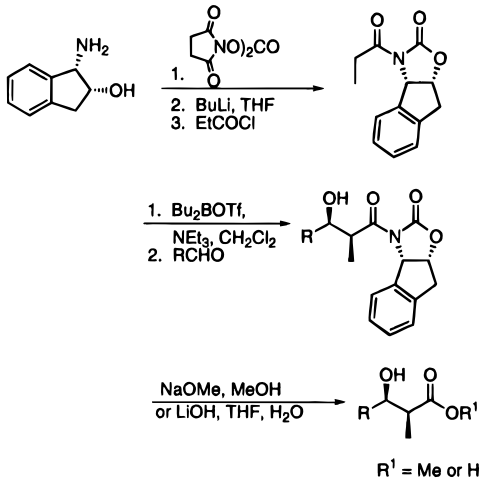
Scheme 114



The presence of an α-alkoxy group does not affect the aldol reaction nor the control of the metal counterion.[423,484,516]

The chiral auxiliary derived from *cis*-1-amino-2-hydroxyindan provides high (>99%) de's in the aldol reaction (Scheme 115).[517]

Scheme 115



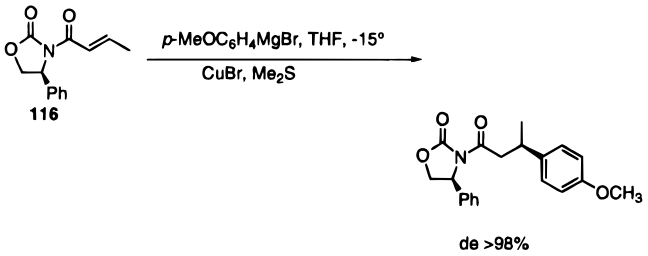
Imines can also be used as the electrophile with the lithium or titanium enolates of *N*-acyloxazolidi-

nones; β-amino ester derivatives result that, in turn, can be converted to β-lactams.[518]

5. Conjugate Additions

Conjugate additions of organocuprates to α,β-unsaturated *N*-acyloxazolidinones **116** proceed with good diastereoselectivity and allow access to β-branched carboxylic acids (Scheme 116),[26] or β-substituted GABA analogs.[519]

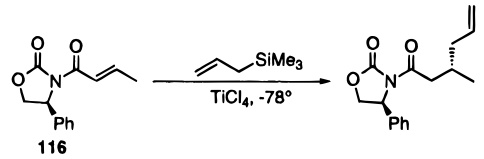
Scheme 116



In addition to copper-based reagents,[26,436,520] aluminum can also be used to deliver a nucleophile in a 1,4-manner.[475,521]

The carbon−carbon bond formation was further extended to prepare allylated products by the conjugate addition of allyltrimethylsilane to α,β-unsaturated *N*-acyloxazolidinone **116** (Scheme 117).[522] This

Scheme 117

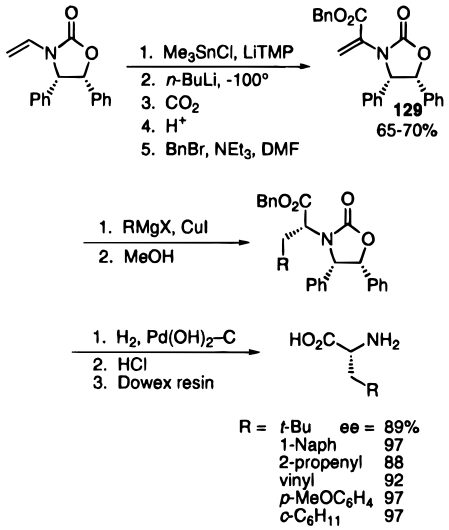


gives a route for the preparation of chiral 3-substituted 5-hexenoic acids.

Heteroatoms can also be used as nucleophilic moieties for conjugate additions. Although lithium thiolates gave reasonable selectivity with tiglic acid derivatives, cinnamyl analogs gave poor induction.[523]

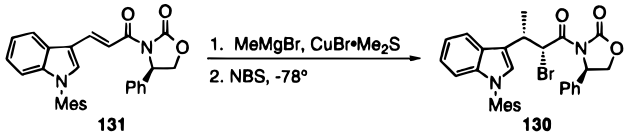
Copper-catalyzed conjugate additions of Grignard reagents to acrylates **129** provides a useful entry to α-amino acids (Scheme 118).[524]

Scheme 118



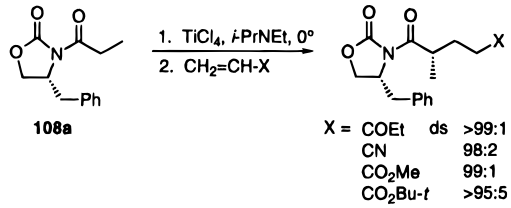
The enolate can be used in subsequent reactions. The stereochemistry of the α-carbon of the amino acid precursor **130** was simultaneously set along with homologation of the β-carbon. This was achieved by stereoselective bromination of the metal−chelate enolate formed by the addition of the higher order methylcuprate to the α,β-unsaturated acyloxazolidinone **131** (Scheme 119).[436,437]

Scheme 119



The alternative, conjugate addition of an oxazolidinone nucleophilic species, is also available. The titanium enolates derived from *N*-propionyloxazolidinone **108a** undergo Michael reactions with α,β-unsaturated systems in high yields and diastereoselectivity (Scheme 120).[422]

Scheme 120

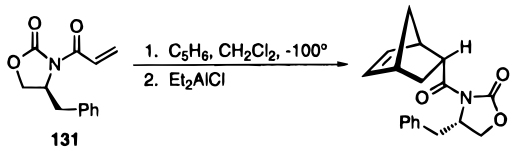


6. Pericyclic Reactions

a. Diels–Alder

The asymmetric Diels−Alder cycloaddition reaction, with formation of two new carbon−carbon bonds in an entirely regio-, diastereo-, and enantioselective manner, can be realized by use of chiral oxazolidinones.[349,350,408,409] α,β-Unsaturated carboximides, e.g. **131**, have been developed as practical dienophiles in the Diels−Alder process (Scheme 121). High dia-

Scheme 121

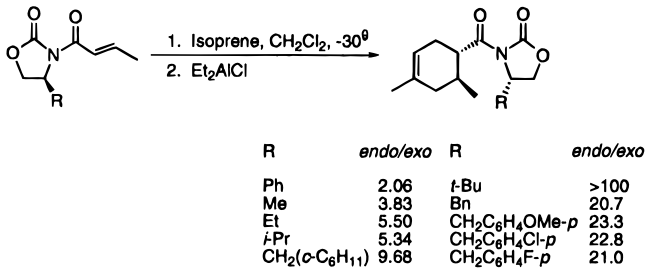


stereoselectivity was obtained when diethyl- or dimethylaluminum chloride were used as Lewis acid catalysts. A cationic-dienophile complex was proposed to account for the high selectivity.[408,409]

The diastereoselectivity is also dependent on both steric and electronic components. This effect is clearly evident in the Diels−Alder reaction of oxazolidinone crotonate−isoprene, where *tert*-butyl group gives the best and phenyl the least diastereoselectivity (Scheme 122).[349,350,408,409,475]

Excellent diastereoselectivity was also observed in the intramolecular Diels−Alder reactions. In these cycloaddition reactions, the substituent at the C_4-position of oxazolidinone directs the π-facial selection to the opposite face of the *cisoid* dienophile−Lewis

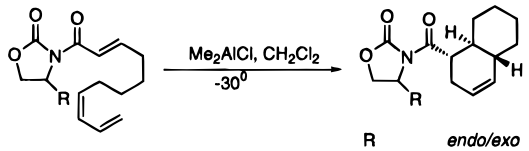
Scheme 122



R	endo/exo	R	endo/exo
Ph	2.06	*t*-Bu	>100
Me	3.83	Bn	20.7
Et	5.50	$CH_2C_6H_4OMe$-*p*	23.3
i-Pr	5.34	$CH_2C_6H_4Cl$-*p*	22.8
$CH_2(c\text{-}C_6H_{11})$	9.68	$CH_2C_6H_4F$-*p*	21.0

acid complex (Scheme 123).[349] This approach was exploited in a synthesis of pulo'upone.[525]

Scheme 123



R	endo/exo
(*S*) *i*-Pr	92:8
(*S*) Bn	97:3
(*R*) *C*-C_6H_{11}	6:94

Intermolecular Diels−Alder reactions of the acrolein derivative **131** have been reported.[526]

b. Ene Reaction

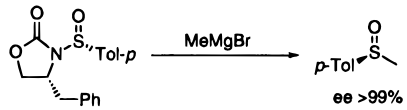
The use of an oxazolidinone as a chiral unit does allow for modest yields and selectivity for an ene reaction with 1,1-disubstituted alkenes in the presence of dimethylaluminum chloride.[521]

7. Other Reactions

a. Synthesis of Organosulfur Compounds

Chiral sulfoxides provide for a wide variety of methodology in organic synthesis as chiral controllers for asymmetric carbon−carbon bond formation.[527−529] A new class of chiral sulfinyl transfer reagents has been developed that is readily prepared from oxazolidinones. The *N*-sulfinyloxazolidinone reagents can be synthesized either by sulfinylation of the metalated oxazolidinones or by oxidation of the derived *N*-sulfenimides. These sulfinylation agents react with a wide range of nucleophiles such as Grignard reagents, enolates, lithium alkoxides, or metalated amides, with inversion of configuration at the sulfur center to afford the derived chiral sulfoxides, sulfinate esters, and sulfinamides in high yields and enantioselectivities (e.g. Scheme 124).[530]

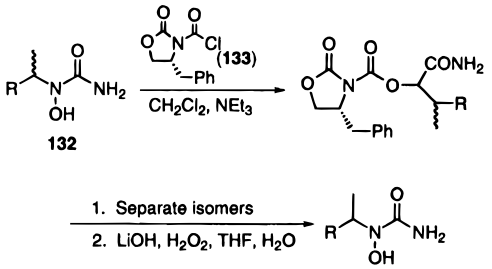
Scheme 124



b. Resolving Agents

Hydroxyureas **132** are of pharmaceutical importance, yet even resolution of this class of compounds can be troublesome. The oxazolidinone carbonyl chloride **133** can be used as a resolving agent for hydroxyureas even on a preparative scale (Scheme 125).[531]

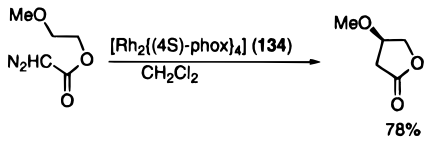
Scheme 125



c. Ligands

The catalyst, tetrakis[(*4S*)-4-phenyloxazolidin-2-one]dirhodium(II) (**134**), $[Rh_2\{(4S)\text{-phox}\}_4]$, prepared from (*4S*)-4-phenyl-2-oxazolidinone and rhodium acetate, has been used for metal carbene transformations, such as inter- and intramolecular cyclopropane formation, intermolecular cyclopropene formation, and intramolecular C−H insertions of diazoacetates and diazoacetamides (Scheme 126).[532,533]

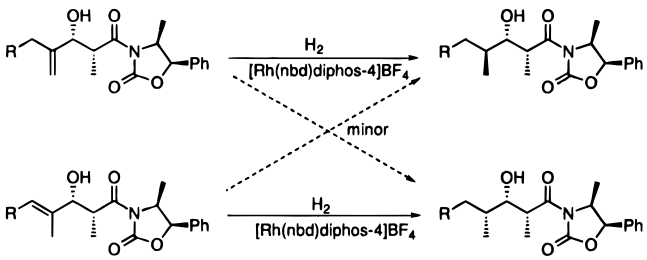
Scheme 126



d. Hydrogenations

The oxazolidinone group has also been used as protection for a carboxylic acid, or derivative. Thus, reactions are available that are not directly influenced by the stereochemistry of the ring system. Such an example is provided by the reduction of an allyl alcohol. The extent of diastereoselection depends upon the catalyst to substrate stoichiometry (Scheme 127). The hydroxy group allows complex formation

Scheme 127



with the catalysts to ensure high facial selectivity.[534,535]

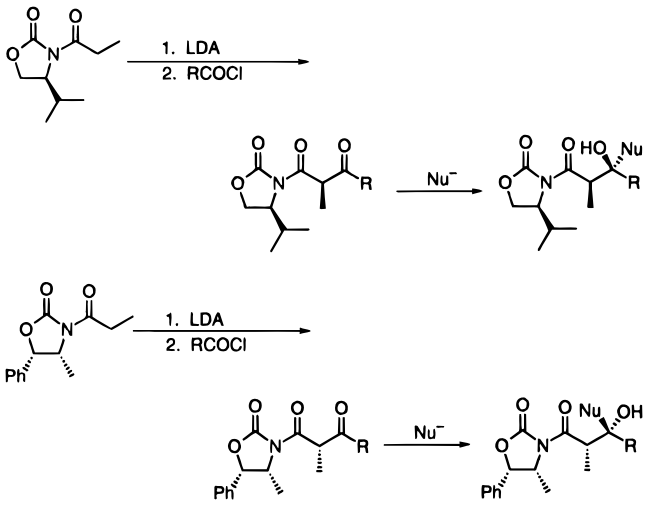
e. Reactions at Remote Carbonyl Centers

Oxazolidinones can also be used to control the face selectivity of nucleophilic additions, including reductions, to a β-carbonyl group (Scheme 128).[435]

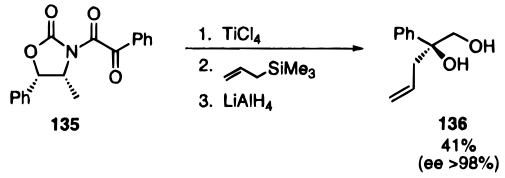
A similar approach with the α-dicarbonyl system **135** provided the diol **136** (Scheme 129).[478] The condensation reaction gave a 91% yield prior to the reduction.

Diastereoselective aldol reactions of β-keto imide-derived enolates provide a versatile approach to prepare *syn* or *anti* aldol products at the distal center by selection of the appropriate metal counterion (Scheme 130).[404,496,536−539]

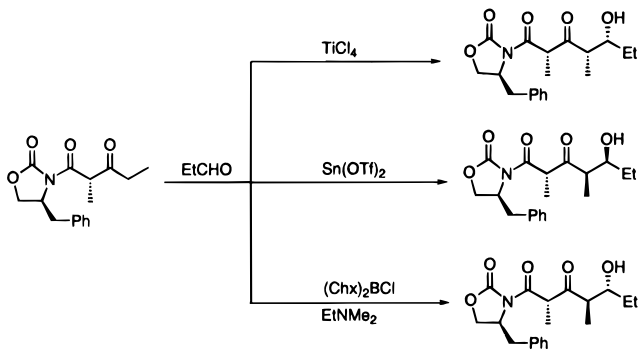
Scheme 128



Scheme 129

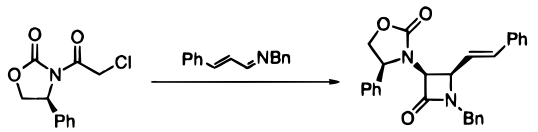


Scheme 130



Oxazolidinones can also control the outcome of a Staudinger reaction (Scheme 131).[414]

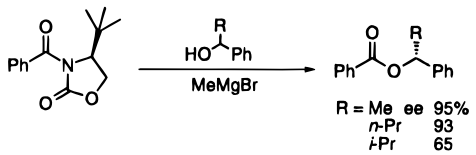
Scheme 131



f. Other Reactions

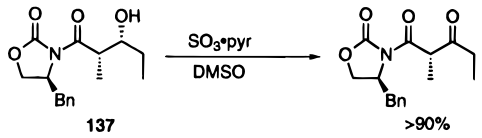
The oxazolidinone group can be used as a chiral activation group in acyl transfers (Scheme 132).[540]

Scheme 132



The aldol adduct **137** can be oxidized to the dicarbonyl derivative with pyridine−sulfur trioxide (Scheme 133); this gives the opposite stereochemistry

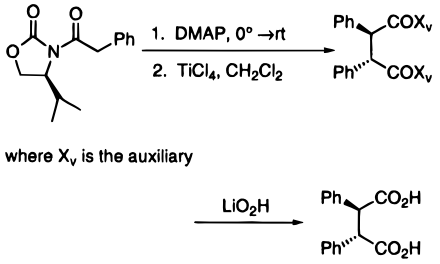
Scheme 133



to that obtained for the acylation of the same oxazolidinone isomer.[435]

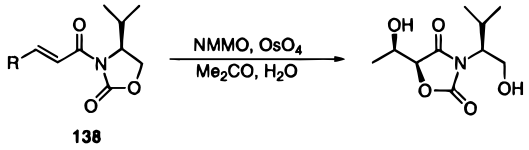
2,3-Disubstituted succinic acids have been prepared by the oxidative coupling of *N*-acyloxazolidinones (Scheme 134).[541]

Scheme 134



Dihydroxylation of an unsaturated acyloxazolidinone **138** results in a face-selective reaction that is accompanied by cleavage of the heterocycle (Scheme 135).[542]

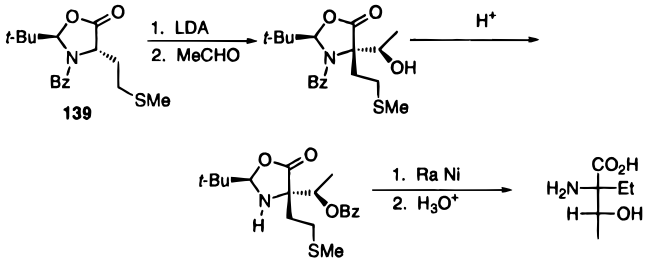
Scheme 135



g. Other Oxazolidinones

4-Oxazolidinones **139** can provide some useful transformations, such as aldol reactions, although the majority of methods of this type are based on the imidazolidone nucleus (Scheme 136).[259]

Scheme 136

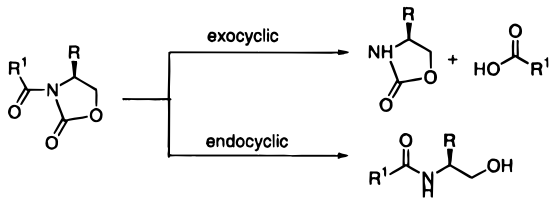


8. Removal

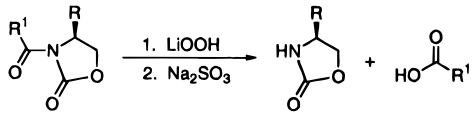
After the stereospecific reaction with the chiral auxiliary, the product must be isolated from the oxazolidinone that, in turn, should have the potential for recycle. Cleavage of the auxiliary can be either exo- or endocyclic (Scheme 137).[543] The larger the R^1 group, the more likely the endocyclic cleavage process is to occur with basic reagents.

Undesired oxazolidinone cleavage can be circumvented by use of lithium hydroperoxide in place of the hydroxide (Scheme 138).[408,544,545] Regioselective exocyclic cleavage is, therefore, observed for all

Scheme 137



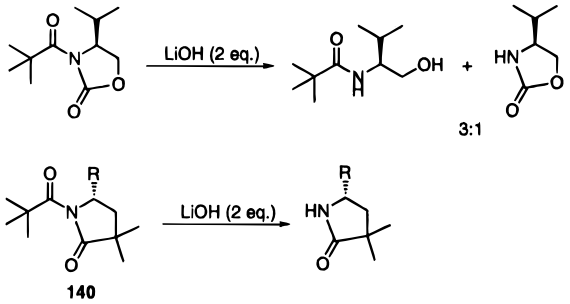
Scheme 138



classes of oxazolidinone derived carboximides, even with bulky R^1 groups when the peroxide reagent is employed.

An alternate way around an undesired endocyclic cleavage is to employ a "quat" (5-substituted 3,3-dimethyl-2-pyrrolidinones **140**) chiral auxiliary (Scheme 139).[543,546] An increase in steric bulk adja-

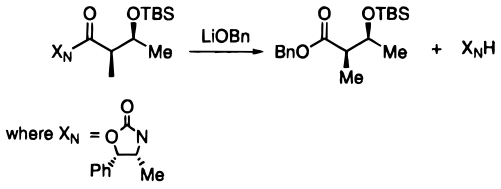
Scheme 139



cent to the endocyclic carbonyl in the quat auxiliary favors exocyclic cleavage.

If an ester is the desired product, cleavage can be accomplished with lithium alkoxides (Scheme 140),[19,485]

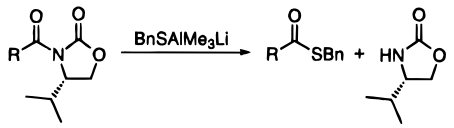
Scheme 140



while thioesters can be accessed through lithium thioalkoxides (*vide infra*). In addition to lithium, other metal counterions, such as sodium, magnesium, and titanium have been employed successfully.[18,429,443,495,505]

Thioesters are obtained when the oxazolidinone is cleaved using an aluminum benzyloxy "ate" complex that is formed *in situ* from trimethylaluminum and lithium benzylthiolate (Scheme 141).[547] The recovery

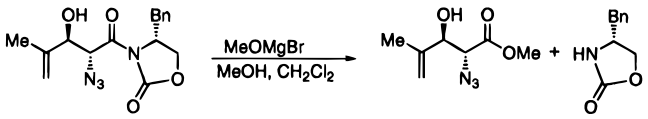
Scheme 141



of the auxiliary is claimed to be virtually complete. The attack of the sulfur nucleophile is *exo* even in sterically demanding systems.[486,548,549]

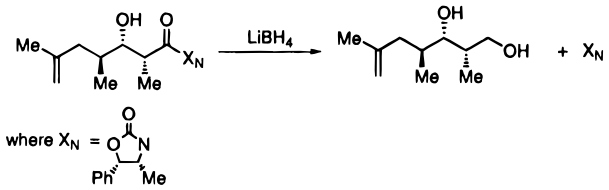
Magnesium methoxide has been utilized to cleave auxiliaries and afford methyl esters (Scheme 142).[495]

Scheme 142

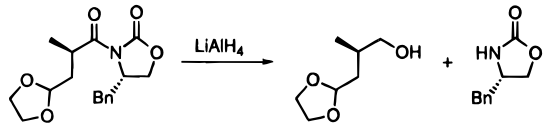


Alcohols are obtained when lithium borohydride (Scheme 143)[19,404,504,550,551] or lithium aluminum hydride are employed (Scheme 144).[19,539,552]

Scheme 143

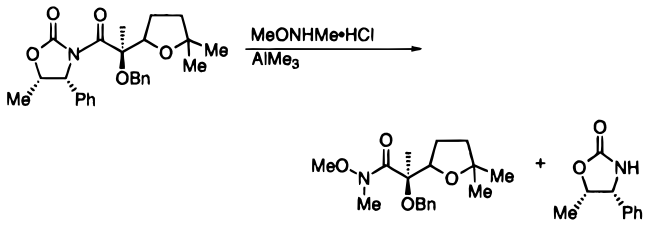


Scheme 144



Aldehydes and ketones are not readily accessible from chiral *N*-acyloxazolidinones, but the aluminum amide derived from trimethylaluminum and *N*,*O*-dimethoxyhydroxylamine hydrochloride yields the *N*-methoxy *N*-methyl amide (Scheme 145).[483,516] These

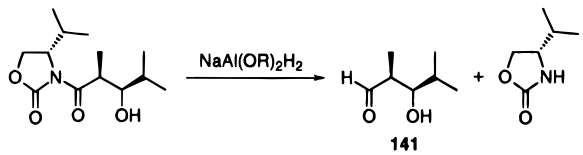
Scheme 145



amides may then serve as precursors to aldehydes and ketones.[516,553−555]

Aldehydes are also available by a two-step process that involves reduction to the alcohol, followed by oxidation.[537] Other methods have been used to prepare aldehydes, such as reduction with Dibal,[516] and treatment of thioesters with triethylsilane.[538] An aldehyde **141** was formed during cleavage of the valine-derived oxazolidinone (Scheme 146), but was

Scheme 146

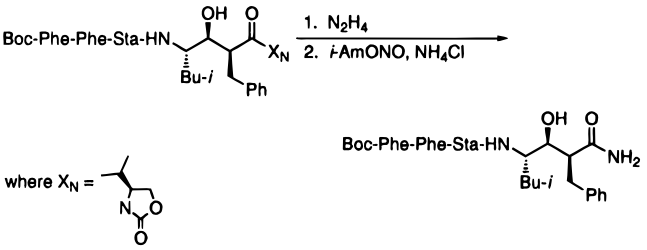


too unstable to isolate, so it was immediately converted to an ester.[556]

Alternatively, amides may be obtained by group IV metal-catalyzed aminolysis;[557] or transamination in

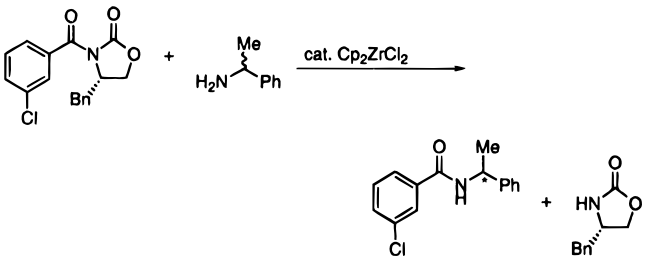
the presence of an aluminum catalyst.[404,523,558] Hydrazide nucleophiles can also be used to accomplish the transformation (Scheme 147).[559] Modest enan-

Scheme 147



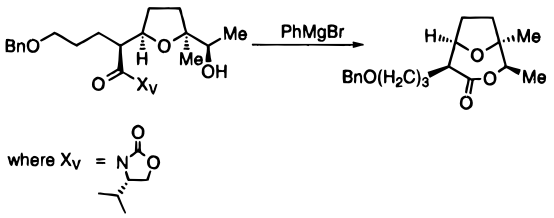
tioselectivity for the (*R*)-amine enantiomer (55%) and a high yield (88%) was observed in a discrimination reaction employing α-phenylethylamine and catalytic Cp_2ZrCl_2 (Scheme 148).

Scheme 148



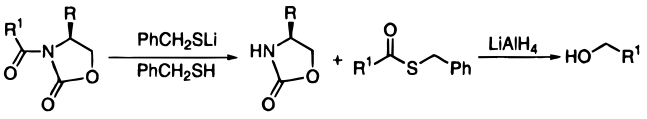
Valine-derived oxazolidinones have a propensity to undergo lactonization (Scheme 149); this was exploited in a total synthesis of ionomycin.[505]

Scheme 149



Attack at the *N*-acyloxazolidinone carbonyl is often observed if R is large. Instead, a thioalkoxide system has been employed to make thioesters that are then reduced to alcohols with lithium aluminum hydride (Scheme 150).[548] The cleavage can be performed in

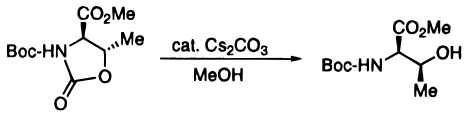
Scheme 150



one pot with quantitative recovery of the auxiliary.

N-Boc-protected oxazolidinones can be cleaved with catalytic amounts of cesium carbonate in methanol at room temperature to give acyclic *N*-Boc amino alcohols (Scheme 151).[560] Lithium hydroxide and

Scheme 151



potassium carbonate in aqueous solutions were also found to be satisfactory for this reaction, but did not give as high yields as cesium carbonate. With Z-protected oxazolidinones, only *N*-deprotection products were observed under the analogous conditions.

E. Oxazolines

The synthetic utility of oxazoline ring system, a cyclic imino ester, is evident by the literature published in last three decades.[396,561−565] This versatile ring system has served as protection, a coordinating ligand, and an activation moiety; it often exhibits all of these characteristics in a single transformation. The emphasis of this review is on the utility and synthesis of chiral oxazoline from chiral amino alcohols. Comprehensive reviews for this class of compounds are already available.[396,561,562]

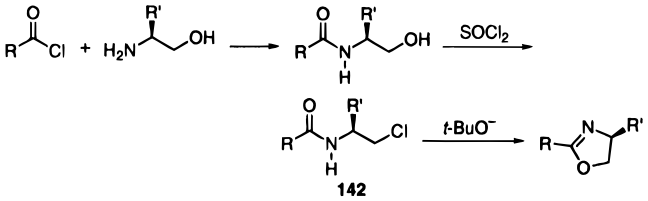
Oxazolines, as well as oxazoles, can be components of natural products.[566,567] Oxazolines are naturally occurring as parts of polypeptides.[566−588] They are also used to afford conformational rigidity in pharmacological candidates,[589−591] such as leukotriene antagonists.[592]

1. Preparations

Although β-amino alcohols do react with carboxylic acids under dehydrative conditions, such as the azeotropic removal of water, to afford oxazolines, the harsh conditions are not compatible with delicate functionality.[593,594]

A common route to oxazolines is by reaction of an acid chloride with an amino alcohol. The resultant hydroxyamide is then treated with thionyl chloride and cyclized with base (Scheme 152).[563] A problem

Scheme 152



with this approach can be the use of highly reactive thionyl chloride—a cause for concern in complex molecules—as well as incomplete reaction that results in formation of the acyclic chloroamide **142**;[595] this can be cyclized by treatment with base or silver triflate.[596]

Phosphorus reagents can be used in place of thionyl chloride.[597−599] A variety of mild approaches have been developed including the use of triphenylphosphine−carbon tetrachloride in the presence of an amine base,[600,601] (diethylamido)sulfur trifluoride (DAST),[597] and tosyl chloride in the presence of DMAP.[602] The Mitsunobu conditions have been successfully employed to prepare oxazolines from dipeptides that contain hydroxymethyl side chains,[589] but the approach can also provide aziridines and alkenes necessitating a care in reagent choice.[590,591]

To circumvent the problems associated with the vigorous conditions of the use of an acid chloride, an alternative approach that employs reaction of the

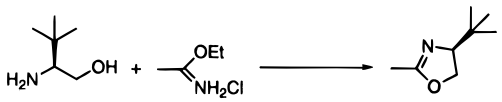
parent carboxylic acid with carbonyldiimidazole and an aziridine has been advocated.[603]

The use of epoxides that are readily available by asymmetric methodologies provide oxazolines when reacted with a nitrile. A wide variety of acid and Lewis acid reagents have been employed to effect the reaction.[604−609] An analogous approach exists for *N*-acylaziridines.[603,609−612] Reaction of an epoxide with trimethylsilyl cyanide in the presence of zinc iodide followed by potassium fluoride and then a palladium chloride catalyst results in formation of an oxazoline.[613]

2-Aryloxazolines are available by displacement of a 2-thio group from an existing oxazoline by an organometallic reagent.[562,614]

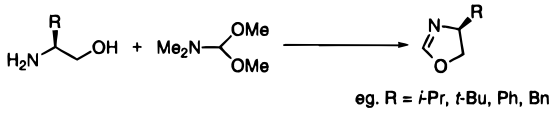
Another common approach to oxazolines is the reaction of chiral amino alcohols with an imidate (Scheme 153).[562,615−618]

Scheme 153



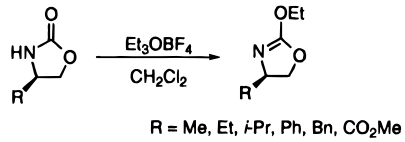
A simple and high yielding route to chiral oxazolines is available from a variety of chiral β-amino alcohols, and involves treatment of the amino alcohols with dimethylformamide dimethyl acetal (DMF-DMA) (Scheme 154).[619]

Scheme 154



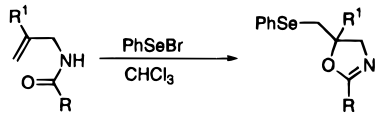
Ethoxy oxazolines are also available from oxazolidinones (Scheme 155).[620]

Scheme 155



Carbocation-induced cyclizations of *N*-allyl amides provide oxazolines through a 5-*exo*-*trig* process. Although strong acid can be used to form the carbocation,[621] milder methods based on selenium- and sulfur-induced reactions avoid side reactions (Scheme 156).[622−624]

Scheme 156

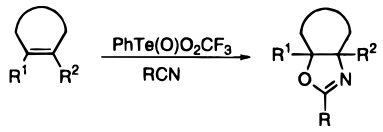


A related, but convergent, approach is based on tellerium chemistry (Scheme 157).[625−627]

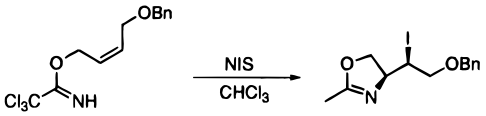
Iodine can also be used to induce cyclization, but the mode of ring closure is substrate dependent (Scheme 158).[628−630]

Oxazolines are readily available through reaction of an aldehyde with an isocyanide in the presence of

Scheme 157

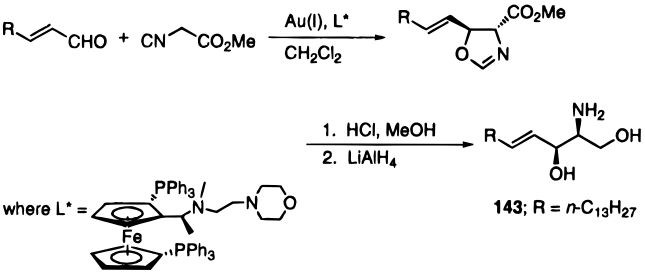


Scheme 158



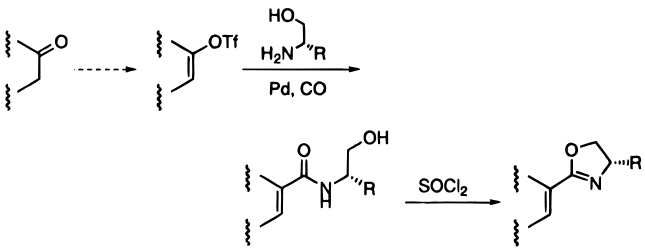
an acidic or basic catalyst.[631−646] Copper catalysis is also effective.[647,648] The use of an asymmetric metal complex allows for the chemistry of oxazolines to be exploited,[649−667] as illustrated by the synthesis of D-*threo*-sphingosine, **143** (Scheme 159).[649]

Scheme 159



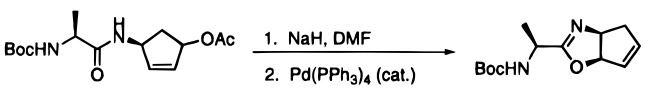
The use of transition metal chemistry allows for an oxazoline ring to be built onto a carbon atom that originated within a carbonyl group (Scheme 160).[668−670]

Scheme 160



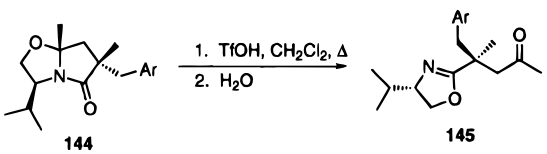
Bicyclic oxazoline can be accessed by a Pd(0)-catalyzed cyclization that employs an allyl acetate substitution reaction (Scheme 161).[671]

Scheme 161



Rearrangement of the bicyclic lactam **144** under acidic conditions results in an oxazoline **145** (Scheme 162).[672]

Scheme 162

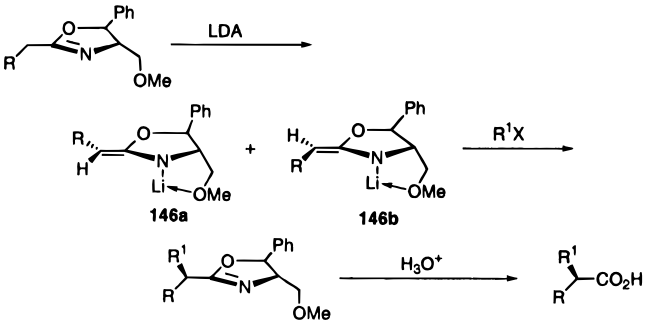


Although potentially useful, electrocyclic reactions have yet to afford general, practical approaches to oxazolines.[673−679]

2. Alkylations

Oxazolines are useful intermediates for the asymmetric synthesis of many classes of compounds. They provide useful methods for the α-alkylation of a masked carbonyl derivative (Scheme 163).[561,616,680−685]

Scheme 163



Indeed, this methodology can be used for kinetic resolution.[616,686]

Metalation of the oxazoline provides an azaenolate **146** whose structure has been the subject of some discussion.[684,685] Scheme 163 shows the enolate **146** as depicted in the original paper. Reaction with an electrophile provides for top face alkylation.[681] In this argument, the formation of the lithium chelate is important. There is also control of the stereochemistry of the α-center by the order in which the electrophilic units are added as the face selectivity is ensured by the auxiliary rather than the substitution pattern.[680] NMR studies showed that for the reaction shown in Scheme 163, two lithiated oxazolines are present in a ratio of about 92:8, and that equilibration does not occur over the usual reaction temperature range while the reactivity of the two species to alkyl halides is similar.[683,684]

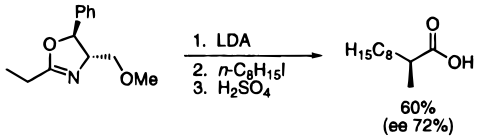
The nature of the base does influence the degree of asymmetric induction; LDA being superior to *n*-butyllithium that, in turn, is better than *tert*-butyllithium.[680,685] In addition, if the azaenolate is left for a period of time before the alkylation, no decrease in stereoselection is observed, while this is not the case if an alkyl lithium is used as base.[685,687] The observation that HMPA can provide access to the alternative enolate geometry[688−690] has been applied to this oxazoline system.[685,691]

The nature of the electrophile is also important. With methyl iodide the enantioselectivity tends to be lower than when a sulfate or tosylate is employed.[681] The effect of temperature has also been studied. As with other alkylations of this type, the temperature for the deprotonation step has little effect on the stereoselection observed. However, the reaction temperature for the reaction with the electrophile has a significant impact on the product diastereoselection. Increases of about 10% were seen when the reaction was run at −100 °C, as compared to −78 °C.[687]

The structure of the amino alcohol used to prepare the oxazoline has a dramatic effect on the stereoselection of reactions. A group is required at C-4 that can form a complex with a metal ion, while a large group has to be at C-5. If one of these requirements is not fulfilled, the stereoselection can drop dramatically.[687]

This alkylation approach has been employed in a synthesis of the European pine saw fly pheromone; the first step is shown in Scheme 164.[692]

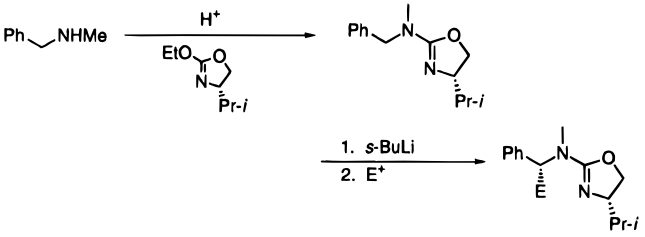
Scheme 164



Functional groups, such as methoxy or chloro, can also be present adjacent to the oxazoline moiety and still undergo alkylation reactions. However, the ee's are moderate, at best (<65%).[693]

If there are no protons α to the oxazoline moiety, reaction can occur at a remote center. This has been exploited in a method for the alkylation of amines (Scheme 165)[694] and nitrogen heterocycles.[620,695−700]

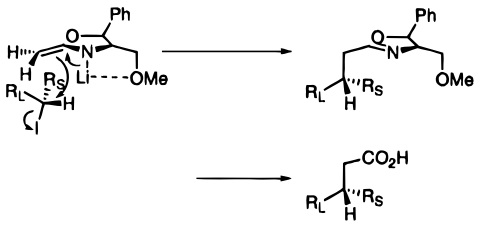
Scheme 165



a. Kinetic Resolutions of Alkyl Halides

Oxazolines can be used, in addition to the preparation of substituted carboxylic acid derivatives, for the kinetic resolution of alkyl halides.[686,701] Although the optical yields are not high (<49% ee), there is potential for further improvements. As with other alkylations of this type, the methoxy side chain has to be present in the oxazoline to allow for complex formation in the enolate. This, in turn, provides the severe steric requirements, through formation of the bicyclic azaenolate, so that the chirality of the alkyl halide has a significant influence on the approach. The *S*-halide reacts preferentially in Scheme 166; the

Scheme 166

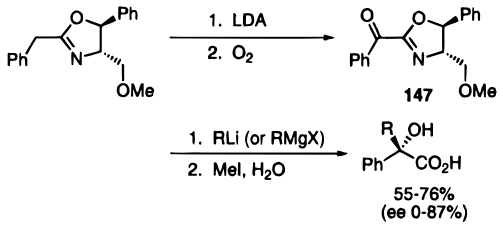


small group of the alkyl halide is in the most sterically congested position.

b. With Heteroatoms

An alternative strategy, which does allow asymmetric induction, is the reaction of an organolithium or Grignard reagent with the ketooxazoline **147** (Scheme 167).[618] This approach relies on the oxazoline to control the approach of the incoming nucleo-

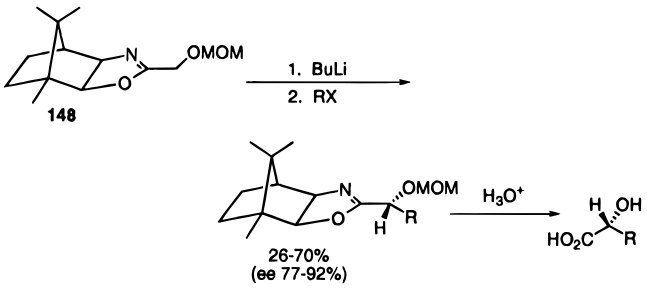
Scheme 167



phile. As with alkylations, the structure of the oxazoline is important to maximize the degree of induction.[618] In many ways, the oxazoline is acting as a masked α-keto acid.[618,702]

An alternative strategy is to alkylate an α-hydroxy acid synthon. The oxazoline **148** provided one such application of this methodology, but some difficulty was encountered in the hydrolytic removal of the chiral auxiliary (Scheme 168).[703]

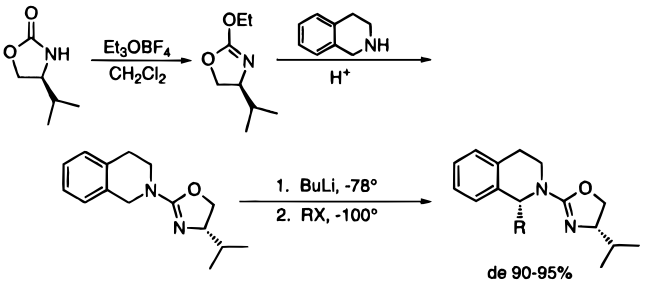
Scheme 168



c. Remote Alkylations

The stereoselective alkylations of (tetrahydroisoquinolyl)oxazolines have been achieved by conversion of the chiral oxazolidinones to chiral ethoxy oxazolines and then treatment with tetrahydroisoquinoline (Scheme 169). It was found that there was not much

Scheme 169



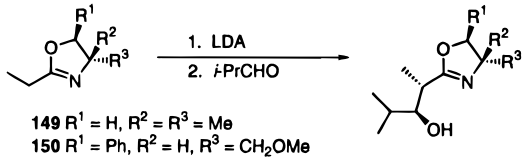
difference in selectivity for alkylation with an alkyl bromide by changing the substituent at the 4-position of the oxazolines or the alkyllithium base. The temperature played an important role. Lower temperatures resulted in a significant increase in selectivity. The electrophile also has an effect. The selectivity is higher with more reactive alkyl halides.[620]

3. Aldol Reactions

As an oxazoline is an enolate equivalent, reaction with a carbonyl electrophile is a derivative of an aldol-type reaction. This provides routes to β-hydroxy and β-alkoxy acids. Although the enantiomeric excesses are usually not high (*ca.* 20−25%),[511] the adducts are useful precursors to 1,4-addition methodology.[561,704−707]

The effect of a heteroatom in the C-4 substituent to form a complex with a metal counterion is very apparent with the aldol reaction. Metalation of the methyl compound **149** with LDA followed by reaction with isobutyraldehyde gave a 56:44 mixture of the product diastereoisomers (Scheme 170).[708] With the

Scheme 170

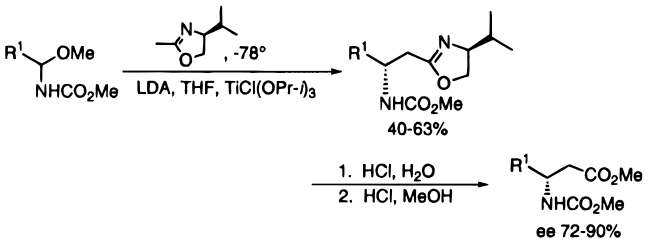


heteroatom analog **150**, a mixture of four diastereoisomers with the *ancat* isomers predominating (82%) from which 75% of the *S,S*-isomer could be obtained by chromatography.

However, use of a chiral boron reagent to form the enolate allows for face selectivity even when the heteroatom is absent from the side chain with reasonable ee's (77−85%).[709]

The addition of an oxazoline derivative to an imine provides a route to β-amino acid derivatives (Scheme 171).[710]

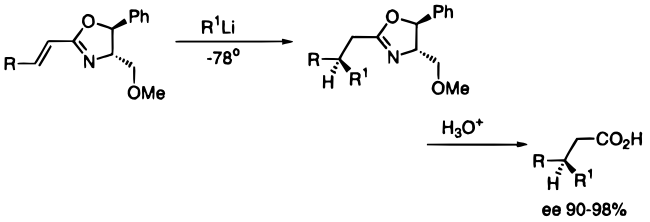
Scheme 171



4. Conjugate Additions

Oxazolines provide a useful vehicle for the introduction of groups by a conjugate addition (Scheme 172).[561,682,705,706,711−715]

Scheme 172

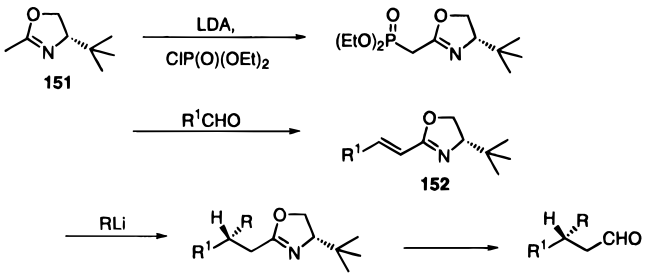


The Michael addition of a stabilized carbanion to these conjugated oxazolines does not provide high degrees of asymmetric induction.[617,687]

Oxazoline **151**, a nonchelating auxiliary, has shown to provide excellent stereoselection in aliphatic systems; the *tert*-butyl substituent provides the best selectivity.[617] Metalation of **151** with LDA and quenching with diethyl chlorophosphonate gave the Horner−Wadsworth−Emmons reagent, which was then reacted with aldehydes to give the alkenes, **152**, with excellent *trans* selectivity. The conjugate addition of various alkyllithiums to **152** then provide

alkylated products, that were then converted to aldehydes with high ee's (Scheme 173).[716]

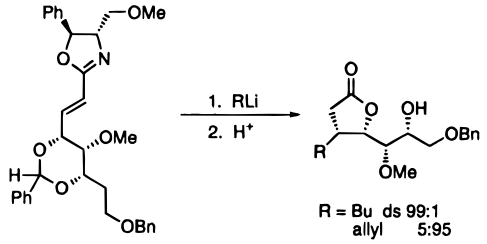
Scheme 173



Oxazolines that do not have a side chain that can form a complex with a metal often do not provide sufficient reactivity to allow for useful employment, particularly when attached to cyclic systems.[717] This problem can be circumvented by acylation of the oxazoline nitrogen.[714,718]

The use of conjugate additions has been exploited in the preparation of lactones (Scheme 174).[706,719,720]

Scheme 174

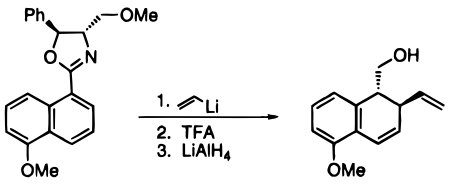


The conjugate addition results in the formation of an azaenolate that can be used in subsequent reactions, such as alkylations. This provides methodology to 2,3-substituted propionic acids.[687]

a. Aromatic-Derived Systems

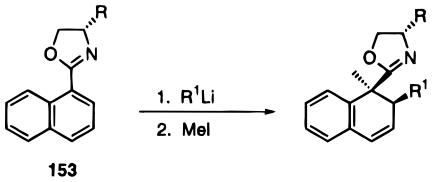
In addition to biaryl coupling reactions (section E.5.a), oxazolines can be used to promote nucleophilic additions of alkyllithiums to naphthyl systems.[721−728] The resultant anion can be quenched by a variety of electrophiles to provide the *ancat* product, although careful control of the conditions can result in the *syncat* isomer when protonation is performed with a strong acid.[729−731] The *trans* addition is adequately illustrated as part of a synthesis of the AB-ring system of aklavinone (Scheme 175).[732]

Scheme 175



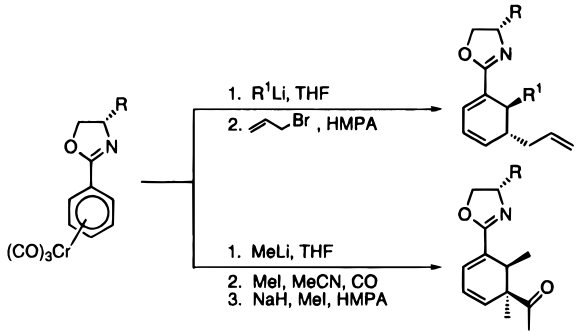
The reaction of the resultant anion to afford the *trans* product has been exploited in a wide variety of polycyclic ring syntheses.[733−735] The steric bulk of the group does play a large role in the determination of the diastereoselectivity; thus, the *tert*-butyl derivative of **153** provided the highest selectivity (Scheme 176).[736]

Scheme 176



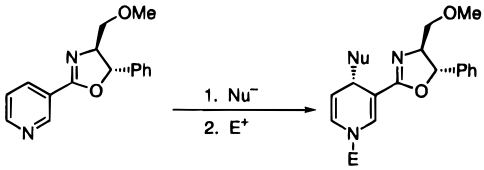
Nucleophilic additions to monocyclic aromatic systems can be accomplished by formation of a tricarbonylchromium complex (Scheme 177).[737−740]

Scheme 177



With heterocyclic analogs, such as pyridyl, that undergo nucleophilic additions more readily than phenyl, the transition metal complex is not required (Scheme 178).[741−746]

Scheme 178



The methods described above can also be augmented by use of the oxazoline unit to direct lithiation reactions in the precursor aromatic system and the subsequent reactions with electrophiles.

5. Directed Metalations

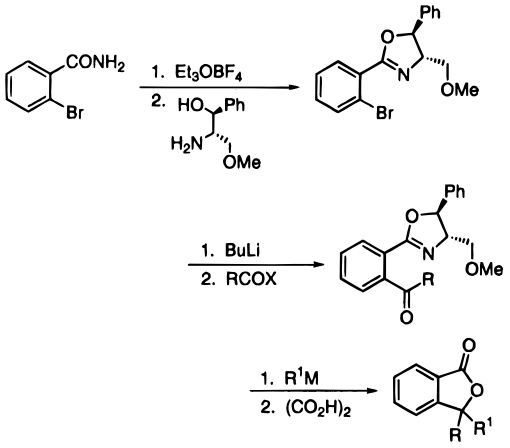
Oxazolines have found widespread use to control metalation reactions.[562] In many cases, a chiral amino alcohol is not required to accomplish this regiochemical task.[747−758] Indeed, many examples of this directed *ortho*-lithiation has been reported with oxazolines derived from 2-amino-2-methyl-1-propanol.[562,759−761] However, the presence of the chiral auxiliary then allows for diastereoselection in subsequent transformations as illustrated by the reaction of Scheme 179. Grignard reagents tend to give higher diastereoselectivity in the addition reaction than organolithium compounds.[687,762−764]

In the absence of *ortho*-hydrogens, benzylic deprotonation may occur.[765]

Aromatic systems, other than phenyl, can also be employed in this type of approach, such as pyridines—the oxazoline group can be used to direct nucleophilic attack at the 4-position to provide 1,4-dihydropyridines.[741−743,766−773]

Highly diastereoselective directed lithiations via chiral oxazoline-substituted ferrocene systems have

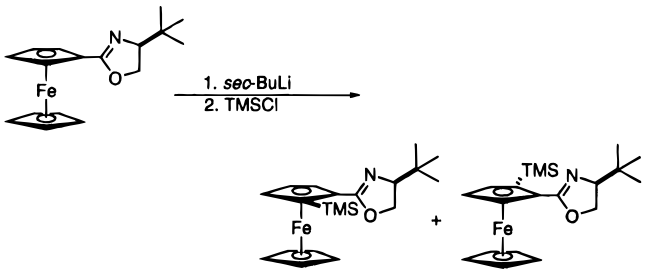
Scheme 179



where $R^1M = R^1MgX$, R^1Li, or $LiB(Bu\text{-}s)_3H$

been reported, where the highest selectivity is observed when the oxazoline is derived from *tert*-leucine (Scheme 180).[602]

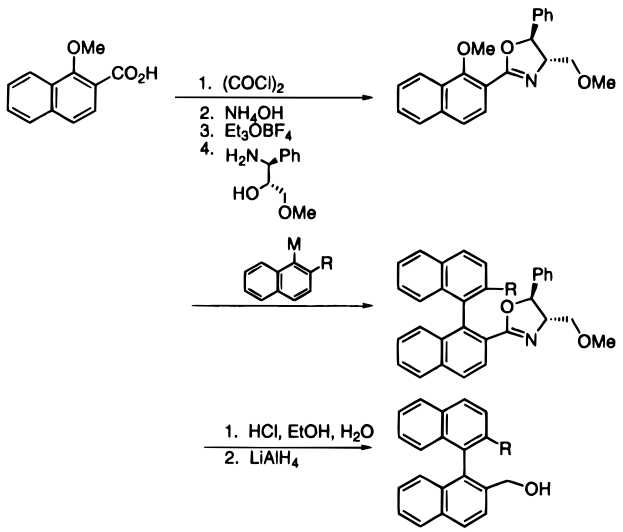
Scheme 180



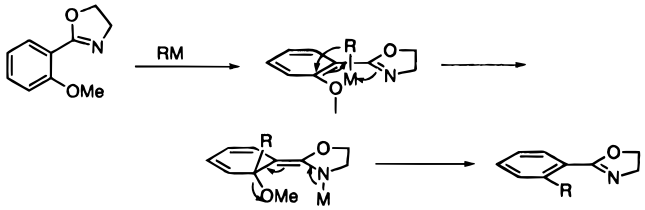
a. Aromatic Coupling Reactions

Aromatic oxazolines allow for coupling reactions when an α-alkoxy group is present. In addition to Grignard and organolithium reagents, aryl organometallic compounds can participate to provide biaryl systems; oxazolines not only provide the means for reaction to occur, but also allow for stereogenic centers to be incorporated into the substrate; this is illustrated by the preparation of binaphthyls (Scheme 181).[759−761,774−776] The mechanism involves a migration of the incoming nucleophilic species (Scheme 182).

Scheme 181



Scheme 182

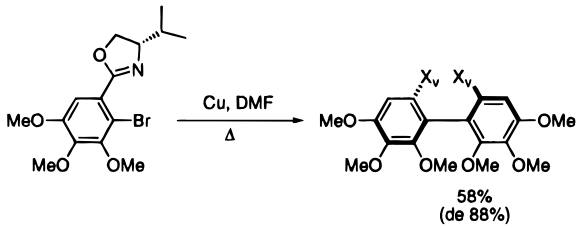


It is also possible to use an achiral oxazoline with the alkoxide containing a stereogenic center.[776]

The two aromatic units that are coupled can be highly functionalized, as illustrated by many syntheses in the alkaloid area,[616,775,777−781] as well as other classes of compounds of pharmacological importance.[592,782−785] The best results are observed with electron-rich aryl systems.[396,786]

Oxazolines can be used as chiral auxiliaries for more traditional Ullmann couplings (Scheme 183).[787]

Scheme 183

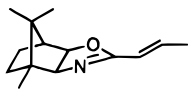


6. Pericyclic Reactions

Oxazolines have proven useful auxiliaries in a number of pericyclic reactions.

a. Diels–Alder Reaction

A camphor-based oxazoline **154** has been used as a dienophile in Diels−Alder reactions. The usage of triflic anhydride, rather than a Lewis acid, provides the imino ether salt that allows reaction at low temperature.[788−790]



154

b. Claisen Rearrangement

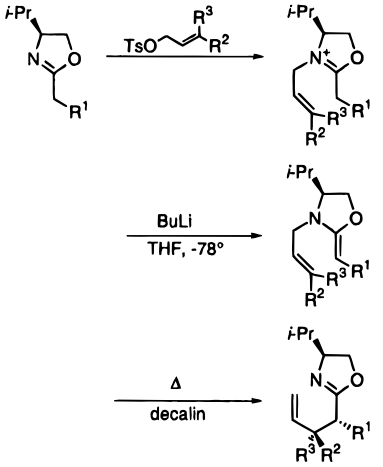
Oxazolines provide a chiral template for an aza-Claisen rearrangement (Scheme 184). The selectivity, however, is only moderate (de's 72−74%).[791−795]

c. Wittig Rearrangement

As an oxazoline can stabilize a carbanion and also contain stereogenic centers, it is a useful moiety for a number of reactions, including the [2,3] Wittig rearrangement.[796−803]

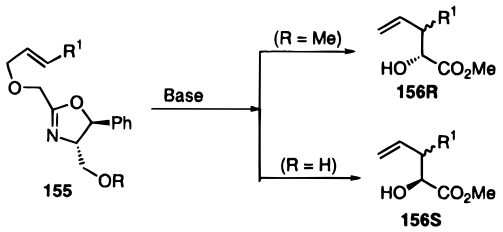
The Wittig rearrangement has a number of variables that can determine its outcome.[5] Oxazolines have been used to stabilize the intermediate carbanion. In this case, the metal counterion has an important role in the determination of the product stereochemistry. With the methyl ether (**155**, R =

Scheme 184



Me) and a lithium counterion, the ester **156** was formed as the *R*-isomer (**156R**) with an ee of 38−78%. With the alcohol (**155**, R = OH) and a potassium counterion, the stereochemical outcome was reversed to provide the *S*-product. The addition of 18-crown-6, however, reverted the product to the *R*-configuration (Scheme 185).[796,797,804]

Scheme 185



d. Ene Reaction

Reaction of singlet oxygen with an α,β-unsaturated oxazoline that contains a stereogenic center gave a 1:1 mixture of diastereoisomers.[805,806]

7. Other Reactions

This section contains reactions that do not conveniently fall into any major category. Some reactions have been covered in other sections, such as the preparation of oxazinones from oxazolines (section C.2).

a. Other Electrophiles

In addition to alkylations and aldol-type reactions, the anions derived from oxazolines react with a number of different electrophiles. Epoxides allow for the preparation of lactones as illustrated in Scheme 186; a trimethylsiloxy alkyl halide can also be used as an oxygen heterocycle surrogate.[807,808]

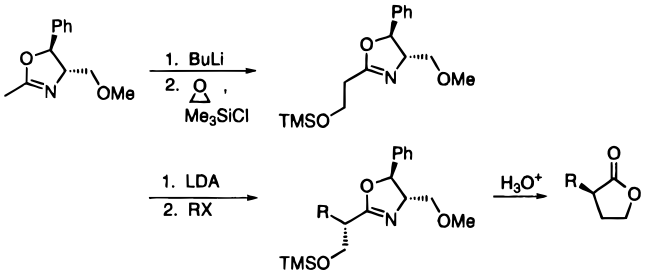
b. Thiooxazolines

These compounds have been used to prepare thiiranes as outlined in Scheme 187. Although the chemical yields were acceptable, ee's were low (19−32%).[809,810]

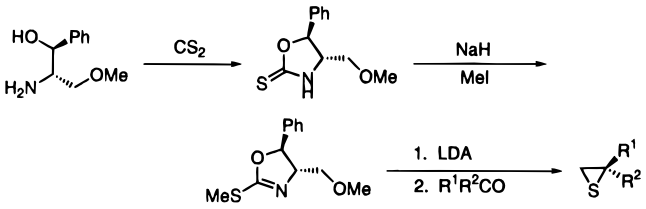
c. As Ligands

The oxazoline **157** (R = Et) has been employed as a chiral ligand with lithium aluminum hydride for

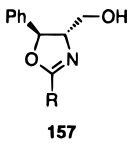
Scheme 186



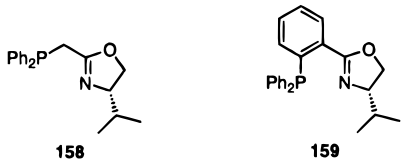
Scheme 187



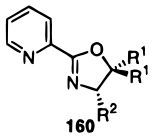
the reduction of carbonyl compounds; ee's were moderate at best (4−65%).[233,234] With Grignard reagents, **157** (R = Me), and the *O*-methyl ether derivative, gave very low degrees of induction for reaction with ketones.[235] Low selectivity was also seen for cuprate additions to conjugated enones in the presence of the ligand.[811] The ligand system can be used to bring about enantioselective additions of diethylzinc to aromatic aldehydes (ee's 25−67%).[812]



The use of bis(oxazolines) (section E.9) has led to the development of the ligands **158** and **159** for the allylic substitution of allylic acetates.[813−815] The sulfur analogs of these ligands have been used in similar applications.[816]



The pyridine-substituted oxazolines **160** have been used to differentiate hydroxy groups in 1,2-diols for bismuth-promoted phenylation reactions, but the enantioselectivity was not high (<30%).[817] Hydro-



silylation of acetophenone with the same chiral ligand on rhodium gave high selectivity (62−89% ee).[818]

8. Removal of the Auxiliary Unit

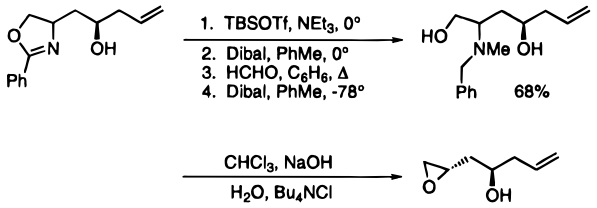
The oxazoline ring system is stable to a wide range of reaction conditions.[396,819] If no labile functional

groups are present within the substrate, simple acid or base hydrolysis of the heterocycle provides the carboxylic acid derivative.[788,820−822]

The conversion of an oxazoline to an aldehyde can be accomplished through formation of a quaternary salt followed by reduction with sodium borohydride and acid hydrolysis;[562] a variation provides chloromethyl compounds rather than aldehydes.[823] If the quaternization is performed with chloromethyl methyl ether (MOMCl) or trimethylsilyl ethoxymethyl chloride (SEMCl), reduction with diisobutylaluminum hydride allows aryloxazolines to be converted to alcohols.[824]

Oxazolines can be transformed to nitriles by reaction with phosphorus oxychloride.[825] These heterocycles can also be converted to epoxides (Scheme 188);[826,827] as the reverse reaction is also available

Scheme 188



(section B.1.d), this provides the potential for protection of the reactive, strained epoxide ring as an oxazoline.

Oxazolines also provide a wide variety of transformations that are not directly related to their usage as chiral auxiliaries, such as the conversion to other heterocyclic systems; these reactions have not been included in this review as they have recently been discussed elsewhere.[396]

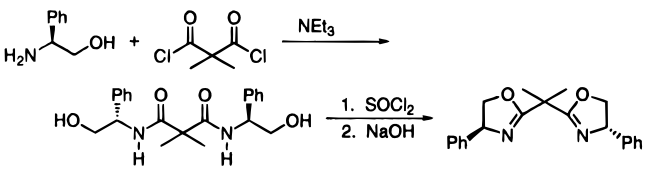
9. Bis(oxazolines)

This aspect of oxazoline chemistry has been reviewed.[828,829]

a. Preparation

Bis(oxazolines) serve as versatile ligands for homogeneous transition metal catalyst systems.[830−832] The 4,4′-bis(oxazoline) systems derived from the amino alcohols of *tert*-leucine, phenylglycine, phenylalanine, alanine, and valine, in addition to the *tert*-leucine derivatives of CMe_2Ph and $CMePh_2$, have all been reported (Scheme 189). The bridge between the

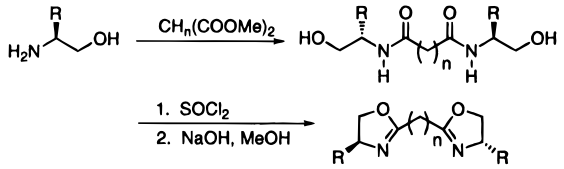
Scheme 189



two oxazolines is derived from oxalyl chloride, malonyl chloride, methyl malonyl chloride, or dimethyl malonyl chloride.[833] Bis(oxazoline) ligand systems containing R = Me, Et, or CH_2OH in the 4-position have also been developed.[834]

Alternate synthetic approaches to bis(oxazolines) have also been pursued.[835,836] The general approach involves reaction of the amino alcohol with dimethyl oxalate or dimethyl malonate, chlorination of the resultant amido alcohol, and finally base-catalyzed cyclization to the oxazoline (Scheme 190).

Scheme 190

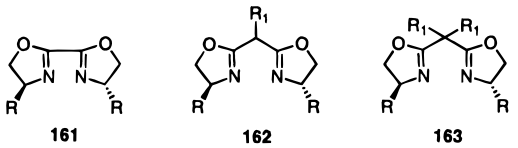


b. Ligands

There are already several reviews on oxazolines.[396,561,562] Our focus in this section is on the use of bis(oxazolines) as chiral ligands in catalysis.

The design of catalytic, asymmetric reactions that proceed with high enantioselectivity is an important goal in chemical synthesis.[837,838] In recent years, chiral oxazoline ligands have been employed in metal-catalyzed asymmetric reactions.[396,813,828,830−832,834,836,839−845] Such ligands are attractive as a consequence of their topography and ease of synthesis from readily available chiral amino alcohols.

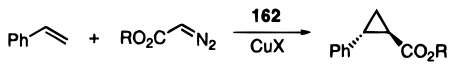
The strong affinity of the oxazoline nitrogen for various metals accounts for the ready formation of bidentate coordination complexes observed for bis(oxazolines). The following bis(oxazolines) have been used most frequently.



161 **162** **163**

Asymmetric cyclopropanations have been achieved with high enantioselectivity as well as *trans* selectivity. Ligands of type **162** have been employed in the enantioselective *trans* propanation of styrene (Scheme 191).[834,846] Best results are obtained when the R

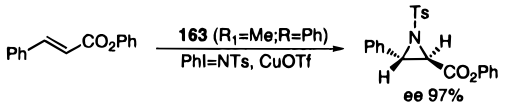
Scheme 191



group is *tert*-butyl. Similar results have been obtained with other asymmetric cyclopropanation reactions.[830,831,834,846−850]

It has been demonstrated that copper complexes of bis(oxazolines) type **163** (R_1 = Me; R = Ph) are highly effective catalysts for aziridation of olefins affording both aziridines and α-amino-β-hydroxy esters in good yield and enantioselectivity (Scheme 192).[832,841]

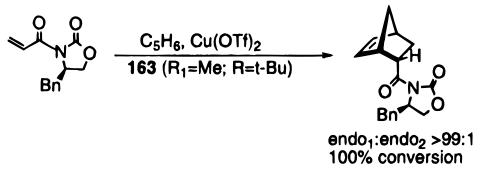
Scheme 192



The combination of the ligand **163** (R_1 = Me; R = Ph) with a Lewis acid catalyst in a enantioselective

Diels−Alder cycloaddition between cyclopentadiene and acryloyloxazolidinone affords the *endo* adduct selectively (99:1) (Scheme 193).[833,851] Copper triflate

Scheme 193

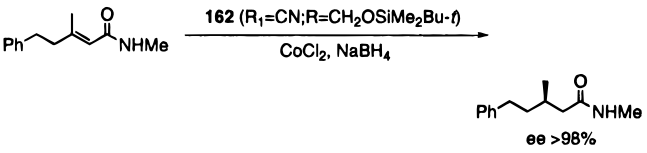


has been used as a Lewis acid catalyst in the Diels−Alder cycloaddition.[840] High *endo* selectivity was obtained with the ligand **163** (R_1 = Me; R = *t*-Bu).

The catalyst reactivity is dependent upon the metal counterion; the reaction rate decreases in the series $SbF_6^- > PF_6^- > OTf^- > BF_4^-$.[842]

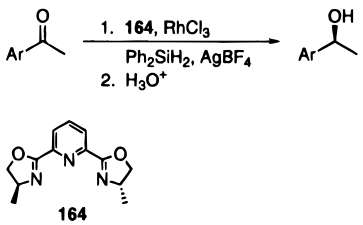
The utility of ligand **161** has also been extended to the iridium-catalyzed transfer hydrogenation of ketones. The valinol-derived ligand, **161** (R = *i*-Pr) was found to give excellent selectivity.[848,849] The enantioselective reduction of α,β-unsaturated carboxides was achieved with sodium borohydride and ligand type **162** (R_1 = CN; R = CH_2OSiMe_2*t*-Bu) (Scheme 194).[839]

Scheme 194



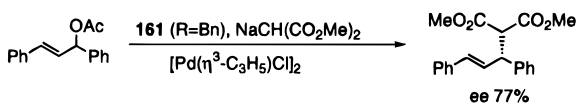
The pyridine-derived bis(oxazoline) derivatives, pybox **164**, as well as related derivatives, allow for the hydrosilylation of carbonyl compounds (Scheme 195).[836,852−856]

Scheme 195



The palladium-catalyzed allylic substitution with ligands **161** and **163** has also been described, and high enantioselectivities were obtained (Scheme 196).[848,849] Ligands **162** have provided the first

Scheme 196



examples for the enantioselective allylmetalation of olefins.[857]

F. Conclusions

The plethora of methods available for the preparation of 1,2-amino alcohols has allowed the chemistry of this useful class of compounds to be exploited for their use as chiral auxiliaries. Although a number of systems have been investigated, the use of 2-oxazolidinones has proven the most successful to date. In addition, a number of ligand systems have been derived from 1,2-amino alcohols; bis(oxazolines) in particular provide for very high enantioselectivities in a number of transformations.

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