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The Synthesis of Vicinal Amino Alcohols

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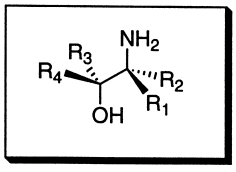
1. Introduction

The vicinal amino alcohol moiety is a common structural component in a vast group of naturally occurring and synthetic molecules. The common name for this group varies, from vicinal amino alcohol, to β-amino alcohol, to 1,2-amino alcohol. Either the amine or the alcohol can be acylated, alkylated or contained within rings. The presence of this moiety and the relative (as well as absolute) stereochemistry are generally important for the biological activity of molecules containing a vicinal amino alcohol. As such, a variety of stereoselective synthetic methods have been developed. This review will focus on methods that have been developed for the synthesis of vicinal amino alcohols.



2. Molecules Containing a Vicinal Amino Alcohol

While the focus of this review is the synthesis of the vicinal amino alcohol moiety, it seems appropriate to provide some background information on the types of molecules containing this grouping of functionality. Three general groups of vicinal amino alcohols have been reported in the literature: (1) naturally occurring molecules containing vicinal amino

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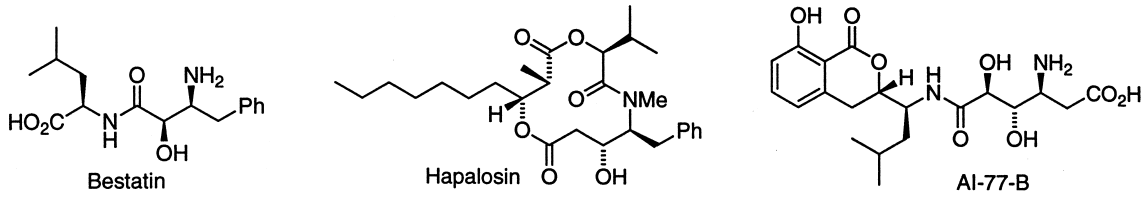


Figure 1. Hydroxyamino acids.

alcohols; (2) synthetic pharmacologically active molecules containing vicinal amino alcohols; (3) catalysts containing vicinal amino alcohols.

2.1. Naturally occurring molecules

Hydroxy amino acids are one of the most common naturally occurring molecules that contain a vicinal amino alcohol. The naturally occurring amino alcohols serine and threonine are both biologically significant as well as being useful members of the chiral pool.[1] Some well-known examples are shown in Fig. 1. Probably the most synthesized of this group is the dipeptide bestatin.[2] Structurally bestatin contains a *syn*-α-hydroxy-β-amino acid. Bestatin is an aminopeptidase inhibitor that exhibits immunomodulatory activity,[3,4] and is used clinically as an adjuvant in cancer chemotherapy.[5] Cyclic depsipeptides are a large group of naturally occurring molecules that commonly contain nonproteogenic amino acids. Hapalosin is an *anti*-β-hydroxy-γ-amino acid containing depsipeptide recently isolated from bluegreen algae.[6] Hapalosin has attracted considerable interest due to its ability to inhibit multidrug resistance (MDR) in drug resistant cancer cells. Several syntheses of hapalosin and analogues have been reported in an effort to understand its mechanism of action.[7–10] Another example of a vicinal amino alcohol containing amino acid is the lactone AI-77-B.[11–15] This compound was isolated from the culture broth of *Bacillus pumilus*. This compound is a structurally unique molecule with gastroprotective activity. AI-77-B is made up of two amino alcohol-containing components. One amino alcohol is part of the aromatic lactone and the other is part of the diacid sidechain. Several syntheses of this compound have been reported.[16–18]

Lipids and lipid-like molecules make up a large class of naturally occurring molecules containing the vicinal amino alcohol moiety (Fig. 2). Possibly, the most synthesized molecule of all amino alcohols is sphingosine.[19] Sphingosine is a compound which was originally considered to be solely a structural biomolecule, but has more recently been found to be important in cell signaling.[20] Structurally sphingosine and analogues are 2-amino-1,3-diols. Frequently the amino group is acylated and the 1-hydroxyl is substituted. A large number of derivatives of sphingosine are known. Sulfobacin B is an interesting sphingosine analog recently isolated.[21] This lipid is a von Willebrand factor receptor antagonist and as such should be a useful antithrombotic agent. Myriocin is one member of a group of structurally similar lipids.[22,23] This densely functionalized amino alcohol contains additional hydroxyl groups as well as a carboxylic acid. These compounds, which are isolated from the thermophilic ascomycete *M. albomyces*, are potent immunostimulatory agents.

A third large group of amino alcohols are the cyclic amino alcohols in which the amino group of the vicinal amino alcohol is contained within a ring (Fig. 3). Some of these compounds are clearly related to the sphingosine lipids, penaresidin A for example.[24] This azetidine amino alcohol was isolated from a marine sponge and is an actomyosin ATPase activator. The pyrrolidine amino alcohol anisomycin was obtained from extracts of a *streptomyces sp*. This cyclic amino alcohol is a potent inhibitor of protein biosynthesis that may be useful as an anticancer agent.[25–28] Febrifugine is a structurally unique amino alcohol in which the amino group is contained within a piperidine ring.[29] This compound is a potential antimalarial agent. The absolute stereochemistry of this compound was recently revised.[30]

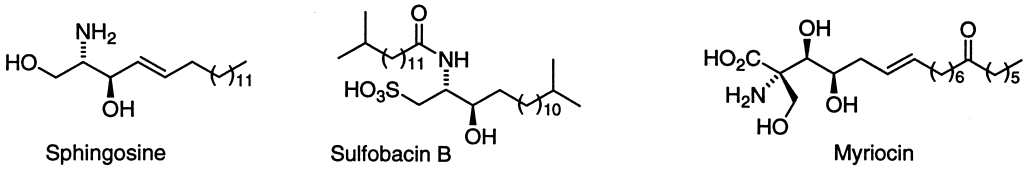


Figure 2. Lipids.

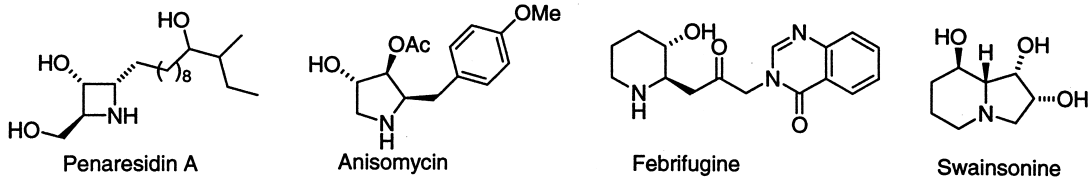


Figure 3. Cyclic amino alcohols.

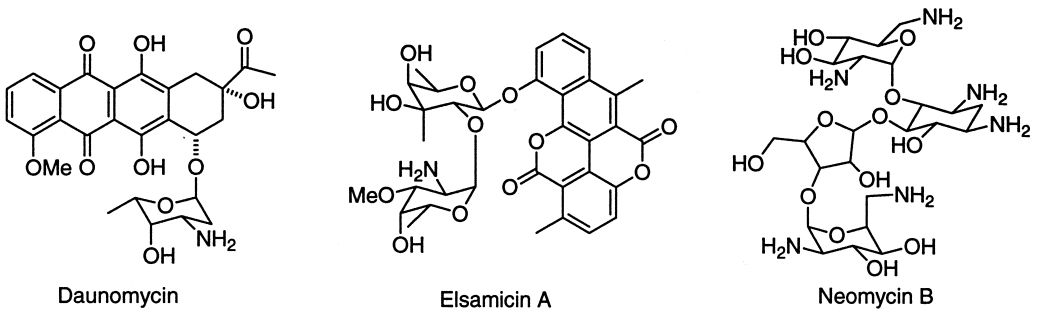


Figure 4. Molecules incorporating sugars which contain a vicinal amino alochol.

Another well known example is swainsonine. Isolated from several sources,[31,32] this compound is an inhibitor of glycoprotein processing.[33]

A fourth class of molecules containing the vicinal amino alcohol moiety are sugars (Fig. 4). Most of the sugars containing an amino alcohol are components of larger molecules either aglycones or other sugars. Daunomycin is one member of a large class of glycosylated anthracycline natural products.[34] The aglycone daunomycinone is glycosylated with the sugar daunosamine to produce daunomycin. As with many glycosylated natural products the sugar portion is essential for biological activity. Elsamicin A is another example of a polycyclic aromatic aglycon linked to an amino sugar.[35–37] Elsamicin A is an antitumor antibiotic in which the presence of the amino sugar, both enhances the biological activity and improves the water solubility of the antibiotic. Neomycin B is one member of a large family of aminoglycoside antibiotics. These compounds are primarily used for the treatment of Gram-negative and Gram-positive bacterial infections.[38]

A final group of naturally occurring vicinal amino alcohols are those which do not readily fit into any of the previous categories (Fig. 5). Cytoxazone is an interesting example in which the amino alcohol moiety is contained within an oxazolidinone ring.[39,40] This compound is reported to be an immunomodulator. Balanol, isolated from the fungus *Verticillium balanoides*, is a structurally interesting amino alcohol in which both the hydroxyl group and amino group are acylated.[41] This azepino amino alcohol has attracted considerable synthetic interest due to its ability to inhibit protein kinase C.[42–44] Aceropterine is a structurally unique alkaloid from the Caribbean sea plume *Pseudopterogorgia acerosa*. While no biological activity has been reported for this compound, its intriguing macrocyclic structure also contains a vicinal amino alcohol.[45]

A variety of compounds containing the vicinal amino alcohol moiety have been isolated from natural sources. These compounds have a wide range of biological activities. It is the intriguing biological activity as well as the structural complexity of these molecules that have piqued the interest of synthetic chemists and fueled extensive efforts to develop methods for the synthesis of vicinal amino alcohols.

2.2. Synthetic pharmacologically active molecules

A host of synthetic molecules used as drugs or pharmacological agents also contain the vicinal amino alcohol moiety. Often these compounds are analogues of natural products which also contain a vicinal amino alcohol. Among the best known are the hydroxyethylene isostere peptidomimetics.[46] This group of peptide analogues is typified by the HIV protease inhibitor saquinavir, **1**.[47] Recently, the amino alcohol **2** has been reported to selectively interact with RNA.[48] This molecule was discovered in a random screening of commercially available amino alcohols. Molecules such as **2**, which contain the vicinal amino alcohol (as a mixture of diastereomers) are being investigated as anti-HIV agents. The amidine containing molecule **3** is reported to be an inhibitor of nitric oxide synthetase (NOS) and has therapeutic implications for the treatment of a wide range of disease states (Fig. 6).[49]

The presence of the vicinal amino alcohol moiety in these pharmacologically active molecules is essential for their biological activity. The need to prepare these compounds as well as analogues has dramatically increased the

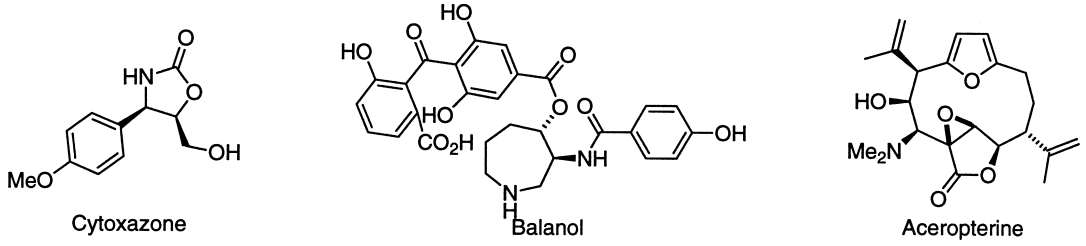


Figure 5. Miscellaneous vicinal amino alcohols.

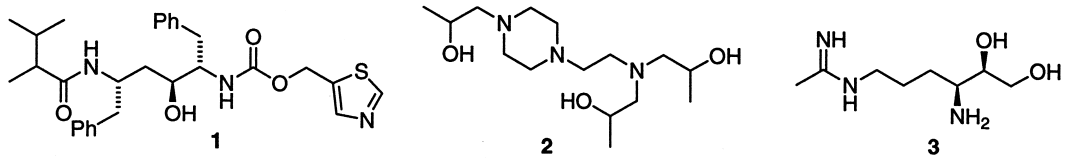


Figure 6. Synthetic molecules containing vicinal amino alcohols.

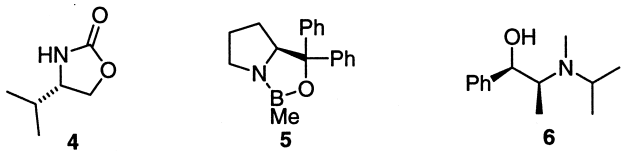


Figure 7. Amino alcohols used as chiral auxiliaries.

importance of the development of methods for the synthesis of vicinal amino alcohols.

2.3. Ligands and chiral auxiliaries

A number of chiral reagents utilize enantiomerically pure amino alcohols as ligands or chiral auxiliaries (Fig. 7).[50,51] The best known are the 'Evans auxiliaries' (e.g. **4**).[52] These amino alcohol derived oxazolidinones have been used for a host of reactions ranging from aldol condensations to Diels–Alder reactions. The oxaborolidines (**5**) derived from proline have been extensively used for the asymmetric reductions of carbonyl compounds.[53] The ephedrine derivative **6** has been used as a chiral proton quench to deracemize an enolate.[54]

Most of the amino alcohols used as ligands or chiral auxiliaries are derived from natural sources such as amino acids. The amino acids are generally modified to improve their chelating ability or enhance their steric blocking effects.

From the listing above, it becomes quite obvious why synthetic organic chemists have devoted significant efforts to the development of methods for the synthesis of vicinal amino alcohols. This listing is by no means comprehensive, and many more examples exist in the literature. Nonetheless it does show the breadth and scope of molecular architectures that contain the vicinal amino alcohol moiety.

3. Synthetic Routes to Vicinal Amino Alcohols

Just as there are many examples of molecules containing the vicinal amino alcohol moiety, there are an equally large number of synthetic routes to these molecules (Fig. 8). We cannot be comprehensive in this review and list every method, but will show several examples that typify the main disconnections used to prepare vicinal amino alcohols. Conceptually one can divide these syntheses into four different classes: (1) functional group manipulation of a molecule containing both heteroatoms; (2) addition of one heteroatom to a molecule which already contains one heteroatom; (3) addition of both heteroatoms to a molecule which has neither; (4) coupling of two molecules, each of which has one heteroatom.

3.1. Functional group manipulation

One of the most commonly used methods for the synthesis of vicinal amino alcohols is the functional group

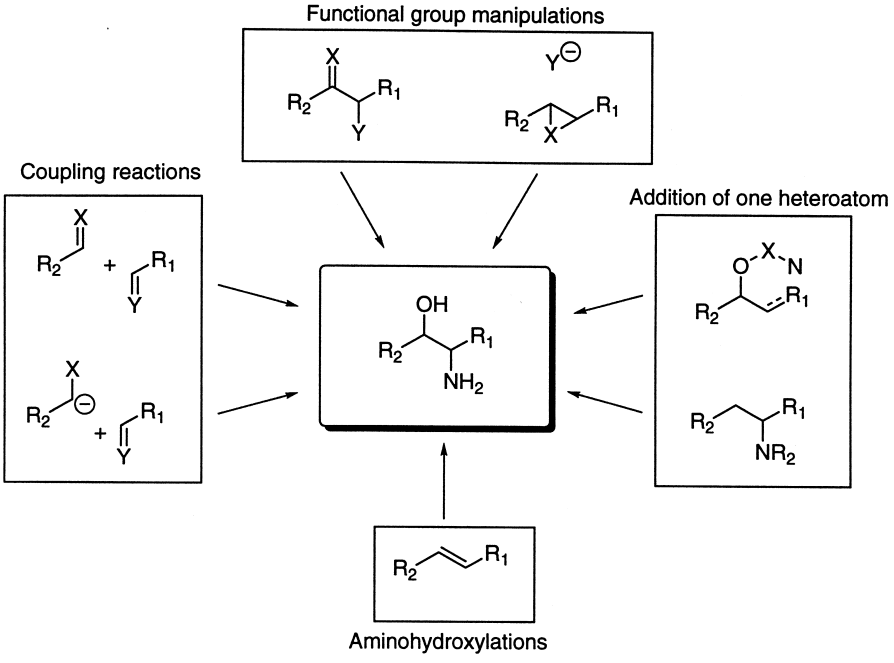
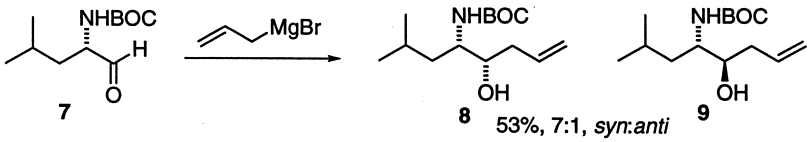


Figure 8. General disconnections for the synthesis of vicinal amino alcohols.



Scheme 1.

manipulation of molecules containing two heteroatoms on vicinal carbons. There are two general versions of this disconnection. One variant of this disconnection utilizes the functional group modification of an imine or carbonyl group, through reduction or nucleophilic addition. The popularity of this route to vicinal amino alcohols stems from the large body of work on stereospecific addition of nucleophiles to carbonyl compounds. A second manner in which functional group manipulation is carried out is to open an epoxide or aziridine with a heteronucleophile (nitrogen or oxygen) to provide the amino alcohol.

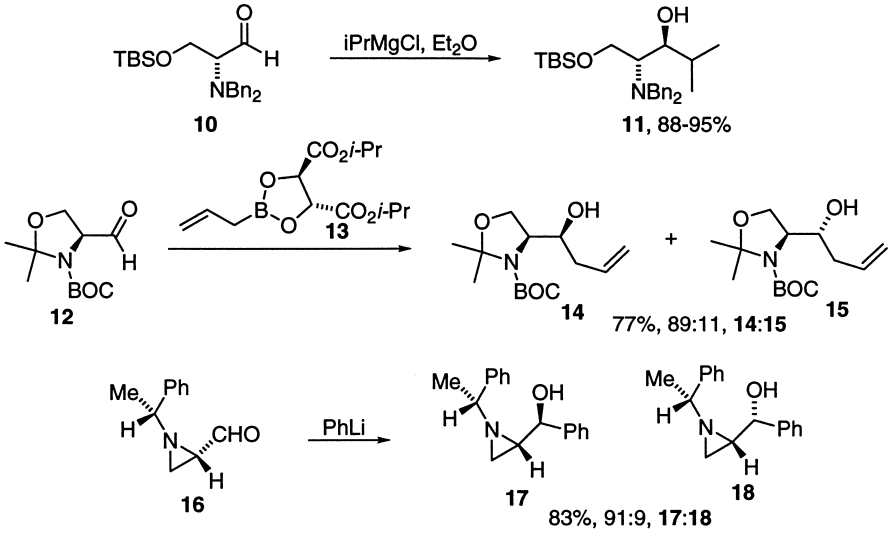
3.1.1. Addition of a nucleophile to an α-amino carbonyl. The most common variant of functional group manipulation is the addition of a nucleophile to an α-amino carbonyl compound. The generation of high levels of diastereoselectivity and the stability of the α-amino carbonyl compound have sometimes been problems with this method. For example, the addition of allyl magnesium bromide to the α-amino aldehyde **7** produces only a moderate yield (50–60%) of a 7:1 mixture of *syn*- and *anti*-isomers **8** and **9** (Scheme 1).[55]

The development of a variety of protected α-amino aldehydes have made this reaction considerably more tractable. The two most commonly used are *N*,*N*-dibenzyl α-amino aldehydes[56,57] (e.g. **10**) and Garner's aldehyde (**12**).[58] Both of these types of α-amino carbonyl compounds are chemically and configurationally more stable than those containing a free N–H on the amine (Scheme 2).

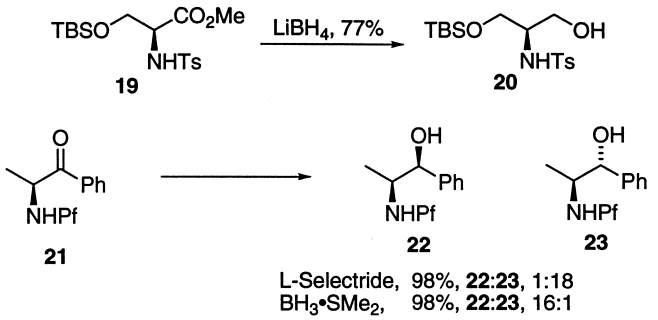
In a recent example, the addition of a Grignard reagent to aldehyde **10** provides the *anti* product **11** in 88–95% yield.[59] The diastereoselectivity of this addition reaction follows the Felkin–Anh model.[60] We should note that the aldehyde **10** is not particularly stable and is either used crude or prepared in situ. While the diastereoselectivity in such additions is usually very high, removal of the benzyl groups can sometimes be problematic. The addition of chiral allylboronates to Garner's aldehyde (**12**) provides an exceptionally nice route to either the *syn*- or *anti*-amino alcohols.[61] In the matched case using (*R*,*R*)-allylboronate **13**, a 89:11 mixture of **14** and **15** are obtained in 77% yield. For the mismatched case using the (*S*,*S*)-allylboronate a 10:90 mixture of **14** and **15** was obtained in 84% yield. Other types of di-*N*-protected α-amino aldehydes can be used in this general reaction. For example, the *N*-alkyl aziridine aldehyde **16** provides a 91:9 mixture of amino alcohols **17** and **18** in excellent yield.[62] A key requirement for stereospecificity of most additions to α-amino aldehydes is that there are no acidic hydrogens on the nitrogen.

The reduction of α-amino carbonyl compounds is a well used route to vicinal amino alcohols. Of course, aldehydes and carboxylic acid derivatives can be readily reduced to the alcohol providing the vicinal amino alcohol, however no stereochemistry is generated in such a reaction. The use of chiral α-amino acids is a common route to chiral vicinal amino alcohols of this nature.[1] For example, the reduction of the serine ester **19** with $LiBH_4$ provides amino alcohol **20** in good yield (Scheme 3).[63]

Of more interest are the reductions of α-amino ketones. Several stereoselective examples of such reductions have been reported. In a particularly nice example, an α-*N*-phenylfluorenyl ketone can be stereodivergently reduced to either the *syn*- or *anti*-amino alcohols.[64] Upon treatment of **21** with $BH_3{\cdot}SMe_2$, the *anti*-isomer **23** is obtained as the



Scheme 2.



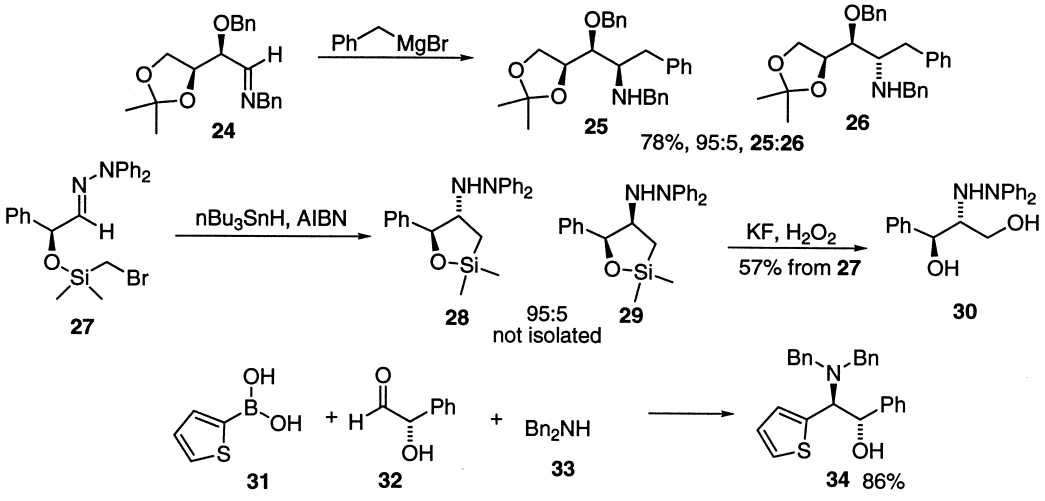
Scheme 3.

predominant product. The use of L-selectride provides the *syn*-isomer **22**. It is not clear how general this particular reaction is but other examples of similar reductions have been reported which generally provide the *anti*-isomer.[65,9]

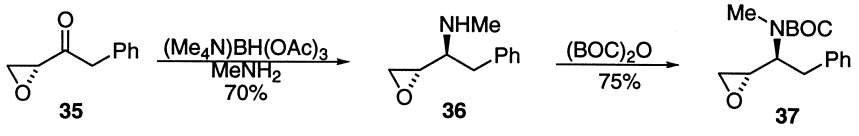
3.1.2. Addition of a nucleophile to an α-hydroxy imine. The corresponding reactions between a protected α-hydroxy imine and a nucleophile are not as well represented due to the relative instability of the imines. One example in which a protected α-hydroxy imine is used directly is shown in Scheme 4.[66] Imine **24** is treated with an organometallic reagent to provide the *syn*-isomer **25** as the major product. Yields for this reaction are generally good (37–78%) (Scheme 4).

A number of nice methods to get around the instability of the imine have been reported. One of the more useful imine derivatives is utilized in the conversion of **27** to **30**. The use of hydrazone derivatives as imine surrogates is a common technique in the synthesis of amino alcohols. The diphenyl hydrazone is a stable isolable imine derivative that can undergo the same types of reactions as an imine. In the very interesting example shown in Scheme 4, an intramolecular addition of a silylmethyl radical to the hydrazone provides the cyclic amino alcohol **28** as the major isomer.[67] Oxidative removal of the silicon provides **30**. This reaction proceeds with good stereoselectivity (dependent on the substitution of the hydrazone) and excellent yields. While this is not a general approach to the synthesis of vicinal amino alcohols, it does utilize a common imine surrogate. A different approach to the addition of nucleophiles to imines is the in situ generation of the imine followed by nucleophilic addition.[68] In a very nice and seemingly general application, an α-hydroxy aldehyde (**32**) is condensed with an amine (**33**) followed by boronic acid derivative (**31**), which adds to the imine to provide the amino alcohol **34**. The only limitation of this method is the necessity of using an aryl or olefinic boronic acid derivatives. The stereoselectivity is excellent providing only the *anti*-amino alcohol in yields ranging from 39–87%.

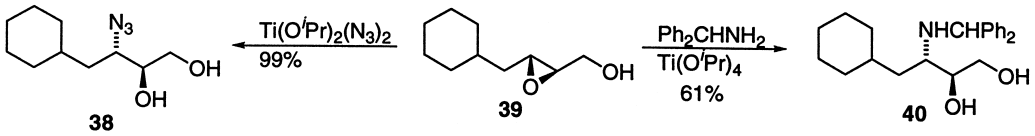
The reduction of α-hydroxy imines has seen relatively little work with isolated imines. The primary examples are those in which an α-hydroxyketone is converted to the amino



Scheme 4.



Scheme 5.



Scheme 6.

alcohol via a reductive amination. An interesting example is the reductive amination of the keto epoxide **35** used for a synthesis of hapalosin.[7] Reaction of **35** with methylamine and $(Me_4N)BH(OAc)_3$ provides the unstable amino epoxide **36**. In situ conversion of the free amine to the BOC derivative provides **37** (Scheme 5).

This disconnection for the synthesis of vicinal amino alcohols is a general and widely used method. Limitations do exist, especially in the stability of some of the precursors. However, the wide use and experience of organic chemists with this type of chemistry makes it one of the most popular routes to amino alcohols.

3.1.3. Ring opening reactions of epoxides. The ring opening reactions of epoxides to provide vicinal amino alcohols has seen a number of examples in recent years. This is no doubt due to the many methods for the synthesis of optically pure epoxides from olefins. A potential problem with this route to vicinal amino alcohols is the issue of regioselectivity. Either carbon of the epoxide can react with the nucleophile to produce regioisomeric amino alcohols (Scheme 6).

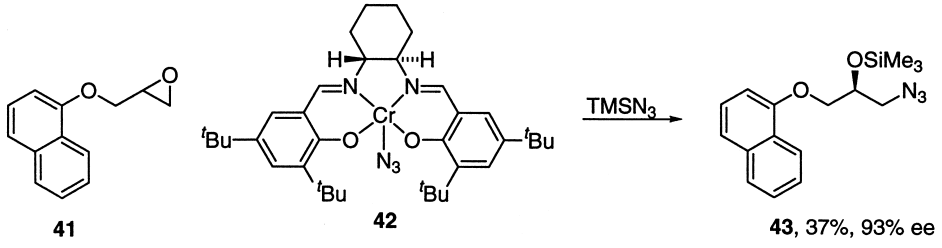
Amines and azide ion can readily open epoxides to form a vicinal amino alcohol or azido alcohol.[69–75] Azido alcohols are readily converted to the amino alcohols.[76] An example of this reaction is shown in Scheme 6.[77] Epoxide **39** is prepared from the corresponding allylic alcohol via a Katsuki–Sharpless asymmetric epoxidation. Treatment of **39** with benzhydryl amine provides vicinal amino alcohol **40** in good yield. Reaction of similarly substituted epoxides generally provides the regiochemistry shown. Similarly, reaction with azide provides the azido alcohol **38** in near quantitative yield. This is a very general transformation with many examples being reported in the literature. The relative stereochemistry of the resulting amino alcohol is controlled by the epoxide stereochemistry.

The chemistry shown above becomes less appealing if the enantiomerically pure epoxide is not readily available. Indeed, there are several types of epoxides which are not readily prepared by the standard methods. Jacobsen has addressed this via a kinetic resolution of racemic terminal epoxides. Using the chiral chromium catalyst **42** and a racemic epoxide provides the azido alcohol **43** with excellent enantiomeric purity (Scheme 7).[78]

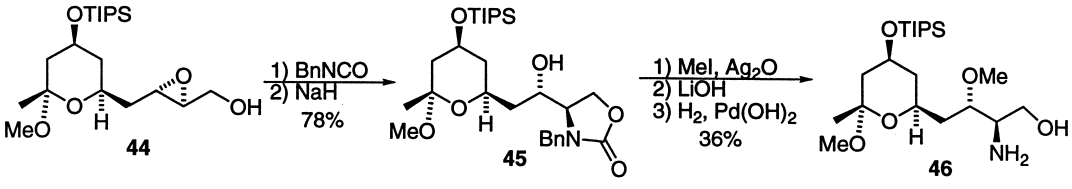
Amides[79] and carbamates also provide useful nucleophiles for epoxide opening.[80,81] In the example shown in Scheme 8, the optically pure allylic alcohol **44** (again from an asymmetric epoxidation) is treated with benzylisocyanate to provide an intermediate carbamate.[82] Amide anion formation is followed by cyclization to oxazolidinone **45**. A small amount of a regioisomeric oxazolidinone is also obtained by acylmigration. Hydrolysis of the oxazolidinone followed by hydrogenation provides the vicinal amino alcohol **46**.

As seen in Scheme 8, the intramolecular opening of an epoxide provides an effective method to control the regiochemistry of ring opening. Amines can also participate in this type of intramolecular ring opening (Scheme 9).[83] Treatment of the epoxyamine **47** with TMS-OTf provides an intermediate silyloxy aziridinium ion **48**. This aziridinium ion can be opened by a nucleophile to provide vicinal amino alcohol **49**.

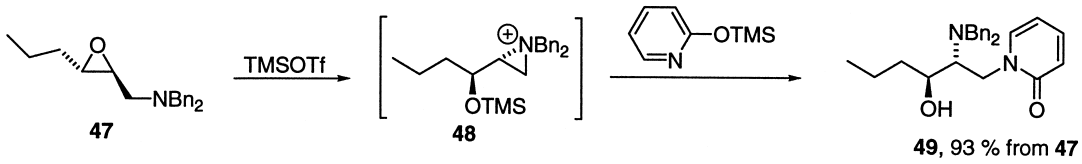
A major advantage of this general route to vicinal amino alcohols is the ready availability of the necessary epoxide. Numerous stereoselective and enantioselective routes to epoxides exist.[84]



Scheme 7.



Scheme 8.



Scheme 9.

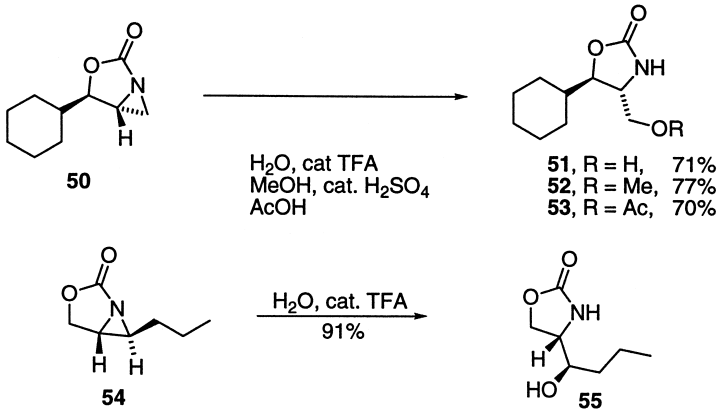
3.1.4. Ring opening reactions of aziridines. The corresponding reactions of aziridines with oxygen nucleophiles have been widely applied to the synthesis of vicinal amino alcohols.[85] Most of the aziridines that are utilized in this reaction are bicyclic and hence somewhat strained. The aziridine ring can be opened with water, alcohols and carboxylic acids.[86–91] As with epoxide opening reactions, the regioselectivity of the ring opening can sometimes be problematic when non-terminal aziridines are used.

We have prepared the very reactive bicyclic aziridines **50** and **54** via an intramolecular acyloxynitrene cyclization. These aziridines can react with a number of oxygen based nucleophiles to provide amino alcohols. Water, methanol and acetic acid have been used in the unsubstituted case to provide amino alcohols **51**, **52** and **53** in generally excellent yields.[92] Substituted bicyclic aziridines also provide the vicinal amino alcohols in excellent yields. For example, in the reaction of **54** with water a single product, **55**, is obtained (Scheme 10).

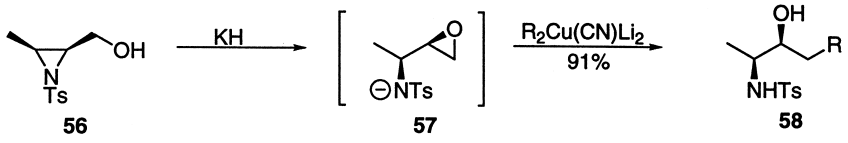
In a similar reaction to that shown in Scheme 9, a Payne-like rearrangement can be carried out with hydroxy aziridines.[93] As an example, the hydroxyaziridine **56** is treated with KH and the resulting alkoxide opens the aziridine to provide epoxy amine intermediate **57**. In a one-pot reaction, this epoxide is then opened with several organocuprate nucleophiles to give the vicinal amino alcohol **58** (Scheme 11).[94]

The intramolecular opening of *N*-acylaziridines with the carbonyl oxygen of the amide has proven to be a useful method for the conversion of an aziridine to a vicinal amino alcohol. In this type of reaction, the acylaziridine is typically treated with some type of acid (usually a Lewis acid) to provide an oxazoline.[95–97] The example shown in Scheme 12 requires no additional acid catalysis, and the rearrangement of **59** to **60** takes place during the acylation reaction.[98] The oxazoline **60** can then be hydrolyzed to the vicinal amino alcohol **61** (Scheme 12).

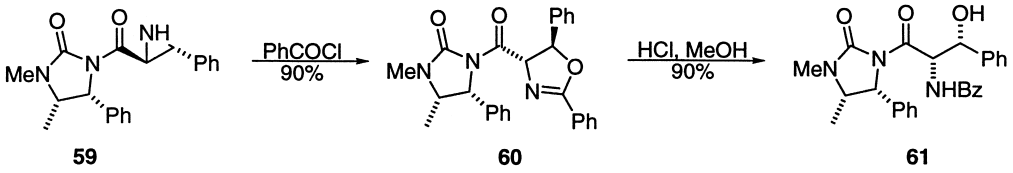
In all of these reactions, the stereochemistry of the



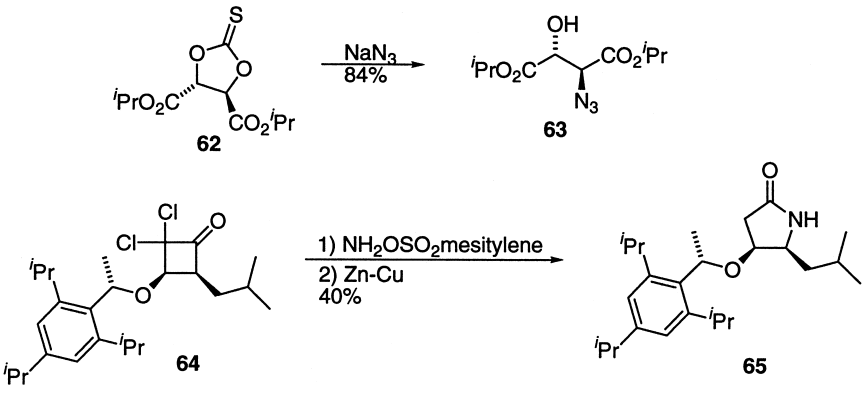
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

resulting amino alcohol is of course dependent upon the stereochemistry of the starting aziridine. A major limitation of this route to vicinal amino alcohols is the relative (to epoxides) dearth of methods to prepare aziridines. The work that we have reported for the stereoselective synthesis of aziridines[2,92] as well as the work of Evans and others[99] for the enantioselective synthesis of aziridines provides some excellent routes to the necessary aziridines.

3.1.5. Miscellaneous reactions. Of course, one can carry out a variety of displacement reactions adjacent to an oxygen or nitrogen to provide the vicinal amino alcohols. A particularly interesting example is the use of thionocarbonates.[100] The thionocarbonate **62** can be obtained in optically pure form from an asymmetric dihydroxylation reaction followed by reaction with thiophosgene. Reaction of **62** with sodium azide provides the azido alcohol **63** in excellent yield. The thionocarbonate is an attractive alternative to cyclic sulfates.

A really interesting approach, which is not a displacement reaction but rather a Beckmann ring expansion, is shown in Scheme 13.[101] The dichlorocyclobutanone **64** is obtained via a 2+2-cycloaddition reaction of dichloroketene and a chiral enol ether. Beckmann rearrangement followed by dehalogenation provides substituted hydroxy lactam **65**. The triisopropylphenethyl ether is removed and the lactam hydrolyzed to provide a synthesis of statine.

A number of routes using functional group manipulation are available to prepare vicinal amino alcohols. Most of these methods rely upon the stereochemical information already contained within the molecule to control the stereochemistry of the new stereocenter. Thus, these methods generally rely upon some other method to ultimately control the stereochemistry of the vicinal amino alcohol.

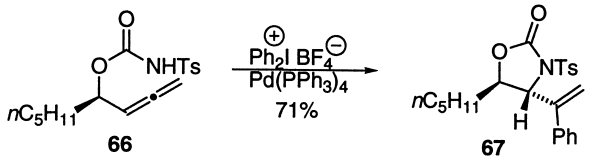
3.2. Addition of one heteroatom

There are a number of methods by which one heteroatom can be added to a molecule already containing a heteroatom. These routes rely upon the stereochemistry of the resident heteroatom to control or direct the stereochemistry of the incoming heteroatom.

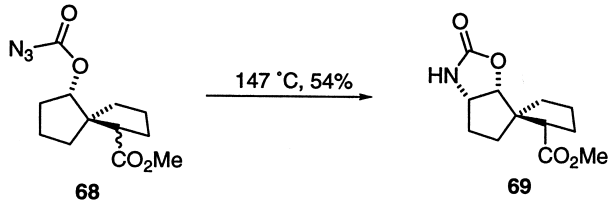
3.2.1. Addition of nitrogen. One method that has been utilized is the intramolecular addition of nitrogen to an electrophilic carbon, typically an olefin which has been activated by an electrophilic reagent. This type of reaction can take many forms.[102–105] A particularly interesting route is the intramolecular cyclization of the allenyl carbamate **66** (Scheme 14). Reaction of **66** with an aryliodonium salt and a palladium catalyst provides oxazolidinone **67**. A limitation of such a method is availability of the aryliodonium species.

The addition of acyloxy nitrenes is an attractive route to prepare similar oxazolidinones. The intramolecular nitrene insertion into a C–H bond is an excellent route to functionalize an aliphatic carbon.[106,107] As shown in Scheme 15, thermolysis of the azidoformate **68** provides the oxazolidinone **69** in 54% yield.[108] A major limitation of such routes is the high reactivity of the nitrenes. A number of side products including addition to olefins as well as nonselective C–H insertion products can be obtained in such reactions.

We have explored the intramolecular addition of an acyloxynitrene to an olefin.[2,92,109] Allylic alcohols (**70**) are readily converted to azidoformates **71** in good yield. Thermolysis of the azidoformate **71** provides bicyclic aziridine **72** in good yield. The diastereoselectivity is somewhat variable; larger groups next to the azidoformate provide excellent (>10:1) levels of diastereoselection, and compound **72** is formed as the only product from **71**.[110] These bicyclic aziridines are generally too reactive for



Scheme 14.



Scheme 15.

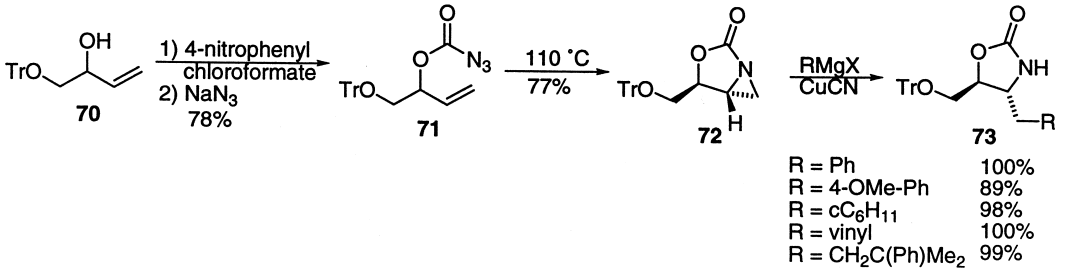
purification, although **72** shows excellent stability and is a crystalline solid. A major advantage of this route to vicinal amino alcohols lies in the reactivity of the bicyclic aziridine **72**. These aziridines can be readily opened with nucleophiles such as organocuprate reagents to provide the oxazolidinones **73** (Scheme 16). Hydrolysis of the oxazolidinones readily provides the corresponding amino alcohol. This method has been used to prepare several analogues of the immunomodulator bestatin from a single bicyclic aziridine.[2] The ready availability of optically pure allylic alcohols makes this an attractive route for the synthesis of natural products as well as for analogue preparation.

A somewhat more limited manner in which to add a nitrogen to a molecule already containing an oxygen is the electrophilic amination of β-alkoxy enolates.[111] In the few examples of this type of reaction a diazocarbonyl compound is used as the electrophilic amine.

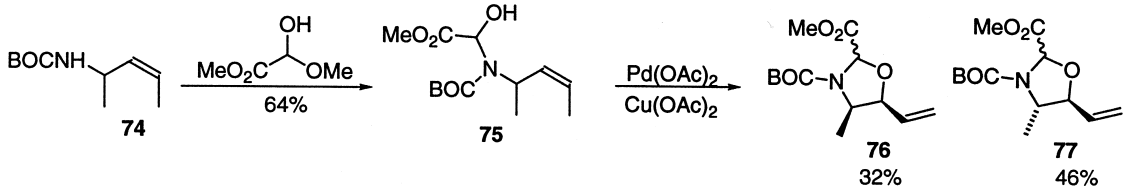
3.2.2. Addition of oxygen. The addition of oxygen to a molecule already containing nitrogen is not a commonly used route to vicinal amino alcohols. One obvious example that has been reported is the addition of an alkoxide to α,β-unsaturated nitro compounds.[112] There are several interesting reactions that provide a nice entry into this pathway to vicinal amino alcohols.

A method analogous to the chemistry shown in Scheme 14 is the intramolecular reaction of a hemiaminal (**75**) with an olefin.[113] The nitrogen counterpart (nitrogen adds to an olefin) has been reported.[105] In this interesting reaction, treatment of **75** with $Pd(OAc)_2$ provides a separable mixture of oxazolidines **76** and **77** in fair yield (Scheme 17). The diastereoselectivity in this very interesting reaction is unfortunately not particularly good. Conversion of **76** or **77** to the N-BOC amino alcohol is accomplished by ester hydrolysis, anodic oxidation and a final hydrolysis to the vicinal amino alcohol in >90% yield.

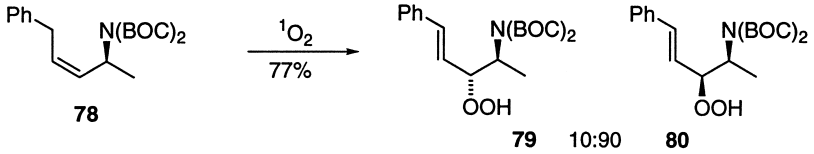
One interesting variant of this disconnection is the reaction of an allylic amine with singlet oxygen, the Schenk reaction.[114,115] It is a directed ene reaction in which the allylic amine directs the formation of the incoming oxygen to provide a hydroperoxide (Scheme 18). The hydroperoxide **79/80** is readily converted to the alcohol with triphenyphosphine. One admirable aspect of this chemistry



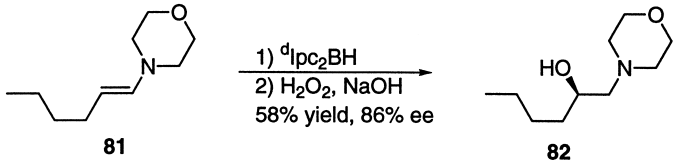
Scheme 16.



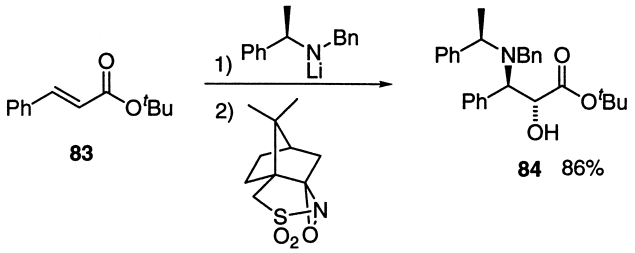
Scheme 17.



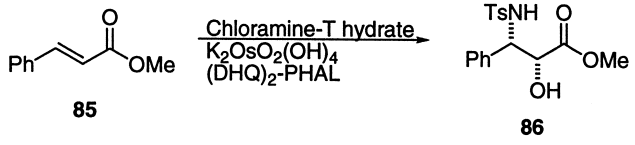
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

is that either relative stereochemistry can be obtained as the major isomer depending upon the nitrogen substitution. One limitation to its use is the regioselectivity of the incoming oxygen; in the example shown, a 23% yield of the regioisomeric hydroperoxide is obtained. Another limitation is that some $A^{1,3}$ strain must be present in the allylic amine in order to obtain good stereocontrol.

The hydroboration of enamines provides another example of the addition of oxygen to a molecule already containing the nitrogen. Both achiral as well as chiral boranes can be utilized in this reaction.[116] In the example shown in Scheme 19, the enamine **81** is treated with ^{d}Ipc$_2$BH to provide the amino alcohol **82** in good chemical yield and moderate enantiomeric excess. Limitations of this method are that the amine must be secondary, and generally the enamines derived from ketones give products of lower enantiomeric excess.

3.3. Aminohydroxylation reactions

The hydroxyamination reaction of an olefin is possibly the most basic route to vicinal amino alcohols. We are defining this type of reaction as one in which both nitrogen and oxygen are added in a single reaction. Two general methods exist for such a transformation. The first is the sequential addition of nitrogen followed by oxygen addition.

A method developed by Davies is the addition of a chiral amide anion to an α,β-unsaturated ester, followed by trapping of the resulting enolate with an oxygen electrophile.[117] This reaction sequence results in excellent diastereoselectivity. Only the *anti*-amino alcohols are obtained. A major limitation of this method for the general synthesis of amino alcohols is that only β-amino-α-hydroxy acids can be prepared. There are however a host of target molecules with that general structure.

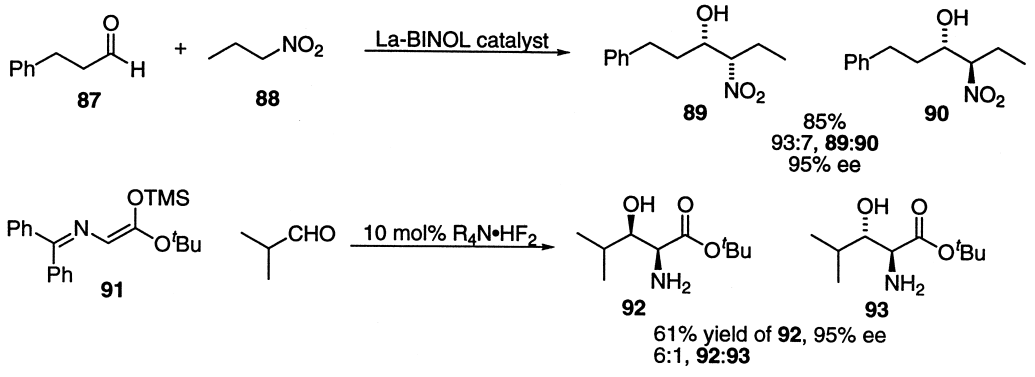
A second route to carry out hydroxyamination is a variant of the well-known metal catalyzed dihydroxylation reaction. Sharpless has utilized a chiral amine ligand to generate asymmetric addition of an amide and OH across a double bond.[118] Amido alcohol **86** is obtained in 64% yield and a 81% initial ee from olefin **85**. A single recrystallization produces material of 99% ee. The yields and enantioselectivity of the aminohydroxylation reaction do not yet equal that reported for the dihydroxylation reaction. Optimal yields and enantioselectivities are observed with α,β-unsaturated esters and phosphonates as substrates. For example, a similar reaction with cyclohexene gives a yield of 48% with 33% ee. Regioselectivity can also be problematic in this reaction.[119]

The methods of Davies (Scheme 20) and Sharpless (Scheme 21) are nicely complementary. Both methods provide α-hydroxy-β-amino esters from the corresponding α,β-unsaturated esters. The Sharpless method is more versatile in that other olefinic substrates can be used.

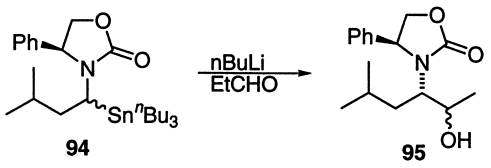
3.4. Coupling reactions

There are two general types of coupling reactions that have been used in the synthesis of vicinal amino alcohols. These are: (1) the reaction of an α-metalloheteroatom with an aldehyde or imine; or (2) a pinacol-type coupling between an aldehyde and imine.

3.4.1. Aldol-type reactions. The generation of an anion α to nitrogen is an actively pursued area of research toward the synthesis of vicinal amino alcohols. Reactions of this class can be divided into two groups, stabilized anions and non-stabilized anions. The most common are those in which the anion is generated adjacent to an anion stabilizing group.[120–122] Two examples are given in Scheme 22. The first is an example of the Henry reaction.[123] In this example the nitro compound **88** reacts with aldehyde **87** in the



Scheme 22.



Scheme 23.

presence of a chiral Lewis acid. This produces primarily the *syn*-amino alcohol **89** in good yield and enantioselectivity. The nitro group can of course be reduced to the amine. The second utilizes a *tert*-butylglycinate-benzophenone Schiff base (**91**).[124] In this example coupling with the aldehyde is catalyzed by a cinchonidine derived difluoride salt ($R_4N{\cdot}HF_2$) to produce the *syn*-amino alcohol **92** as the major product. The yield and enantioselectivity shown in Scheme 22 are typical of those reported with this system.

The generation of non-stabilized anions adjacent to an amine has seen a lot of synthetic activity in recent years. These types of anions are quite useful and react with a variety of electrophiles, although only a few examples have been used for the synthesis of amino alcohols.[125–129] An example is shown in Scheme 23.[130] In this example, transmetallation of the α-amido stannane **94** produces the organolithium reagent which then adds to the aldehyde. While the overall yield of product **95** is good (79%), a 54:46 mixture of diastereomers is obtained. This mixture of diastereomers was converted to the *syn*-isomer by an oxidation reduction sequence.

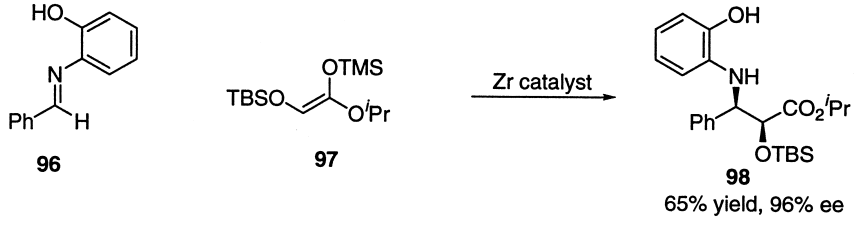
The corresponding formation and reaction of anions α to an oxygen with imines has seen much less attention. No doubt, much of this is due to the paucity of suitable imines and imine equivalents. The reaction of the silyl enol ether **97** with imine **96** exemplifies the difficulty in finding suitable imines.[131] In this synthesis of the taxol side chain, only *N*-aryl imines are used. Most of the examples reported make use of arylaldehydes, only one example of an aliphatic aldehyde is reported (cyclohexane carboxyaldehyde, 44% yield) (Scheme 24).

3.4.2. Pinacol-type reactions. The use of Pinacol-type coupling reactions to form vicinal amino alcohols has great potential, but again few examples have been reported. Most of the reported examples are intramolecular.[132,133] As shown in Scheme 25 the Pinacol-type coupling of the oximino aldehyde **99** proceeds in good yield but only a 7:1 mixture of the *trans*:*cis* amino alcohol **100**:**101** is obtained.[134] Intermolecular examples are quite rare due to the homocoupling of the imines or carbonyl component.[135–140] One typical example is the SmI_2/NiI_2 catalyzed coupling of an arylimine and an aldehyde.[141] Most of these examples utilize only an aryl aldimine. Distereoselectivity, where it exists, is usually favors the *syn*-isomer.

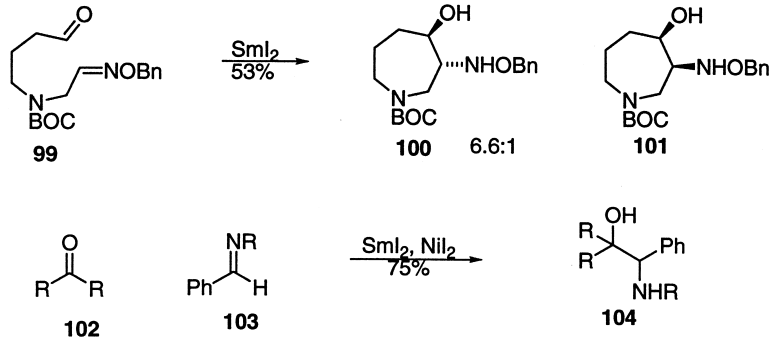
4. Conclusions

Clearly there are numerous routes to the vicinal amino alcohol moiety, only a broad overview of which has been presented in this review. The choice of synthetic route for a given application will vary depending upon substitution, as well as the relative and/or absolute stereochemistry desired. A key theme in many methods presented here is the generation of enantiomerically pure compounds. This is done via enantiomerically pure starting material as well as chiral catalysis.

There are still many challenges in the area of vicinal amino alcohol synthesis. In preparing this review one point was made extremely clear. Limitations exist for all of these methods. For many it is a question of substrate. Many of



Scheme 24.



Scheme 25.

the methods work well for a fairly limited set of molecules. For others it is an issue of stereochemistry, both absolute and relative. While many of the methods shown in this review do, or try to, prepare enantiomerically pure amino alcohols, many methods cannot. In summary the synthesis of vicinal amino alcohols has seen much work in recent years, but much remains to be done.

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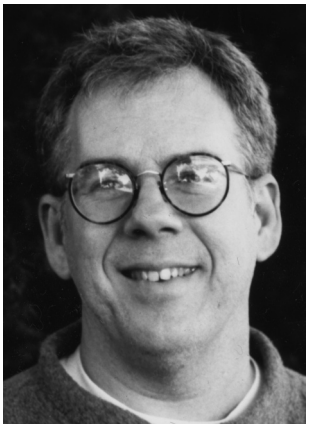
Biographical Sketch



Stephen Bergmeier was born and raised in south-eastern Iowa and attended Iowa State University, graduating with a BS in chemistry in 1981. While there he carried out research with and was introduced to organic synthesis by Prof. George A. Kraus. After Iowa State he attended the University of Nebraska and obtained a Masters degree in organic chemistry, working with Prof. Ray Funk. Following this, he obtained employment at Parke–Davis Pharmaceutical Research in Ann Arbor, Michigan. He then went across the road to the University of Michigan to obtain a Ph.D in medicinal chemistry under the direction of Prof. William H. Pearson. Postdoctoral research was done in the laboratories of Prof. Henry Rapoport at the University of California, Berkeley. His first independent position was as an assistant professor in the Division of Medicinal Chemistry and Pharmacognosy in the College of Pharmacy at Ohio State University. While there he has investigated the use of aziridines for the synthesis of vicinal amino alcohols among other targets. He is also working on the development of novel oligonucleotide analogues and the design and synthesis of novel nicotinic antagonists. As of July 1, 2000, he will be an associate professor in the Department of Chemistry and Biochemistry at Ohio University in Athens, Ohio.