

GREEN, MILD, AND VERSATILE SYNTHETIC METHODS

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Preparation of Chiral Diamines by the
Diaza-Cope Rearrangement (DCR)

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Preparation of Chiral Diamines by the Diaza-Cope Rearrangement (DCR)



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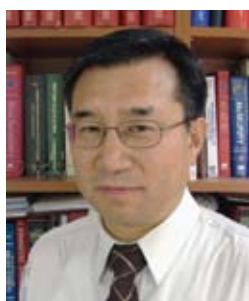


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1. Introduction

Chiral vicinal diamines are of considerable interest as ligands for developing stereoselective catalysts and as intermediates in the synthesis of drugs (**Figure 1**). Diamine-based catalysts have been used for all types of reactions including oxidation, reduction, hydrolysis, and carbon-carbon-bond-forming reactions. Bioactive compounds that are based on vicinal diamines include anticancer, antiviral, antibacterial, antidepressant, and antihypertensive agents. In fact, the vicinal diamine structural motif could be considered “privileged”¹ when it comes to developing catalysts and drugs. Numerous

publications, including several review articles,²⁻⁴ have appeared on the synthesis and applications of chiral diamines. Although much progress has been made, it has been a challenge to develop a facile, efficient, and general route to a wide range of chiral diamines in enantiomerically pure form. Such an approach would greatly facilitate the development of new diamine-based catalysts and drugs, and would be advantageous for optimizing the performance of known diamine-based catalysts by tuning the steric and electronic properties of the attached ligands. Libraries of chiral diamines and their derivatives, such as imidazolines and piperazines, would be valuable for exploring the chiral space of selected drug receptors. The present review will start with the diaza-Cope rearrangement (DCR) as a method for preparing chiral vicinal diamines. Subsequent sections will describe some diamine-based catalysts and drugs.

2. Synthesis of Chiral, Vicinal Diamines by the Diaza-Cope Rearrangement (DCR)

The prevalence of the vicinal diamine motif in the structures of catalysts and bioactive compounds has led to the development of dozens of methods for the synthesis of vicinal diamines. Some of the more practical routes to C_2 -symmetrical diaryl- and dialkyl-substituted primary diamines are shown in **Scheme 1**.

There is considerable interest in developing syntheses of vicinal diamines that are broad in scope.² It is often difficult or tedious to make enantiomerically pure vicinal diamines on a large scale. Moreover, the efficient production of diphenylethylenediamine (DPEN)⁵ and 1,2-diaminocyclohexane (DACH)⁶ (see Scheme 1) has undoubtedly contributed to the explosive growth of the field. However, a greater variation in the diamine structure is needed for discovering better catalysts and drugs. We recently developed a method for synthesizing

chiral vicinal diamines by using the diaza-Cope rearrangement (DCR).^{7,8} This process provides one of the simplest and most versatile approaches to preparing a wide variety of chiral vicinal diamines, including diaryl- and dialkyl-substituted ones in C_2 -symmetrical or unsymmetrical forms, from a single diamine, 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (HPEN in Scheme 1). This rearrangement (i) generally takes place *under mild conditions without the need for any catalyst*; (ii) is highly stereospecific, thus providing an efficient and direct route to enantiopure chiral vicinal diamines; and (iii) eliminates the need for tedious and time-consuming optimizations of the chiral resolution conditions.

2.1. Diaryl Vicinal Diamines

The diaza-Cope rearrangement was first used in 1976 by Vögtle and Goldschmitt to prepare a variety of meso vicinal diamines.⁹ More recently, we developed the chiral version of this rearrangement reaction.⁸ DFT computation revealed that resonance-assisted hydrogen bonding is the driving force behind all of our reactions for preparing chiral vicinal diamines in high yields and enantiopurities under mild conditions. Since 1,2-bis(2-hydroxyphenyl)-1,2-diaminoethane (HPEN, **1**) is the key starting material in the synthesis of all of our chiral vicinal diamines (see Scheme 1), we refer to it as the “mother” diamine, from which all “daughter” diamines are produced

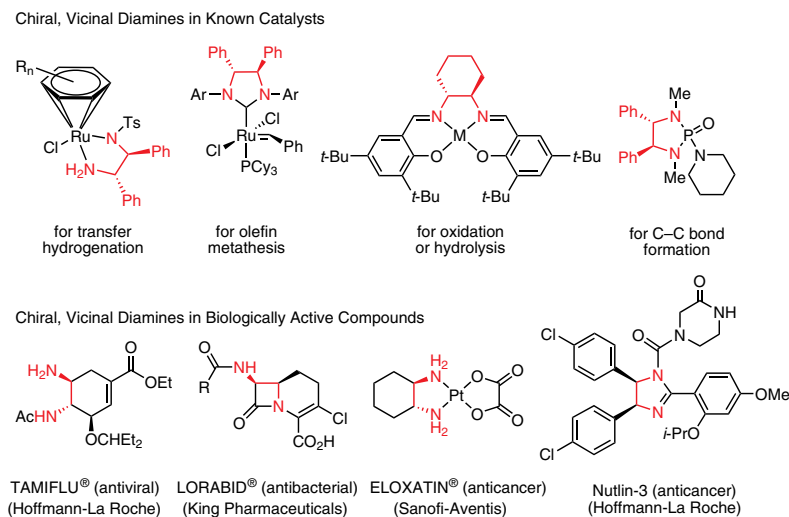
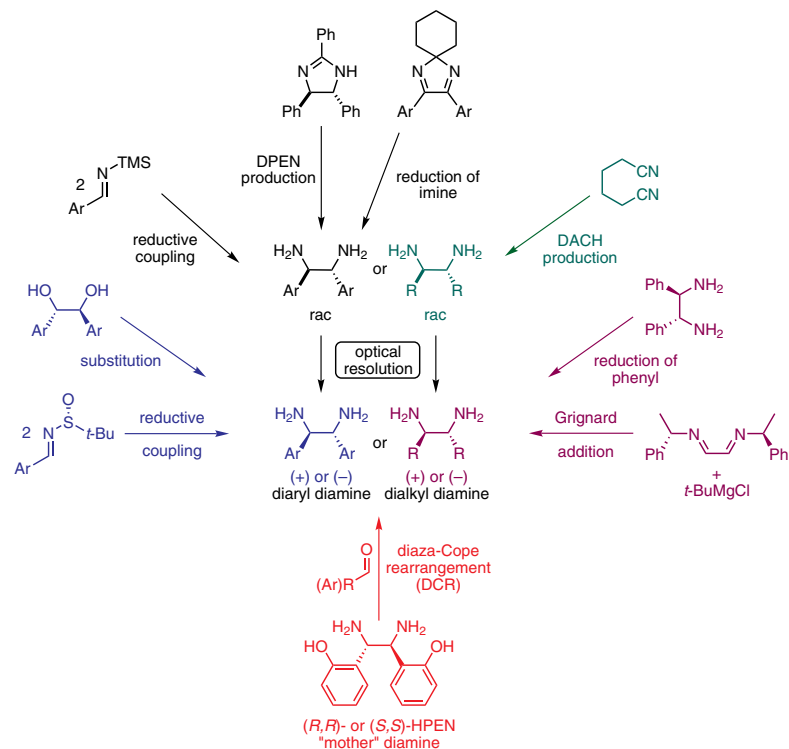
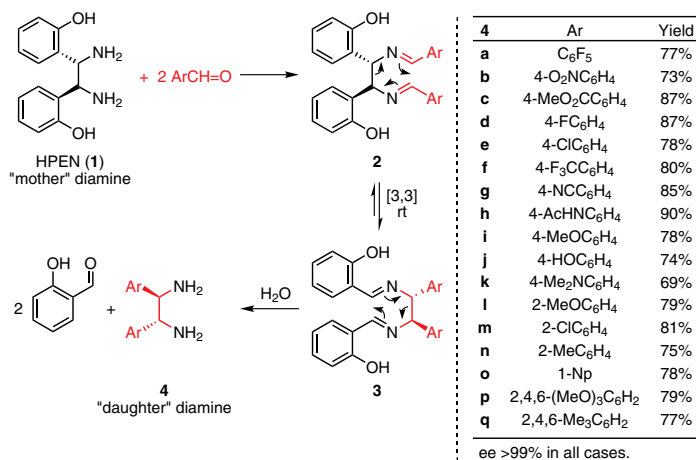


Figure 1. Vicinal-Diamine-Based Catalysts and Bioactive Compounds.



Scheme 1. Known Syntheses of C_2 -Symmetrical, Primary Vicinal Diamines.



Scheme 2. "Mother-to-Daughter" Diamine by DCR. (Ref. 7,8)

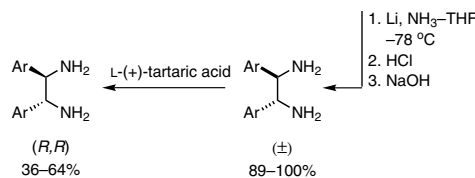
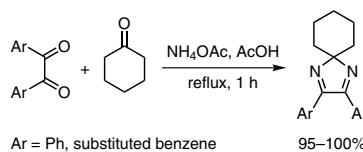
(Scheme 2). In a typical reaction, addition of two equivalents of an aromatic aldehyde to **1** results in the formation of the corresponding diimine, **2**, which undergoes the DCR reaction to give the rearranged diimine, **3**. The rearranged diimine is then hydrolyzed to give the product diamine, **4**.^{7,8}

In general, the rearrangement reaction goes to completion within minutes at ambient temperature without the need for any catalyst. The stability of the two resonance-assisted hydrogen bonds in the rearranged diimine, **3**, drives the rearrangement reaction to completion for the synthesis of electron-poor (**4a–4g**), electron-rich (**4h–4k**), and sterically bulky (**4l–4q**) diamines.^{7,8} As shown in Scheme 2, all of the diamines are produced in uniformly high enantiopurities (>99% ee's).

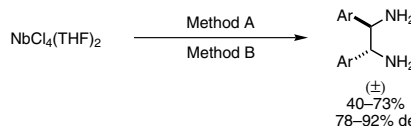
Some of the diamines in Scheme 2 were previously synthesized by other methods. Two of these most useful methods are (a) Corey's reductive amination of benzil analogues (Scheme 3a),¹⁰ and (b) Pedersen's reductive coupling of imines (Scheme 3b).¹¹ Corey and co-workers showed that chiral vicinal diamines can be prepared as racemic mixtures in 85–100% yields from the corresponding benzil analogues. However, the yields for resolution of the diamines with tartaric acid were low (36–64% of the theoretical yield). Busacca's¹² and Denmark's¹³ groups used the reductive coupling method for preparing a variety of chiral vicinal diamines as racemic mixtures. The highly bulky diamine (**4q**) was also previously synthesized by the reductive coupling method.¹⁴ Although the reductive coupling reaction has the advantage of requiring only simple starting materials, the yield for the coupling step is 40–73% without optical resolution^{11,13} and generally much lower (14–19%) after optical resolution.¹² Tartaric acid resolution gave acceptable separation of some diamine enantiomers,^{10,12,13} but it failed to give satisfactory results for the separation of others such as **4a**¹⁵ and **4n**,¹⁶ even after several recrystallizations. In such cases, various chiral acids were screened for resolution¹⁶ or the diamines were derivatized with a chiral reagent and separated by column chromatography.^{13,15} Thus the overall yields for the synthesis of diamine enantiomers are often low (on the order of 10% of the theoretical yield).^{12,13}

One obvious way to avoid the tedious resolution of racemic diamines is to synthesize the diamine enantiomers stereoselectively. Recently, the samarium-mediated reductive coupling of chiral sulfinyl imines has been reported by Xu and

(a) Corey's Reductive Amination of Benzil Analogues



(b) Pedersen's Reductive Coupling of Imines

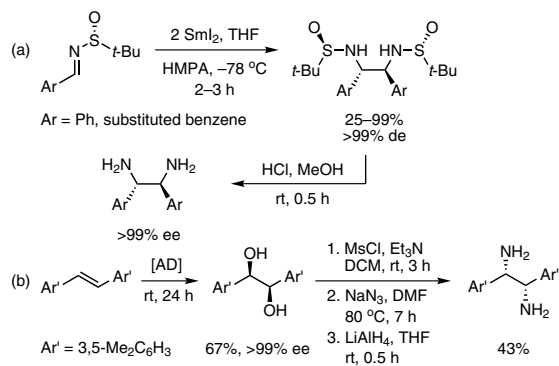


Method A: (i) (*E*)-ArCH=NTMS, DME, rt, 4 h; (ii) KOH, rt, 20 min.
Method B: (i) ArCN, (*n*-Bu)₃SnH, THT, rt, 6 h; (ii) KF, KOH, rt, 20 min.
Ar = Ph, substituted benzene, furan-2-yl, thien-2-yl

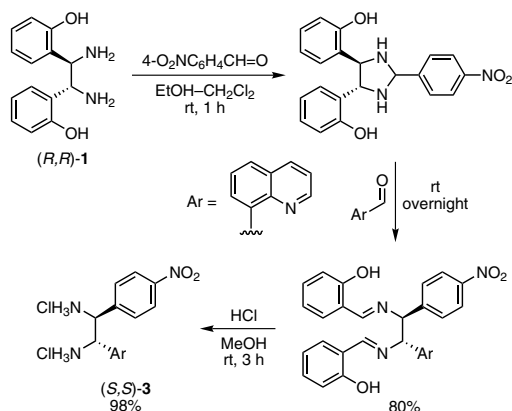
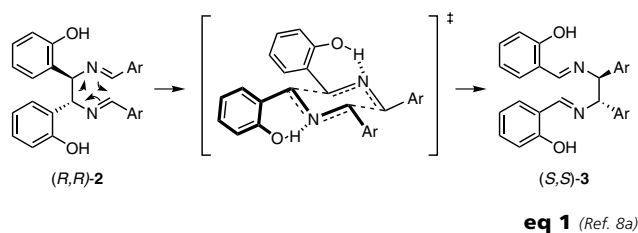
Scheme 3. Two of the Most Used Syntheses of Racemic Diaryl Vicinal Diamines. (Ref. 10,11)

co-workers as a direct approach to synthesize enantiomerically pure diaryl vicinal diamines (Scheme 4a).¹⁷ This method gives diamine enantiomers with variable yields (25–99%). The Sharpless asymmetric dihydroxylation (AD) of alkenes can also lead to enantiopure diamines without the need for chiral resolution (Scheme 4b).^{18,19} This method has the advantage of being catalytic, although scale-up may be difficult with a step requiring sodium azide.

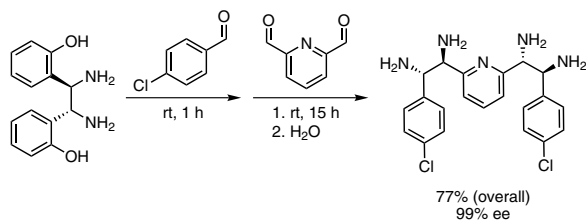
DFT computation is useful for predicting the equilibrium constant for the DCR reaction. The progress of the rearrangement reaction can be conveniently monitored by the appearance of the ¹H NMR signal from the resonance-assisted hydrogen bond that is highly downfield-shifted away from other signals.⁸ The DCR reaction takes place by a chair-like, six-membered-ring transition state with all the substituents in pseudoequatorial positions (eq **1**).^{8a} This results in a highly stereospecific



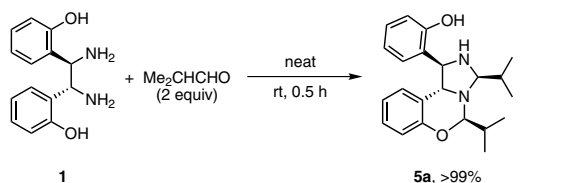
Scheme 4. Known Enantioselective Syntheses of Diaryl Vicinal Diamines. (Ref. 17,19)



Scheme 5. Synthesis of Mixed-Diaryl Vicinal Diamines by DCR. (Ref. 8b)



Scheme 6. Synthesis of a Tetraamine by DCR. (Ref. 8c)



eq 2 (Ref. 8c)

transfer of stereochemistry from the starting diimine to the rearranged diimine.⁸ Indeed, chiral HPLC shows that there is no detectable loss of enantiopurity in the preparation of the daughter diamines from the mother diamine.

The rearrangement reaction takes place in various solvents including chloroform, THF, ethanol, and DMSO. The rearranged diimine (**3**) often precipitates out of solvents like ethanol and THF, simplifying the isolation of the key intermediates in pure form. Alternatively, the rearrangement in DMSO-*d*₆ may be monitored by ¹H NMR, and water may be added to precipitate out the rearranged diimine once the reaction is complete. The DCR method for the preparation of a wide range of C₂-symmetrical diamines should be useful for the steric and electronic tuning of catalysts that are based on chiral vicinal diamines (see Diamine Catalysts in Section 3).

Unsymmetrically substituted, chiral, diaryl vicinal diamines can be prepared in excellent yield and enantiopurity by a slight modification of the above method.^{8b} Addition of *one* equivalent of an aromatic aldehyde to (*R,R*)-**1** or (*S,S*)-**1** gives the five-membered-ring aminal intermediate (**Scheme 5**).^{8b} Electron-deficient aromatic aldehydes are particularly well suited for the preparation of the five-membered-ring compound, and may often be precipitated out of DMSO by addition of water. Addition of a second aldehyde to the intermediate gives the mixed diimine, which rearranges to give the product diimine. Hydrolysis of the product diimine gives the mixed diamine in excellent yield and enantiopurity.

The above process for synthesizing mixed diamines can be extended to mixed tetraamines (**Scheme 6**).^{8c} Sequential addition of one equivalent of a monoaldehyde to the mother diamine, followed by addition of a half equivalent of a dialdehyde, gives the mixed tetraamine in excellent yield and enantiopurity. This reaction was utilized to make a novel pentadentate ligand with four chiral centers in enantiomerically pure form.

2.2. Dialkyl Vicinal Diamines

There has been considerable interest in developing new methods for the synthesis of aliphatic vicinal diamines, as they are found in a wide variety of bioactive compounds including antiviral, antibacterial, and anticancer drugs (e.g., TAMIFLU[®], LORABID[®], and ELOXATIN[®]).^{20–22} The methods employed in the synthesis of diaryl vicinal diamines aren't always applicable to the preparation of their dialkyl counterparts. In addition, alkyl substituents are generally less effective than aryl substituents in facilitating [3,3] sigmatropic rearrangements. Initially, we encountered difficulties in synthesizing dialkyl vicinal diamines by the DCR method.

When two equivalents of an aliphatic aldehyde such as isobutyraldehyde are added to the mother diamine, the corresponding diimine, or the rearranged diimine, does not form as in the corresponding reaction with aromatic aldehydes (see Scheme 2). Instead, a compound, **5a**, containing fused imidazolidine–dihydro-1,3-oxazine rings is formed in a highly selective and stereospecific fashion (eq 2).^{8c} In principle, one, two, or three equivalents of isobutyraldehyde could add to **1** to form one, two, or three new rings, respectively. Fourteen different products could result from the cyclization reactions including all possible stereoisomers. Interestingly, only one major product is formed when the diamine is added to two or more equivalents of the aldehyde.

Although **5a** is stable at room temperature, it cleanly gives the rearranged diimine, **7a**, with excellent stereospecificity when heated at 150 °C for 3 h (eq 3).^{8c} We propose that **5a** is in

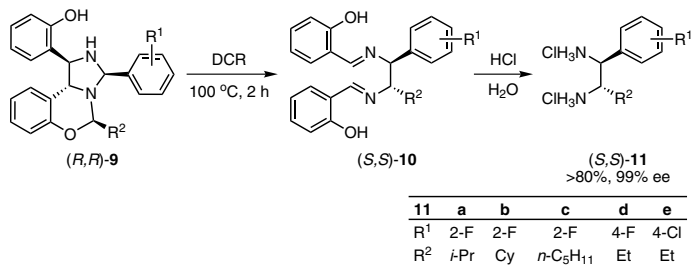
equilibrium with the initial diimine, **6a**, which rearranges to give the product diimine, **7a**. Monitoring of the reaction by ^1H NMR spectrometry shows that the concentration of diimine intermediate **6a** does not accumulate to any observable extent during the conversion of **5a** to **7a**. Thus, the equilibrium appears to greatly favor **5a** over **6a**. In contrast, **2** does not form the corresponding fused-ring compound to any observable extent. The dramatic difference in the tendencies of **2** and **6a** to form the fused-ring compounds is likely due to the fact that the two imine functional groups in **2** are stabilized by conjugation whereas those in **6a** are not. Acid hydrolysis of the product diimine, **7a**, gives the corresponding dialkyl diamine (*S,S*)-1,2-diamino-1,2-diisopropylethane dihydrochloride (**8a**) in high enantiopurity (>99% ee).

A variety of aliphatic aldehydes were used to make dialkyl vicinal diamines by the modified DCR method (Scheme 7).^{8c} The enantioselectivity of the rearrangement reaction was determined by HPLC. Rearrangement of (*R,R*)-**5a** in DMSO gave (*S,S*)-**7a** in 93% yield with no observable loss in enantiopurity (>99%), while a one-pot reaction of (*R,R*)-**1** and isobutyraldehyde in toluene gave (*S,S*)-**7a** in 85% yield. The inversion of stereochemistry, confirmed by CD spectroscopy, is expected from the chair-like transition state with all substituents in equatorial positions. Although the rearrangement reaction leading to dialkyl vicinal diamines requires considerably higher temperatures than the one giving rise to diaryl vicinal diamines, the observed yield and stereoselectivity of the former remain exceptionally high.

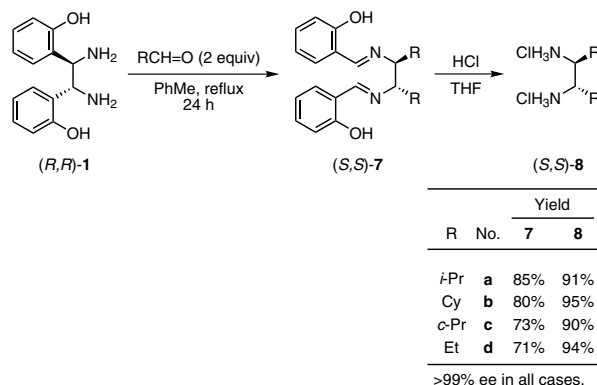
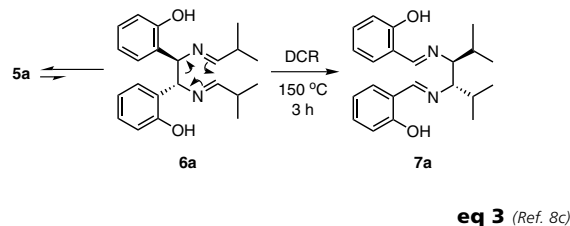
Some of the diamines in Scheme 7 were previously synthesized by other methods (Scheme 8).^{23,24} Diamines **8a** and **8c** were synthesized by addition of Grignard reagents to chiral bisimines for the purpose of preparing NHE3 inhibitors.²⁵ However, the observed diastereoselectivity for this reaction was low except in the case where the bulky *tert*-butylmagnesium chloride was used.²³ 1,2-Diamino-1,2-dicyclohexylethane (**8b**) was synthesized in 85% yield by hydrogenation of DPEN at ambient temperature.²⁴

2.3. Alkyl-Aryl Vicinal Diamines

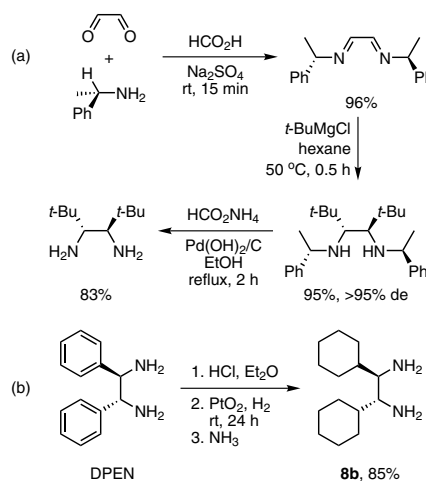
The breadth in scope of the DCR method can be demonstrated in the synthesis of mixed alkyl-aryl vicinal diamines. Sequential addition of an aromatic aldehyde and an aliphatic aldehyde gives the fused imidazolidine-dihydrooxazine-ring compound in a highly regioselective and stereospecific manner. The aromatic aldehyde forms the imidazolidine ring while the aliphatic aldehyde forms the dihydrooxazine ring. When *o*-fluorobenzaldehyde and isobutyraldehyde are added in sequence to the mother diamine, compound **9** forms as the major product. Although **9** is stable at room temperature, it cleanly gives the rearranged diimine, **10**, in excellent enantiopurity when heated at 100 °C for 2 h (Scheme 9). Hydrolysis of the rearranged diimine gives the product diamine, **11**.



Scheme 9. Synthesis of Mixed Alkyl-Aryl Vicinal Diamines from the Fused-Ring Compound **9**. (Ref. 8c)



Scheme 7. Dialkyl Vicinal Diamines by a Modified DCR. (Ref. 8c)



Scheme 8. Known Syntheses of Dialkyl Vicinal Diamines. (Ref. 23,24)

(*S,S*)-1,2-Diamino-1-(4-fluorophenyl)butane (**11d**) had previously been synthesized by a much longer route and in a lower overall yield (~10%) for the purpose of preparing cisplatin analogues.²⁶

3. Vicinal-Diamine-Based Catalysts

Chiral vicinal diamines are some of the most important ligands in the design of stereoselective catalysts.²⁷ They have been utilized in creative ways to develop a wide variety of innovative chiral catalysts (see Figure 1). Some of the diamine-based, stereoselective catalysts developed to date include reduction,²⁸ oxidation,²⁹ and hydrolysis catalysts.³⁰ Other diamine-based compounds catalyze a variety of carbon-carbon-bond-forming reactions such as allylic alkylation,³¹ metathesis,³² Michael addition,³³ Aldol,³⁴ Mannich,³⁵ cycloaddition,³⁶ and Strecker³⁷ reactions. Chiral vicinal diamines are useful not only for developing transition-metal-based catalysts but also organocatalysts.³⁸ Efficient methods for obtaining 1,2-diaminocyclohexane (DACH)⁶ and 1,2-diphenylethylenediamine (DPEN)⁵ in enantiomerically pure form have led to their widespread use over other vicinal

diamines. However, a single vicinal diamine is not expected to be the best ligand for all catalysts. Even for a single catalytic system, one vicinal diamine is not expected to be the best catalyst ligand for all substrates. A greater variation in the diamine structure is desirable for developing stereoselective catalysts.³⁹ The DCR method for making chiral vicinal diamines may be useful for a number of applications in catalysis including (a) steric and electronic tuning of known catalysts, (b) designing new ligands, (c) developing polymer-supported catalysts, and (d) making water-soluble diamine-containing catalysts.

3.1. Steric and Electronic Tuning of Catalyst Structure

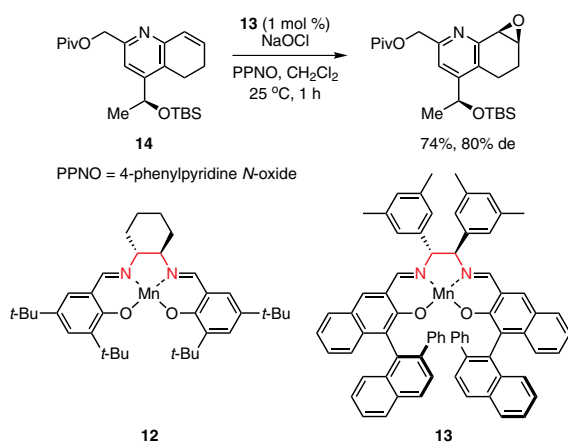
It is well established that steric and electronic tuning of catalysts can result in dramatic improvements in reactivity and stereoselectivity. Jacobsen and Katsuki independently developed chiral, vicinal-diamine-based Mn complexes for the catalytic epoxidation of cis alkenes. Extensive steric and electronic tuning of the salen catalysts resulted in the development of highly reactive and stereoselective epoxidation catalysts **12** and **13**.^{40,41} Not surprisingly, no single catalyst is the best for all substrates. Although **12** has a broad scope in the epoxidation of alkenes, Nicolaou et al. found that **13** is much better for the epoxidation of **14** in terms of yield and stereoselectivity (eq 4).⁴² Thus, tuning of the salen ligand, including the diamine backbone, had a profound effect on the reactivity and selectivity of the catalyst.

More recently, Katsuki and co-workers reported a titanium-salen based epoxidation catalyst that uses 30% H₂O₂ as an oxidant (**15**) (Figure 2).⁴³ Beller's group developed an iron complex of **16** for the catalytic epoxidation of trans alkenes with H₂O₂.⁴⁴ Although this catalyst is not very stereoselective, iron has the advantage of being cheap and nontoxic. While oxidation catalysts **12** and **13** have been extensively tuned, the newer ones, **15** and **16**, have yet to be tuned. Thus, it would be of considerable interest to tune the vicinal-diamine backbone of these environmentally friendly catalysts for higher reactivity and enantioselectivity.

Interestingly, the same diamine-based salen ligand that was used in the manganese complex **12** for obtaining highly stereoselective epoxidations of cis alkenes also leads to a highly stereoselective hydrolysis of epoxides when the manganese is exchanged with cobalt.³⁰ Thus, a properly tuned ligand for one reaction can also be highly effective for a completely different reaction.

Catalysts based on sterically bulky vicinal diamines can provide much improved stereoselectivity when compared to those based on less bulky diamines. Yamada and co-workers have shown that two such catalysts, **17** and **18** (Figure 3), are much more stereoselective than those based on less bulky diamines in cycloaddition⁴⁵ and cyclopropanation reactions,⁴⁶ in the borohydride reduction of ketones,⁴⁷ and in the deuteration of aldehydes and imines.⁴⁸ The DCR method provides a convenient, highly stereoselective route to the bulky diamines in **17** and **18**, as well as to novel bulky diamines such as **19**⁴⁹ in a one-pot reaction.

One of the most remarkable chiral catalysts reported to date is Noyori's catalyst, **20**,²⁸ which is used for the hydrogenation of prochiral ketones (Figure 4).⁵⁰ A turnover number of over a million has been reported for this highly stereoselective ruthenium catalyst, which consists of a chiral diphosphine ligand and a chiral vicinal diamine ligand. Ding and co-workers recently showed that the chiral diphosphine ligand could be replaced with an achiral one, leading to catalyst **21**, without sacrificing the stereoselectivity of the reaction.



eq 4 (Ref. 42)

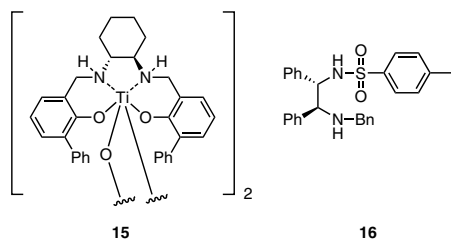


Figure 2. Oxidation Catalysts That Use Hydrogen Peroxide.

(Ref. 43,44)

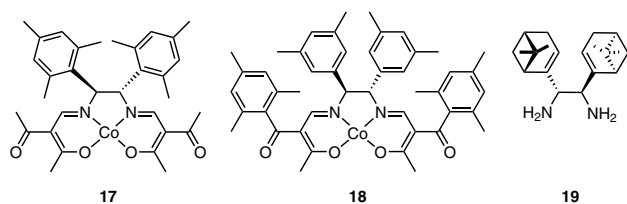


Figure 3. Catalysts Based on Sterically Bulky Vicinal Diamines.

(Ref. 45-49)

Noyori's *transfer*-hydrogenation catalyst, **22**, which uses isopropanol or formic acid instead of molecular hydrogen to reduce ketones, is also based on a chiral vicinal diamine.⁵¹ The availability of a wide range of chiral vicinal diamines should allow for tailor-fitting of the catalyst to the ketone substrate in order to achieve a high stereoselectivity. Mioskowski and co-workers showed that **23** is more reactive and stereoselective than **22** as a transfer-hydrogenation catalyst for the reduction of β -keto ester **24** under dynamic kinetic resolution conditions to give **25** (eq 5).⁵² Electron-withdrawing sulfonyl groups increase the reactivity of the catalyst by acidifying the primary amine. While the DPEN backbone itself was not tuned in this study, electron-withdrawing substituents on the phenyl rings are expected to further modulate the activity and selectivity of the catalyst. Substituents on DPEN can significantly affect the basicity (or acidity) of the vicinal diamine. For example, the pK_a value of the protonated decafluoro-DPEN (**4a**, Scheme 2) is about three units lower than that of protonated DPEN.¹⁵

Busacca et al. reported on the steric and electronic tuning of the phosphinoimidazoline (BIPI) ligands that are used for the catalytic asymmetric Heck reaction (eq 6).¹² The reactivity and stereoselectivity of the in situ formed palladium complex was reported to be highly sensitive to the structure of the chiral vicinal diamine in the imidazoline group. The BIPI ligands have the advantage of being easier to tune than the phosphinooxazoline ligands and the BINAP ligands. The diamines in the BIPI ligands were initially synthesized by Corey's¹⁰ or Pedersen's¹¹ methods. More recently, they have been prepared by the DCR method.

In addition to the metal-based catalysts described above, many organocatalysts that incorporate chiral vicinal diamines are known. Denmark et al. reported that chiral, vicinal-diamine-based phosphoramidate Lewis base **26** catalyzed the aldol addition of ketone silyl enolates to aromatic aldehydes (eq 7).¹³ Both the diastereoselectivity and enantioselectivity of the reaction were highly sensitive to the structure of the diamine portion of the organocatalyst.

We recently showed that chiral vicinal diamines themselves can be used as organocatalysts for the stereoselective synthesis of warfarin, a blood thinner for treating thrombosis (eq 8).⁵³ As was observed with **26**, the stereoselectivity of this Michael reaction is sensitive to the diamine structure. The enantioselectivity of the reaction increases from 47% ee to 92% ee on changing the diamine catalyst from DACH to the ortho-methyl-substituted DPEN, **4n**.

3.2. New Diamine Designs

The DCR method is not only useful for tuning the properties of known ligands, but is also valuable for developing novel ones. Diamines may be developed into monodentate, bidentate, tridentate, tetradentate, and pentadentate ligands with N, O, S, or P as coordinating atoms. We have reported a novel amino alcohol receptor based on a Co(III)-salen complex, **28**, possessing an axial aromatic substituent in the diamine backbone (eq 9).^{8b} The vicinal-diamine-based, unsymmetrical, tridentate ligand, **27**, was prepared in enantiomerically pure form using the DCR method. The stereoselectivity of **28** in the coordination of amino alcohols increases from about 2.9 to 36.0 with increasing steric bulk of the amino alcohols used in the reaction.

Chiral oxazoline ligands are useful in the design of many catalysts.⁵⁴ Most of the oxazoline ligands are based on a few readily available chiral amino alcohols. Replacing chiral oxazoline ligands with a wide range of chiral diamine-based imidazoline ligands should be of considerable interest.¹²

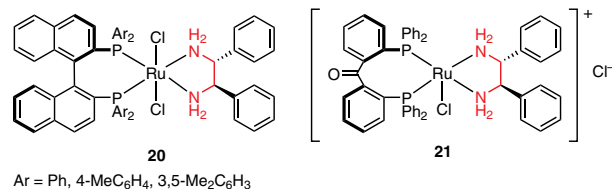
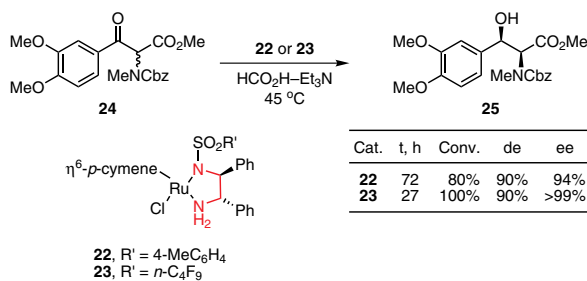
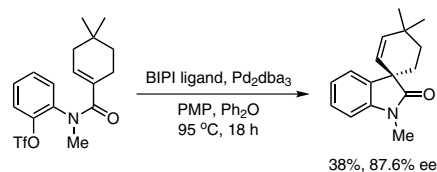


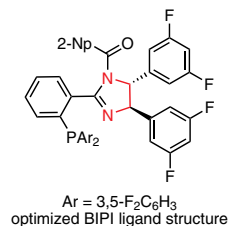
Figure 4. Vicinal-Diamine-Based Catalysts for the Hydrogenation of Prochiral Ketones. (Ref. 50)



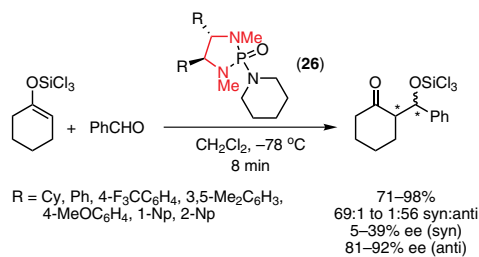
eq 5 (Ref. 52)



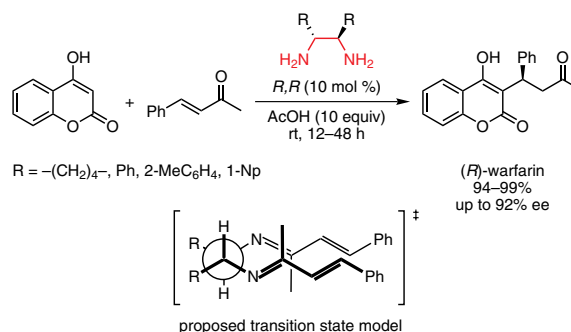
38%, 87.6% ee



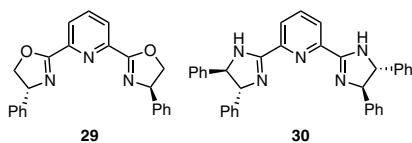
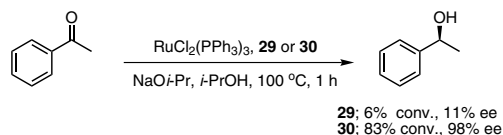
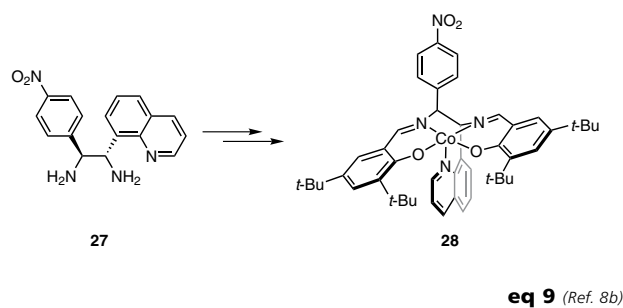
eq 6 (Ref. 12)



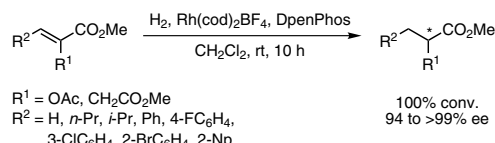
eq 7 (Ref. 13)



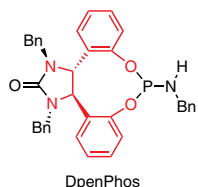
eq 8 (Ref. 53)



eq 10 (Ref. 56,57)



$\text{R}^1 = \text{OAc}, \text{CH}_2\text{CO}_2\text{Me}$
 $\text{R}^2 = \text{H}, n\text{-Pr}, i\text{-Pr}, \text{Ph}, 4\text{-FC}_6\text{H}_4,$
 $3\text{-ClC}_6\text{H}_4, 2\text{-BrC}_6\text{H}_4, 2\text{-Np}$



eq 11 (Ref. 61b)

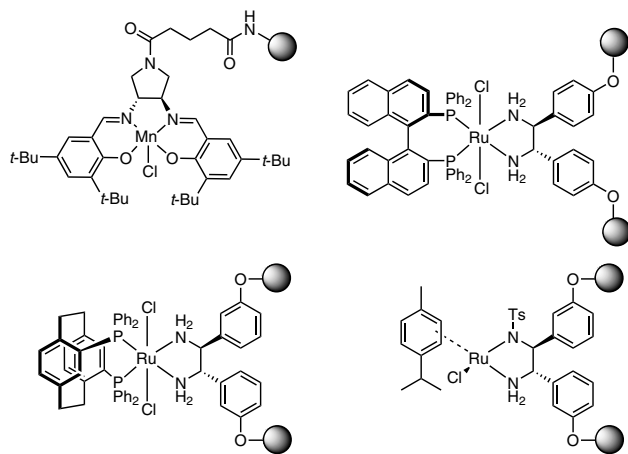


Figure 5. Chiral, Vicinal-Diamine-Based Catalysts on Solid Support. (Ref. 63)

Beller and co-workers have recently reported that ruthenium complexes of chiral tridentate pyridinebisimidazolines (Pybim, **30**) are effective catalysts for epoxidation^{55,56} and transfer-hydrogenation reactions.⁵⁷ They found that Ru-Pybim complexes are much more reactive and stereoselective than the Ru-Pybox complex in the transfer hydrogenation of acetophenone (eq 10).⁵⁷

There has been much interest in monodentate phosphorus ligands ever since the pioneering work of Feringa,⁵⁸ Reetz,⁵⁹ and Pringle.⁶⁰ The “mother” diamine (HPEN) is not only useful for making “daughter” diamines by the DCR method, but it can also be converted into an interesting monodentate phosphorus ligand (DpenPhos). Ding and co-workers showed that DpenPhos is an excellent ligand for the Rh(I)-catalyzed enantioselective hydrogenation of acrylates (eq 11).⁶¹

3.3. Diamines on Solid Support

Chiral vicinal-diamine-based catalysts are often expensive to prepare, but their polymer-supported counterparts have the advantage of being recyclable.⁶² The DCR method also provides a simple route for preparing diamines that can be conveniently attached to a solid support; it also simplifies the purification of the product. Diphenylethylenediamines (DPENs) with hydroxyl groups attached at the meta or para positions of the two benzene rings (e.g., **4j**) have been used to prepare various polymer-supported catalysts (Figure 5).⁶³ Such catalysts effected the stereoselective hydrogenation of ketones and epoxidation of olefins.

3.4. Water-Soluble Diamine Catalysts

The growing interest in green chemistry and the need for environmentally friendly catalytic systems has led to the development of water-soluble, chiral, vicinal-diamine ligands.⁶⁴ Deng and co-workers⁶⁵ reported water-soluble versions of Noyori’s transfer-hydrogenation catalyst (see eq 5) prepared from disulfonated *N*-tosyl-DPEN, **32** (Figure 6).⁶⁵ These catalysts gave excellent results in the reduction of prochiral ketones, imines, and iminium ions in aqueous solvents. The DCR method provides a convenient route to a variety of water-soluble vicinal diamines in enantiomerically pure form.^{8c}

4. Diamine Drugs

A number of vicinal diamines possess a wide range of bioactivities. The amine groups are useful for modulating the solubility of the drug as well as for donating or accepting hydrogen bonds to and from a biological receptor. In addition, vicinal diamines can easily be converted into five- and six-membered rings like imidazolines and piperazines. These rigid heterocyclic compounds provide entropic advantage for binding to the biological target. Some representative diamine and diamine derivatives with interesting bioactivities are discussed below.

4.1. Acyclic Diamines

Ever since the serendipitous discovery by Rosenberg et al. of the anticancer activity of cisplatin,⁶⁶ there has been much interest in developing cisplatin analogues that are more active and less toxic (Figure 7). Oxaliplatin (ELOXATIN[®], Sanofi-Aventis)²² is one such analogue that is based on a chiral vicinal diamine [(*R,R*)-1,2-diaminocyclohexane (DACH)] and that is active against colorectal cancer.⁶⁷ Other studies indicate that it is also active against ovarian cancer,⁶⁸ non-small-cell lung cancer,⁶⁹ and breast cancer.⁷⁰ The wide availability of DACH undoubtedly was

an important factor in the discovery of oxaliplatin, as it was in the discovery of various stereoselective DACH-based catalysts. In a recent breast cancer and prostate cancer cell line studies, **33** showed the highest activity among a variety of platinum complexes.²⁶

Interestingly, (*S,S*)-**33** gave the best result against the MDA-MB 231 breast cancer cell line and LnCaP/FGC prostate cancer cell line, while (*R,R*)-**33** gave the best result against the MCF-7 breast cancer cell line. The chiral vicinal diamine ligand in **33** (see **11d**, Scheme 9) was difficult to prepare, requiring seven steps with an overall yield of about 10%. With the DCR process, this diamine and other close analogues can be prepared in excellent yield (>90%) and stereoselectivity (99% ee) in a one-pot reaction under mild conditions.^{8c}

4.2. Imidazolines

Scientists at Hoffmann–La Roche in Nutley, New Jersey, recently reported a novel strategy for cancer therapy. A cis imidazoline, that they named Nutlin-3, was shown to activate the p53 tumor suppressor pathway.⁷¹ Initially, they screened a library of cis imidazolines that was generated from a variety of meso vicinal diamines, which were, in turn, prepared by DCR.^{7,9} Another series of cis imidazolines possessing anti-inflammatory activity have been reported by Merriman et al.⁷² In addition to the cis imidazolines, trans imidazolines, similarly prepared from chiral vicinal diamines, also exhibited biological activities. Clonidine, moxonidine, and ZANAFLEX® are imidazoline II receptor agonists that lower blood pressure. While all of these compounds are based on unsubstituted vicinal diamines, clonidine analogues made with chiral vicinal diamines were shown to be active (**Figure 8**).²⁵ The diamine in **34** was prepared as a racemic mixture in low yield by the Grignard method (see Scheme 8a). The DCR process is useful for making a variety of chiral dialkyl vicinal diamines in enantiomerically pure form (see Scheme 7).

4.3. Piperazines

Simple N-substituted piperazines are found in numerous drug molecules. However, chiral piperazines are only beginning to make their mark as useful therapeutics. Chiral vicinal diamines can be readily converted into chiral piperazines and piperazinones. Tagat et al. reported piperazine-based CCR5 antagonists as potent HIV inhibitors (**Figure 9**).⁷³ Wurster and co-workers recently showed that a chiral, piperazine-based molecule, **35**, is a selective α_2C -adrenoceptor antagonist and has potential therapeutic use in several psychiatric disorders.⁷⁴

4.4. Other Diamines

α,β -Diamino acids are a special class of chiral vicinal diamines that have potent biological activities.⁷⁵ For example, viomycin is an inhibitor of protein synthesis, and capreomycin IA, used for the treatment of tuberculosis, contain L-capreomycidine⁷⁶ as a key structural element. In addition, the appearance of penicillin- or cephalosporin-resistant pathogens has led to the development of loracarbef (LORABID®),²¹ a diamino acid based antibiotic (**Figure 10**).

There has been much recent interest in oseltamivir (TAMIFLU®) and zanamivir (RELENZA®) due to the possibility of a human influenza pandemic (**Figure 11**).⁷⁷ The two inhibitors of sialidase (also known as neuraminidase) are effective therapeutics for the treatment of the avian H5N1 influenza virus. Oseltamivir is a chiral vicinal diamine monoamide that is prepared from shikimic acid.²⁰ The total synthesis of oseltamivir has been recently reported by several research groups.⁷⁸ While

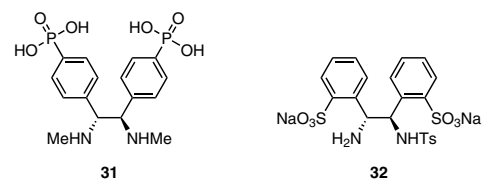


Figure 6. Water-Soluble, Chiral, Vicinal Diamine Ligands.

(Ref. 64,65)

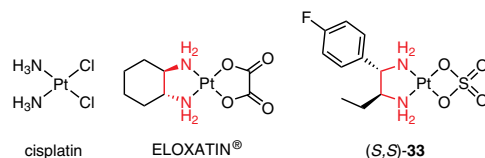


Figure 7. Cisplatin and Other Anticancer Analogues.

(Ref. 22,26,66–70)

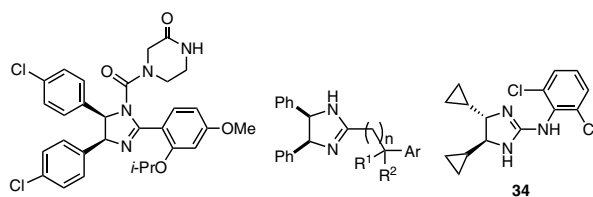


Figure 8. Bioactive Imidazolines. (Ref. 25,71,72)

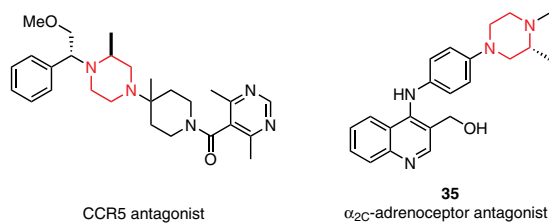


Figure 9. Bioactive Piperazines. (Ref. 73,74)

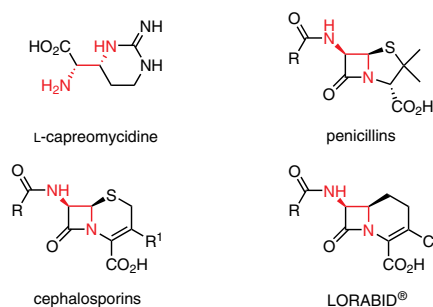


Figure 10. Biologically Active α,β -Diamino Acids and Derivatives That Incorporate a Vicinal Diamine Motif. (Ref. 21,75,76)

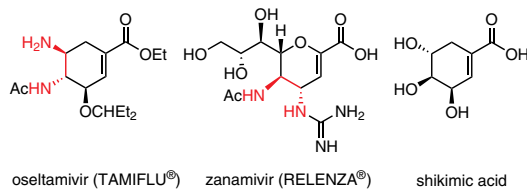


Figure 11. Vicinal-Diamine-Based Antiviral Agents and Shikimic Acid. (Ref. 20,77,78)

the DCR process may not be easily applied to the synthesis of these challenging targets, it may be useful for making libraries of their analogues.

5. Conclusions

Many of the best stereoselective catalysts that we know today contain a chiral, vicinal-diamine structural element, and most of these catalysts are based on DACH or DPEN. The DCR method provides a convenient and efficient route to a wide range of “daughter” chiral, vicinal diamines in enantiomerically pure form starting from a single “mother” diamine (**1** or HPEN). This method allows not only the synthesis of C_2 -symmetrical diaryl diamines but also dialkyl diamines and even mixed alkyl-aryl diamines in excellent yields and enantiopurities. Some of the advantages of the DCR method are: (a) The reaction is highly efficient and stereospecific; (b) No metals are required as catalysts or reagents; (c) The reaction generally takes place rapidly at ambient temperatures; and (d) A wide variety of diamines can be made in a one-pot process. The “daughter” diamines can be used for electronic and steric tuning of known diamine-based catalysts as well as for developing novel monodentate, bidentate, tridentate, tetradentate, and pentadentate ligands. These ligands can have N, O, S, or P as coordinating atoms. Stereoselective catalysts are becoming ever more important for the preparation of chiral drugs and materials. In addition, many bioactive compounds themselves are based on diamines or their derivatives like imidazolines and piperazines. Synthetic methods of broad scope and high efficiency for making chiral vicinal diamines in enantiomerically pure form should facilitate the discovery of new catalysts and drugs.

6. Acknowledgements

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Keywords: chiral diamine; organocatalyst; diamine drug; diamine catalyst; vicinal diamine.

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Jik Chin received his B.Sc. degree in chemistry and biochemistry (1977) from the University of Toronto. He worked on physical organic and bio-organic projects (ketophosphate and maleamic acid hydrolysis; thiamine mechanisms) with Professor Ron Kluger for his M.Sc. (1978) and Ph.D. (1981)

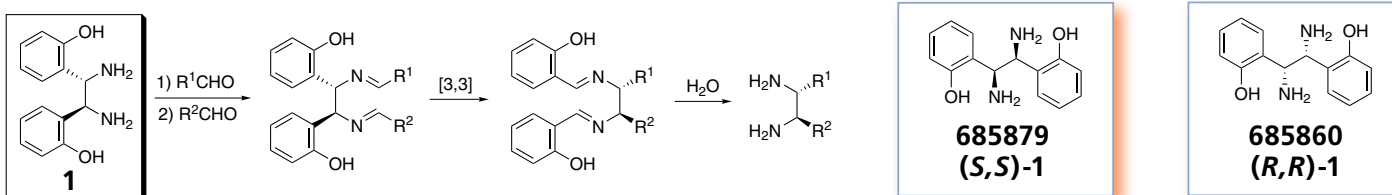
degrees. He then studied carbonic anhydrase mechanisms at Columbia University with Professor Ron Breslow as an NSERC postdoctoral fellow. In 1983, he joined the faculty at McGill University, where he developed mono- and dinuclear metal complexes as unified mechanistic models of esterases, proteases, nitrilases, and nucleases. He returned to the University of Toronto as a professor in 2000, working on anion and cation recognitions as well as on stereoselective recognition and catalysis. More recently, he has been investigating the preparation of chiral vicinal diamines by the DCR method for which he received the Bernard Belleau Award (2006). He is the founder and CEO of DiaminoPharm, Inc., and has been a visiting professor at the California Institute of Technology (1990), the Institute for Molecular Science in Okasaki (1997), Pohang University of Science and Technology (1998), and Seoul National University (2003, 2008).

B. Moon Kim obtained his B.S. and M.S. degrees from the Department of Chemistry, Seoul National University. In 1983, he began his Ph.D. level research in the laboratory of the late Professor Satoru Masamune at M.I.T., where he studied asymmetric synthesis using organoboron compounds. Five years later, he became a postdoctoral fellow in Prof. K. B. Sharpless's laboratory at M.I.T., where he investigated the asymmetric, osmium-catalyzed dihydroxylation reaction. In 1990, he accepted a senior research chemist position at Merck Research Laboratories in West Point, Pennsylvania, where he was then promoted to research fellow. In 1995, he moved back to his alma mater in Korea as an assistant professor. In 2003, he spent a year in the laboratory of Dr. Kenner C. Rice as an adjunct investigator at the National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, in Bethesda, Maryland. In 2003, he was a DAAD-sponsored Innovatec Guest Lecturer at Regensburg University in Germany. He is now Professor and Chairman of the Department of Chemistry, Seoul National University, and Head of the Brain Korea 21 Division of Chemistry & Molecular Engineering. His research is centered on the development of efficient synthetic methodologies based on asymmetric catalysis, and on the design and synthesis of small molecules that could be used for the treatment of various diseases such as cancer, obesity, and depression. ☞

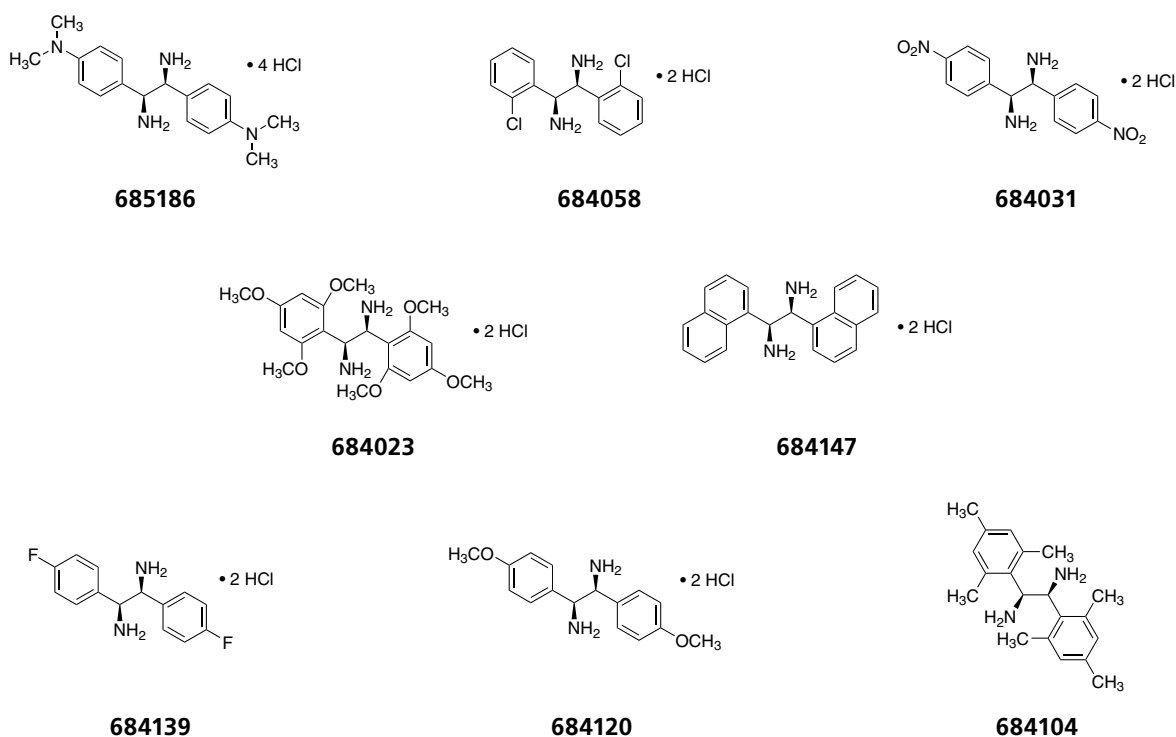
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Other NEW Chiral Vicinal Diamines



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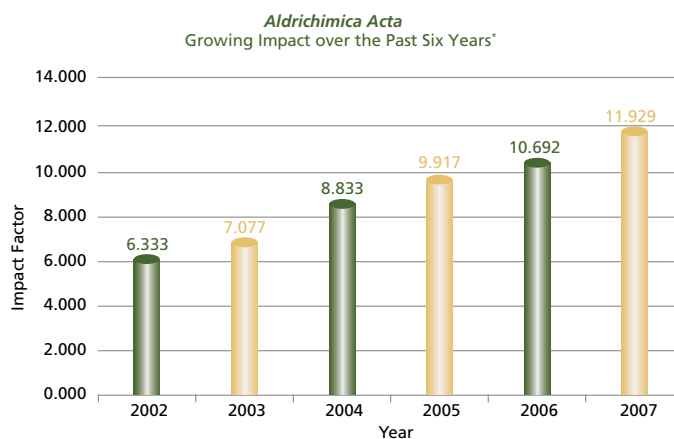
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