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(54) Title: DIRECT ORGANOCATALYTIC ASYMMETRIC REACTIONS OF ENOLIZABLE α -AMINO ALDEHYDES OR KETONES TO FORM HIGHLY ENANTIOMERICALLY ENRICHED AMINE PRODUCTS

(57) Abstract: A method for asymmetrically forming a (diprotectedamino)-product having a chiral center and in which one enantiomer is in excess over the other is disclosed. The method comprises reacting an enolizable α -(diprotectedamino)-aldehyde or -ketone donor molecule with an excess of an unsaturated acceptor molecule that has one or no hydrogen atoms bonded to a carbon atom α to the carbon of the unsaturation. The donor and acceptor molecules are dissolved or dispersed in a liquid solvent and are in the presence of a chiral amine catalyst to form an addition product reaction medium. The reaction medium is maintained for a time sufficient to form an α -(diprotectedamino)-aldehyde or -ketone product having a chiral center formed at a carbon atom bonded to the α -(diprotectedamino) group and in which one enantiomer is in excess over the other.



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DIRECT ORGANOCATALYTIC ASYMMETRIC REACTIONS OF
ENOLIZABLE α -AMINO ALDEHYDES OR KETONES TO FORM
HIGHLY ENANTIOMERICALLY ENRICHED AMINE PRODUCTS

CROSS-REFERENCE TO RELATED APPLICATION

This application is based on Serial No.
60/603,175 filed on August 20, 2004.

GOVERNMENTAL SUPPORT

The present invention was made with
governmental support pursuant to USPHS grant CA27489
from the National Institutes of Health. The
government has certain rights in the invention.

TECHNICAL FIELD

The present invention contemplates a method
for asymmetrically forming a (diprotectedamino)-
product having at least one chiral center and in
which one enantiomer is in excess over the other.
More particularly, the invention contemplates a
method of reacting an enolizable alpha-
(diprotectedamino)-aldehyde or -ketone donor molecule
with an unsaturated acceptor molecule in the presence
of a chiral catalyst to provide a chiral product in
which one enantiomer predominates over the other.

BACKGROUND ART

Asymmetric molecules are ubiquitous in
nature, and particularly, in living organisms. That
commonality, led to a change in organic chemical
nomenclature from use of the terms symmetric and
asymmetric, which emphasized symmetric molecules as
the norm, to the terms chiral and achiral that

affirmatively places emphasis on asymmetric molecules.

In keeping with the enlarged knowledge of the importance of chiral compounds and because pharmaceutical compounds interact primarily with chiral compounds, emphasis has been placed in the recent past on syntheses of potential pharmaceutical compounds in which the chirality of at least some steps is known or predictable. That mode of synthetic design can be compared to the prior technique of carrying out a synthesis and then trying to recover a particular enantiomer once the synthesis is complete, as by using one or the other enantiomer of an acid or base such as *d*-camphorsulphonic acid or brucine sulfate as a salt-forming resolving agent.

Amine-containing small molecule drugs, as compared to proteinaceous pharmaceuticals, are common, due in part to their water solubility and ability to bind to anionic sites on proteins. The ability to prepare chiral amine-containing compounds would therefore be beneficial in the synthesis of pharmaceutical products. The histamine H3 receptor agonist Sch 50971,1 (trans-4-methyl-3-imidazoyle pyrrolidine dihydrochloride) is one such compound, and analogs of that compound can be beneficial for comparative study.

In another example, β -hydroxy- α -amino acids are components of natural products with wide-ranging biological properties, including antibiotic, anti-cancer, and immunosuppressant activities. [(1)(a) McDonald et al., *J. Am. Chem. Soc.* **2002**, 124, 10260. (b) Umezawa et al. *J. Org. Chem.* **1999**, 64, 3034. (c) Taniguchi et al., *Tetrahedron* **2003**, 59, 4533. (d) Ford et al., *J. Am. Chem. Soc.* **1999**, 121, 5899;

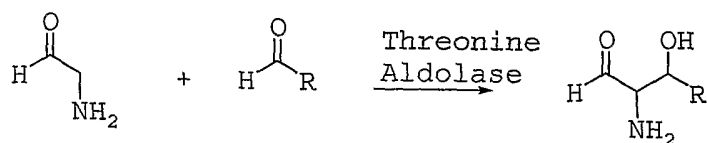
(2) (a) Saravanan et al., *J. Org. Chem.* **2003**, *68*, 2760. (b) Jackson et al., *Tetrahedron* **2000**, *56*, 5667. (c) Laib, et al., *J. Org. Chem.* **1998**, *63*, 1709. (d) Nagamitsu et al., *J. Am. Chem. Soc.* **1996**, *118*, 3584. (e) Panek et al., *J. Org. Chem.* **1998**, *63*, 2382; (3) (a) Makino et al., *Angew. Chem. Int. Ed.* **2004**, *43*, 882. (b) Mordant et al., *Chem. Commun.* **2004**, 1296. (c) Ooi et al., *Angew. Chem. Int. Ed.* **2002**, *41*, 4542. (d) Yoshikawa et al., *Tetrahedron* **2002**, *58*, 8289 and references cited therein. (e) MacMillan et al., *Org. Lett.* **2002**, *4*, 1883. (f) Evans et al., *Angew. Chem. Int. Ed.* **2001**, *40*, 1884. (g) Kobayashi et al., *J. Am. Chem. Soc.* **2004**, *126*, 9192. (h) Ooi et al., *J. Am. Chem. Soc.* **2004**, *126*, ASAP (ja048865q); (4) (a) Silvestri et al., *Top. Stereochem.* **2003**, *23*, 267. (b) Kimura et al., *J. Am. Chem. Soc.* **1997**, *119*, 11734. (c) Tanaka et al., *Tetrahedron Lett.* **1998**, *39*, 5057.]

β -Hydroxy- α -amino acids are also precursors for pharmaceuticals and useful chiral building blocks in organic synthesis. [(2) (a) Saravanan et al., *J. Org. Chem.* **2003**, *68*, 2760. (b) Jackson et al., *Tetrahedron* **2000**, *56*, 5667. (c) Laib, et al., *J. Org. Chem.* **1998**, *63*, 1709. (d) Nagamitsu et al., *J. Am. Chem. Soc.* **1996**, *118*, 3584. (e) Panek et al., *J. Org. Chem.* **1998**, *63*, 2382.] Consequently, tremendous efforts have been directed towards the development of syntheses of optically pure β -hydroxy- α -amino acids and their derivatives. [(2) (a) Saravanan et al., *J. Org. Chem.* **2003**, *68*, 2760. (b) Jackson et al., *Tetrahedron* **2000**, *56*, 5667. (c) Laib, et al., *J. Org. Chem.* **1998**, *63*, 1709. (d) Nagamitsu et al., *J. Am. Chem. Soc.* **1996**, *118*, 3584. (e) Panek et al., *J. Org. Chem.* **1998**, *63*, 2382; (3) (a) Makino et al., *Angew.*

Chem. Int. Ed. **2004**, 43, 882. (b) Mordant et al., *Chem. Commun.* **2004**, 1296. (c) Ooi et al., *Angew. Chem. Int. Ed.* **2002**, 41, 4542. (d) Yoshikawa et al., *Tetrahedron* **2002**, 58, 8289 and references cited therein. (e) MacMillan et al., *Org. Lett.* **2002**, 4, 1883. (f) Evans et al., *Angew. Chem. Int. Ed.* **2001**, 40, 1884. (g) Kobayashi et al., *J. Am. Chem. Soc.* **2004**, 126, 9192. (h) Ooi et al., *J. Am. Chem. Soc.* **2004**, 126, ASAP (ja048865q); (4) Silvestri et al., *Top. Stereochem.* **2003**, 23, 267. (b) Kimura et al., *J. Am. Chem. Soc.* **1997**, 119, 11734. (c) Tanaka et al., *Tetrahedron Lett.* **1998**, 39, 5057.] Nonetheless, demand still exists for highly efficient diastereo- and enantioselective syntheses of β -hydroxy- α -amino acid derivatives.

One successful method for the synthesis of optically pure β -hydroxy- α -amino acids involves the use of threonine aldolases and serine hydroxymethyl transferases. [(2) (b) Jackson et al., *Tetrahedron* **2000**, 56, 5667. (4) (a) Silvestri et al., *Top. Stereochem.* **2003**, 23, 267. (b) Kimura et al., *J. Am. Chem. Soc.* **1997**, 119, 11734. (c) Tanaka et al., *Tetrahedron Lett.* **1998**, 39, 5057.] These enzymes catalyze asymmetric aldol reactions between glycine donor and aldehyde acceptors, reactions that constitute one of the simplest strategies to access β -hydroxy- α -amino acids. An illustrative reaction using a threonine aldolase is illustrated in Scheme 1, below, using glycine aldehyde as a donor and a hypothetical aldehyde having an α -substituent "R" as acceptor.

Scheme 1



Although glycinate Schiff bases have been used as donors in asymmetric aldol reactions for the synthesis of β-hydroxy-α-amino acid ester derivatives [(3) (c) Ooi et al., *Angew. Chem. Int. Ed.* **2002**, 41, 4542. (e) MacMillan et al., *Org. Lett.* **2002**, 4, 1883. (h) Ooi et al., *J. Am. Chem. Soc.* **2004**, 126, ASAP (ja048865q)], glycine aldehyde derivatives have not been examined as donors in direct asymmetric aldol reactions previously.

Asymmetric organocatalysis with L-proline and other small molecules has received renewed attention because of its broad applicability, simplicity, and efficiency. [(5) Reviews: (a) Dalko et al., *Angew. Chem., Int. Ed.* **2001**, 40, 3726. (b) Jarvo et al., *Tetrahedron* **2002**, 58, 2481. (c) Allemann et al., *Acc. Chem. Res.* **2004**, 37, 558. (d) Notz et al., *Acc. Chem. Res.* **2004**, 37, 580. (6) (a) Northrup et al., *Angew. Chem. Int. Ed.* **2004**, 43, 2152. (b) Torii et al., *Angew. Chem. Int. Ed.* **2004**, 43, 1983. (c) Hartikka et al., *Tetrahedron: Asymmetry* **2004**, 15, 1831. (d) Halland et al., *J. Am. Chem. Soc.* **2004**, 126, 4790. (e) Brochu et al., *J. Am. Chem. Soc.* **2004**, 126, 4108. (f) Mathew et al., *Angew. Chem. Int. Ed.* **2004**, 43, 3317. (g) Brown et al., *J. Am. Chem. Soc.* **2003**, 125, 10808. (h) Zhong *Angew. Chem. Int. Ed.* **2003**, 42, 4247. (i) Momiyama et al., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101,

5374. (j) Cobb et al., *Synlett* **2004**, 558. (7) (a) Joly et al., *J. Am. Chem. Soc.* **2004**, 126, 4102. (b) Okino et al., *J. Am. Chem. Soc.* **2003**, 125, 12672. (c) Akiyama et al., *Angew. Chem. Int. Ed.* **2004**, 43, 1566. (d) Uraguchi et al., *J. Am. Chem. Soc.* **2004**, 126, 5356. (e) Thadani et al., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5846. (f) Denmark et al., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5439. (8) (a) Mase et al., *Angew. Chem. Int. Ed.* **2004**, 43, 2420. (b) Mase et al., *Org. Lett.* **2003**, 5, 4369. (c) Cordova et al., *J. Org. Chem.* **2002**, 67, 301. (d) Chowdari et al., *Tetrahedron Lett.* **2002**, 43, 9591. (e) Sakthivel et al., *J. Am. Chem. Soc.* **2001**, 123, 5260. (9) (a) Chowdari et al., *Org. Lett.* **2004**, 6, 2507. (b) Notz et al., *J. Org. Chem.* **2003**, 68, 9624. (c) Cordova et al., *J. Am. Chem. Soc.* **2002**, 124, 1866. (d) Chowdari et al., *Synlett* **2003**, 1906. (10) (a) Betancort et al., *Synthesis*, **2004**, 1509. (b) Mase et al., *Org. Lett.* **2004**, 6, 2527. (c) Betancort et al., *Org. Lett.* **2001**, 3, 3737.]

Reactions involved in organocatalysis are also environmentally benign. The use of naked aldehyde donors in organocatalytic aldol, [See (8) above] Mannich, [See (9) above] and Michael [See (10) above] reactions was previously reported.

On the basis of the results of enzyme-catalyzed aldol reactions, it would be beneficial if one could utilize enzyme-free organic reactions to prepare β -hydroxy- α -amino aldehydes for subsequent use in the preparation of β -hydroxy- α -amino acids. The description that follows illustrates such enzyme-free organic chemical reactions using glycine aldehyde derivatives as donors in aldol reactions to

provide β -hydroxy- α -amino aldehydes that can be easily transformed into β -hydroxy- α -amino acids.

BRIEF SUMMARY OF THE INVENTION

The present invention contemplates a method for asymmetrically forming an α -(diprotectedamino)-aldehyde or -ketone product having a chiral center and in which one enantiomer is in excess over the other. This method comprises the steps of reacting an enolizable α -(diprotectedamino)aldehyde or -ketone donor molecule with an excess of an unsaturated acceptor molecule that preferably has one or no hydrogen atoms bonded to a carbon atom alpha to the carbon of the unsaturation. Those donor and acceptor molecules are dissolved or dispersed in a liquid solvent and are reacted in the presence of a chiral (an optically active) amine catalyst to form an addition product reaction medium. Preferably, the amine catalyst contains up to about 25 carbon atoms such as D- or L-pyrrolidine. The addition product reaction medium is maintained for a time sufficient to form an α -(diprotectedamino)aldehyde or -ketone product having a chiral center formed at least at the carbon atom bonded to the α -(diprotectedamino) group and preferably also at a carbon atom where the unsaturation had been in the acceptor part of the new molecule, and in which one enantiomer is in excess over the other.

A method of asymmetrically forming a beta-hydroxy-alpha-amino aldehyde is contemplated in one specific embodiment. In accordance with that method, an alpha-(diprotectedamino)aldehyde or -ketone donor is reacted with an excess of an alpha-disubstituted

(or alpha-branched) aldehyde acceptor dissolved or dispersed in a solvent and in the presence of a chiral amine catalyst to form a reaction medium. That reaction medium is maintained for a time sufficient to form a beta-hydroxy alpha-(diprotectedamino)aldehyde or -ketone. If desired, the beta-hydroxy alpha-(diprotectedamino)aldehyde can be converted directly into a beta-hydroxy alpha-amino acid without prior isolation or can be isolated, purified further if desired and thereafter converted into the amino acid.

In another embodiment, the invention contemplates the reaction of an excess of an alpha-(diprotectedamino)aldehyde acceptor is reacted with an alpha-unsubstituted (or alpha-non-branched) aldehyde or ketone donor dissolved or dispersed in a solvent and in the presence of a chiral amine catalyst to form a reaction medium. That reaction medium is maintained for a time sufficient to form a β -hydroxy- γ -(diprotectedamino)aldehyde or ketone. As above, the β -hydroxy- γ -(diprotectedamino)aldehyde can be converted directly into a β -hydroxy- γ - amino acid without prior isolation or can be isolated, purified further if desired and thereafter converted into the amino acid.

The two specific embodiments discussed above illustrate aspects of an aldol addition. Also contemplated herein is a similar specific reaction using a Mannich reaction acceptor that contains imine unsaturation. Another specific embodiment contemplates use of a Michael addition reaction acceptor molecule that contains ethylenic unsaturation.

The present invention has several benefits and advantages.

One benefit of the invention is that its method can be utilized to prepare α -(diprotectedamino)aldehyde or -ketone products such as beta-hydroxy α -(diprotectedamino) aldehyde products in high yields.

An advantage of the invention is that the α -(diprotectedamino)aldehyde or -ketone products so prepared are present in excellent diastereoselectivity and high enantioselectivity.

Another benefit of the invention is that the prepared α -(diprotectedamino)aldehyde products can be readily oxidized and diprotected to form the corresponding amino acid.

A further advantage is that the amino acids so formed retain the diastereomeric ratios and enantiomeric excesses of the α -(diprotectedamino)-aldehyde products.

Still further benefits and advantage of the invention will be apparent to the skilled worker from the disclosure that follows.

DETAILED DESCRIPTION OF THE INVENTION

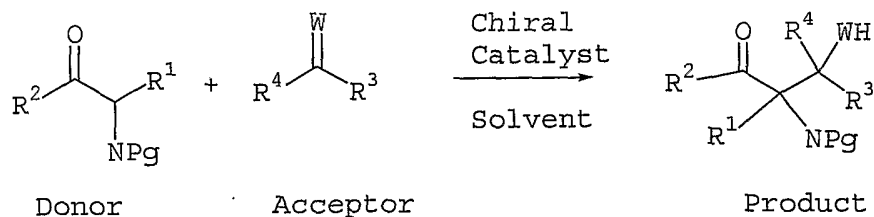
The present invention contemplates a method for asymmetrically forming a (diprotectedamino)-product having at least one chiral center and in which one enantiomer is in excess over the other. A contemplated method comprises the steps of reacting an enolizable α -(diprotectedamino)aldehyde or -ketone donor molecule with an unsaturated acceptor molecule. The donor and acceptor molecules are dissolved or dispersed in a solvent and are in the presence of a chiral amine catalyst to form an

addition product reaction medium. The reaction medium so formed is maintained for a time sufficient to form a diprotectedamino-product having at least one chiral center formed at the carbon atom bonded to the α -(diprotectedamino) group and in which one enantiomer is in excess over the other. Preferably, a second chiral center is also formed at the carbon of the former acceptor molecule that is alpha to the unsaturated carbon atom. The maintenance time for a given reaction can vary from about 0.5 to about 72 hours, and is more typically about one hour to about 48 hours.

The contemplated method can be used to form a contemplated product in which an enantiomeric excess (ee) is about 50 percent or greater. More preferably, that ee is about 75 percent or greater, and most preferably the ee is about 85 to about 100 percent. In addition, because two enantiomeric centers are most usually formed, diastereomers are usually prepared, and the diastereomeric ratio (dr) of those isomers is also noted and can reflect the fact that an diastereomeric excess of one product over the other is formed.

This reaction is depicted generally in Scheme 2, below, in which NPg is a nitrogen atom protecting group, the "R" groups are as defined hereinafter, and "W" is an oxygen atom, a nitrogen or a carbon atom that is substituted as discussed hereinafter.

Scheme 2



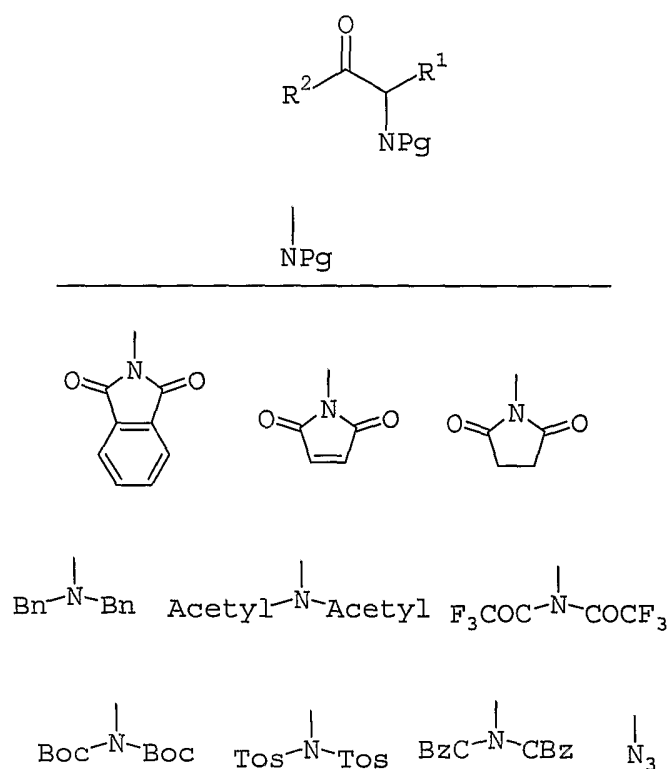
The donor molecule contains an amino group bonded to the carbon atom that is bonded to the carbonyl carbon of the ketone or aldehyde, and that amine-containing carbon atom is referred to as the alpha-carbon. The alpha-carbon also includes at least one hydrogen atom that is relatively acidic and thus can be removed to form an enolate anion at the alpha-carbon so that the donor molecule is an enolizable molecule. The alpha-carbon of the donor molecule becomes at least one chiral center in the product molecule. A donor molecule contains 2 to about 28 carbon atoms, excluding any carbon atoms present in the amine protecting group, "Pg". A donor molecule more preferably contains 2 to about 10 carbon atoms, exclusive of those that may be in the amine protecting group.

As utilized in a contemplated method, the amine group of the donor molecule α-carbon is doubly blocked or doubly protected so that the two valences remaining on the amine nitrogen atom after bonding to the α-carbon atom are taken up by the blocking group or groups. The amine is thus referred to as a "diprotectedamino" group. The protecting groups are removable and are illustrated hereinafter. Further examples of amino-protecting groups are well known in organic synthesis and the peptide art and are

described by, for example, T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Synthesis, 2nd ed., John Wiley and Sons. New York., Chapter 7, 1991; M. Bodanzsky, Principles of Peptide Synthesis, 1st and 2nd revised eds., Springer-Verlag, New York, 1984 and 1993; and Stewart and Young, Solid Phase Peptide Synthesis, 2nd ed., Pierce Chemical Co, Rockford. IL 1984. Exemplary donor ketones and aldehydes and acceptor aldehydes are also illustrated hereinafter.

Exemplary donor diprotected amines are illustrated in Table 1, hereinbelow, wherein -NPg is nitrogen and its protecting group, and substituent R¹ and R² groups are as noted.

Table 1

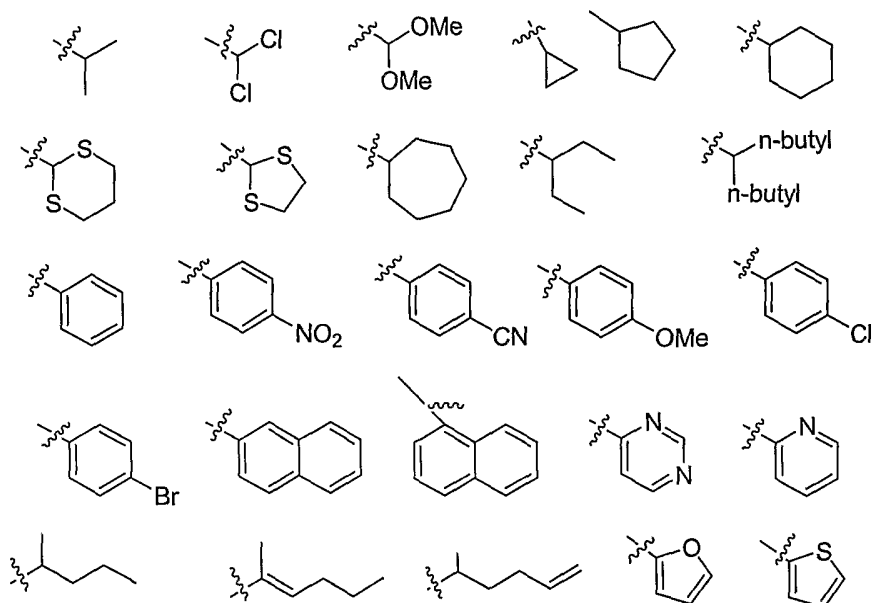
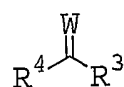


wherein R^1 is selected from the group consisting of hydrido, C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl, halogen, cyano and trifluoromethyl groups; and

R^2 is selected from the group consisting of hydrido (H-), a C_1 - C_{18} straight chain, branched chain or cyclic hydrocarbyl group, an aryl group such as a phenyl, a naphthyl, pyridyl, pyrimidyl, furanyl, thiofuranyl or pyrazinyl group, or an aryl group substituted with a substituent selected from the group consisting of C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, hydroxyl, and a $-CO_2R^a$ group, wherein R^a is a C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group.

A contemplated acceptor molecule is unsaturated and thus contains a double bond, with a carbon atom that participates in the unsaturation being the site of a new carbon-to-carbon bond that is formed and is usually a site of a newly formed chiral center except where formaldehyde is the acceptor. The second atom of the unsaturated bond, W, can be an oxygen atom where the acceptor is an aldehyde or ketone and the reaction is an aldol reaction, a protected nitrogen atom as is present in an imine where the reaction is a Mannich reaction, and a substituted carbon atom where the reaction is a Michael addition reaction. Illustrative acceptor compounds are shown below in Table 2, where the wavy line indicates the position of the bond between the alpha-carbon of the substituent group and the adjacent (α -) unsaturated carbon of the acceptor molecule.

Table 2



Approached differently, the acceptor molecule contains one, and preferably two, carbon atoms and can contain up to about 30 carbons. An acceptor more preferably contains 2 to about 12 carbons, exclusive of any carbons that may be present in an amine protecting group as where the group "W" contains a substituted nitrogen atom of an imine. The R^3 substituent can be hydrido. Alternatively, the R^3 group can include an alpha-carbon that is bonded to one or no hydrogen atoms, and contains up to 29 carbon atoms. Such an R^3 group comprises a substituent selected from the group consisting of:

a branched chain hydrocarbyl,

- a cyclic hydrocarbyl,
- a cyclic group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,
- an aryl group such as a phenyl group, a naphthyl group, as well as a single ring or two ring heterocyclic group containing one to four heteroatoms that are oxygen, sulfur and trisubstituted nitrogen atoms such as a pyridyl, pyrimidyl, furanyl, thiofuranyl, pyrazinyl, an N-blocked imidazolyl, thiazolyl, oxazolyl, isoxazolyl, 1,2,4- or 1,2,3-triazolyl, 1,2,3- 1,2,4- 1,2,5- or 1,3,4-oxadiazolyl, 1,2,3,5-oxatriazolyl, benzofuranyl, isobenzofuranyl, thionaphthalenyl, indolyl, quinolyl, quinazolinyl, and a cinnolinyl group, wherein a third nitrogen substituent is a removable substituent as discussed previously and further including trityl groups and the like,
- a sulfonylaryl group such as a -SO₂-phenyl or a -SO₂-furanyl group or other of the above aryl groups,
- a nitro group,
- a C₁-C₈-hydrocarbyloxycarbonyl [-C(=O)-O-C₁-C₈] group,
- a substituted aryl group as discussed above wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈-hydrocarbyloxy and hydroxyl, and
- a straight chain hydrocarbyl group substituted with 1, 2 or 3 substituents selected from

the group consisting of (a) a halogen, (b) a C₁-C₈-hydrocarbyloxy group, (c) an aryl group as above, or (d) a substituted aryl group as above.

It is preferred that the alpha-carbon that is part of the R³ group contain no hydrogen atoms, as where R³ is an aryl group. If one hydrogen atom is present bonded to the alpha-carbon, the remaining R³ substituent is preferably bulky and contains at least four carbon atoms so that the R³ group can sterically hinder the approach of the amine catalyst to that alpha-carbon-bonded hydrogen. Formaldehyde is the simplest acceptor molecule and R³ is hydrido where formaldehyde is the acceptor.

The R⁴ group can be the same as or different from an R³ group. However, when R⁴ is other than hydrido, the sum of the carbon atoms in R³ and R⁴ can be a total of 29 atoms, the number of carbon atoms in each of R³ and R⁴ is adjusted accordingly so that the sum of carbon atoms in the acceptor molecule is about 30 or fewer. It is preferred that the R⁴ group be hydrido for an acceptor utilized in each of an aldol reaction, a Mannich reaction and a Michael addition reaction.

The word "hydrocarbyl" is used herein as a short hand term to include aliphatic as well as alicyclic groups or radicals that contain only carbon and hydrogen. Thus, alkyl, alkenyl and alkynyl groups are contemplated as are aralkyl groups such as benzyl and phenethyl, whereas aromatic hydrocarbons such as phenyl and naphthyl groups, which strictly speaking could also be included as hydrocarbyl groups, are referred to herein as aryl groups,

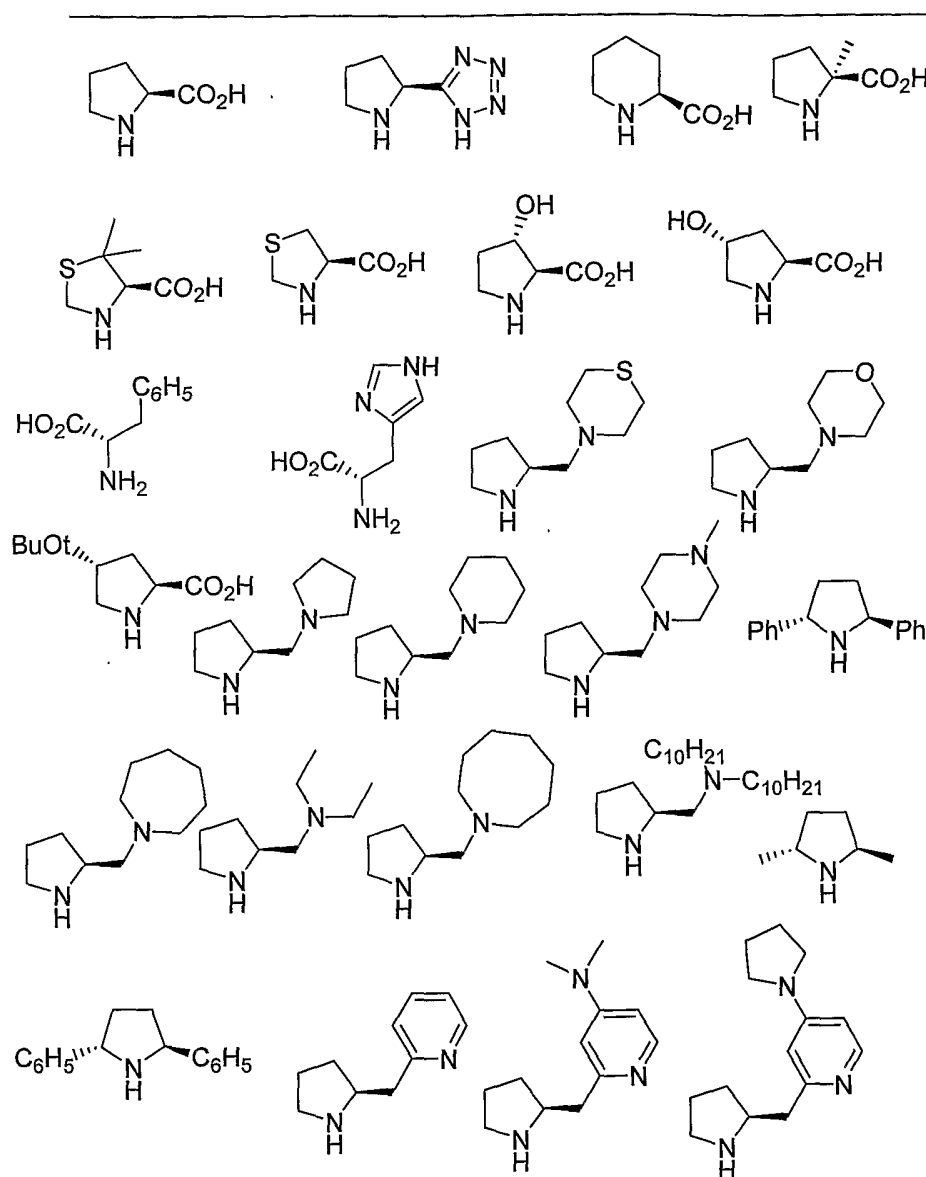
substituents or radicals. Where a specific aliphatic hydrocarbyl substituent group is intended, that group is recited; i.e., C₁-C₄ alkyl, methyl or dodecenyl. Exemplary hydrocarbyl groups contain a chain of 1 to 18 carbon atoms, and preferably one to about 8 carbon atoms. A hydrocarbyloxy group is an ether containing a hydrocarbyl group linked to an oxygen atom.

As noted before, a chiral (optically active) amine containing up to about 25 carbon atoms such as a D- or L-pyrrolidine catalyst is utilized in a contemplated method. As asymmetric products are desired, the catalyst should be one or the other of the racemates. More usually, that chiral amine catalyst contains about 5 to about 10 carbon atoms.

A catalyst is utilized in an amount of about 1 to about 50 mole percent of the amount of the donor aldehyde or ketone, and preferably at about 10 to about 30 mole percent of that reagent. A contemplated catalyst can be utilized with or without an acid co-catalyst. Exemplary acid co-catalysts include 2,4-dinitrobenzenesulfonic acid, acetic acid, (S)-(+)-camphorsulfonic acid and trifluoroacetic acid (TFA).

Illustrative chiral catalyst structural formulas are provided in Table 3, below.

Table 3
Catalysts



An excess of the acceptor over the donor molecule is preferably utilized in a contemplated method. The excess utilized can be a minor amount such as about 5 to about 10 mole percent, but is preferably about 1- to about 20-fold over the donor molecule, and more preferably about 5- to about 10-

fold of the acceptor over the donor molecule on a molar basis.

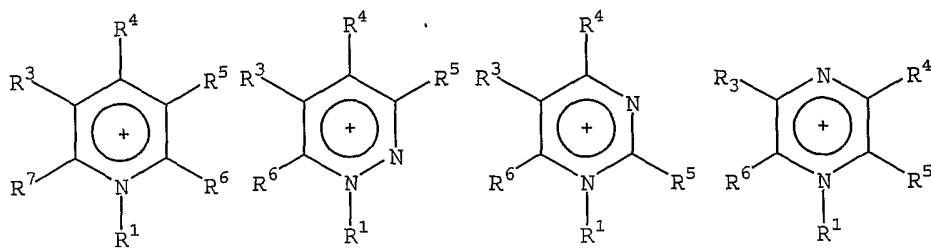
A synthetic method contemplated herein is carried out in a liquid solvent, and substantially any solvent that is a liquid at a temperature of about -50°C to about 150°C , and more preferably is liquid at a temperature of about zero $^{\circ}\text{C}$ to about 50°C , and most preferably is liquid at a temperature of about zero $^{\circ}\text{C}$ to about 40°C . Ambient room temperature (about $20\text{--}25^{\circ}\text{C}$) is a particularly preferred temperature for carrying out a contemplated method.

A contemplated solvent is free of aldehydic, ketonic, acidic or ester carbonyl groups, and can dissolve or disperse the donor, acceptor and catalyst. Illustrative solvents include dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), N-methyl pyrrolidinone (MNP), acetonitrile, methanol, isopropanol, ethanol, diethyl ether, dioxane, methylene chloride, chloroform, poly(ethylene glycol) having an average molecular weight of about 200 to about 1450 and preferably about 200 to about 600, an ionic liquid, water and a combination of one of the above solvents and water.

A contemplated ionic liquid is molten at a temperature of about -50°C to about 150°C . More preferably, a contemplated ionic liquid is liquid (molten) at or below a temperature of about 120°C and above a temperature of minus 44°C (-44°C). Most preferably, a contemplated ionic liquid is liquid (molten) at a temperature of about -10° to about 100°C .

An ionic liquid is comprised of a cation and an anion. A cation of an ionic liquid is

preferably cyclic and corresponds in structure to a formula selected from the group consisting of

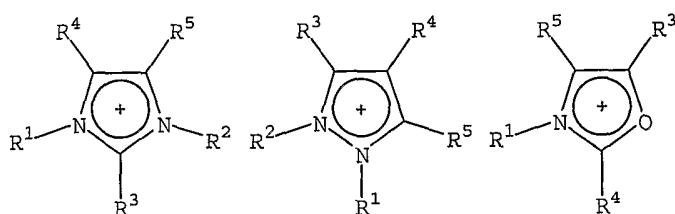


PYRIDINIUM

PYRIDAZINIUM

PYRIMIDINIUM

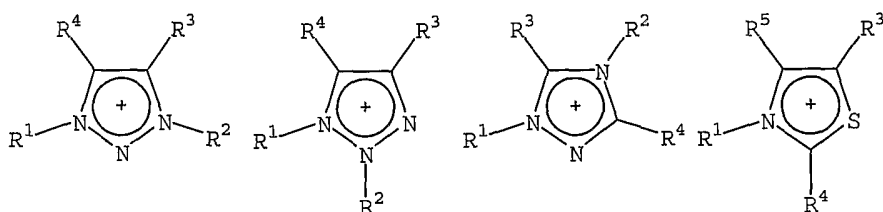
PYRAZINIUM



IMIDAZOLIUM

PYRAZOLIUM

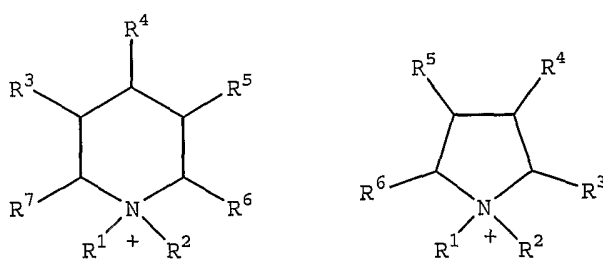
OXAZOLIUM



1,2,3-TRIAZOLIUM

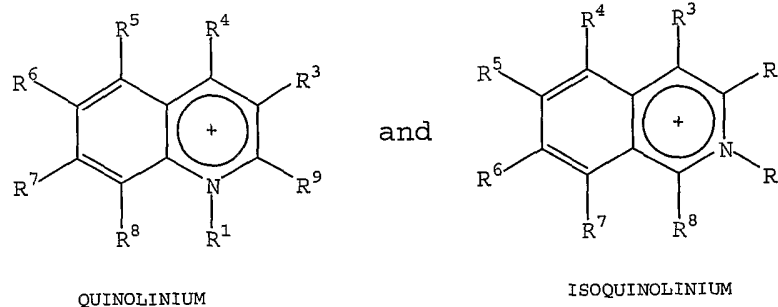
1,2,4-TRIAZOLIUM

THIAZOLIUM



PIPERIDINIUM

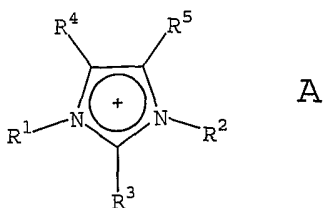
PYRROLIDINIUM



wherein R^1 and R^2 are independently a C_1 - C_6 alkyl group or a C_1 - C_6 alkoxyalkyl group, and R^3 , R^4 , R^5 , R^6 , R^7 , R^8 and R^9 (R^3 - R^9), when present, are independently a hydrido, a C_1 - C_6 alkyl, a C_1 - C_6 alkoxyalkyl group or a C_1 - C_6 alkoxy group. The "R" groups of the ionic liquids are different from those utilized with donor or acceptor molecules discussed elsewhere herein. The anions of the ionic liquid are those monovalent anions well known to those skilled in chemistry. Illustrative anions include trifluoromethanesulfonate, trifluoroacetate, tetrafluoroborate (BF_4^-), hexafluorophosphate (PF_6^-), halogen, pseudohalogen, and C_1 - C_6 carboxylate. Preferred anions include tetrafluoroborate and hexafluorophosphate. It is to be noted that there are two isomeric 1,2,3-triazoles. It is preferred that all R groups not required for cation formation be hydrido.

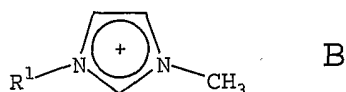
A cation that contains a single five-membered ring that is free of fusion to other ring structures is a more preferred cation. Of the more preferred cations that contain a single five-membered ring free of fusion to other ring structures, an imidazolium cation that corresponds in structure to

Formula A is particularly preferred, wherein R^1 , R^2 , and R^3 - R^5 , are as defined before.



A 1,3-di-(C_1 - C_6 alkyl)-substituted-imidazolium ion is a more particularly preferred cation; i.e., an imidazolium cation wherein R^3 - R^5 of Formula A are each hydrido, and R^1 and R^2 are independently each a C_1 - C_6 -alkyl group or a C_1 - C_6 alkoxyalkyl group. A 1-(C_1 - C_6 -alkyl)-3-(methyl)-imidazolium [C_n -mim, where $n = 1$ -6] cation is most preferred, and a tetrafluoroborate is a preferred anion.

A most preferred cation is illustrated by a compound that corresponds in structure to Formula B, below, wherein R^3 - R^5 of Formula A are each hydrido and R^1 is a C_1 - C_6 -alkyl group or a C_1 - C_6 alkoxyalkyl group.



Exemplary C_1 - C_6 alkyl groups and C_1 - C_4 alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, pentyl, isopentyl, hexyl, 2-ethylbutyl, 2-methylpentyl and the like. Corresponding C_1 - C_6 alkoxy groups contain the

above C₁-C₆ alkyl group bonded to an oxygen atom that is also bonded to the cation ring. An alkoxyalkyl group thus contains an ether group bonded to an alkyl group, and here contains a total of up to six carbon atoms.

An anion for a contemplated ionic liquid cation is preferably tetrafluoroborate or hexafluorophosphate ion, although other ions such as a trifluoromethanesulfonate or trifluoroacetate anion, as well as a halogen ion (chloride, bromide, or iodide), perchlorate, a pseudohalogen ion such as thiocyanate and cyanate or C₁-C₆ carboxylate.

Pseudohalides are monovalent and have properties similar to those of halides [Schriver et al., Inorganic Chemistry, W.H. Freeman & Co., New York (1990) 406-407]. Pseudohalides include the cyanide (CN⁻¹), thiocyanate (SCN⁻¹), cyanate (OCN⁻¹), fulminate (CNO⁻¹) and azide (N₃⁻¹) anions. Carboxylate anions that contain 1-6 carbon atoms (C₁-C₆ carboxylate) are illustrated by formate, acetate, propionate, butyrate, hexanoate, maleate, fumarate, oxalate, lactate, pyruvate and the like.

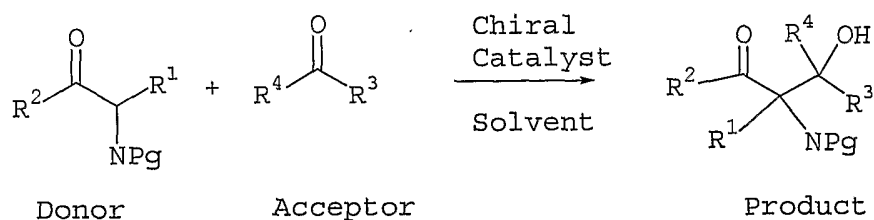
Contemplated donor and acceptor molecules can be used in the relative amounts dissolved or dispersed in a previously discussed solvent with a chiral amine catalyst as also discussed before. In one more specific embodiment of the before-described more general asymmetric addition reaction, the present invention contemplates a method for asymmetrically forming a beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone using an aldol reaction. In accordance with this embodiment of a contemplated method, (a) an alpha-(diprotectedamino)-

aldehyde or -ketone donor is reacted with an excess of an alpha-disubstituted (or alpha-branched) aldehyde acceptor dissolved or dispersed in a solvent and in the presence of a chiral amine catalyst such as a D- or L-pyrrolidine to form a reaction medium. That reaction medium is maintained for a time sufficient to form a beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone. The protecting groups can be removed once the product is formed, or can be left in place for subsequent steps.

The acceptor aldehyde other than formaldehyde is referred to as being "alpha-disubstituted" or "alpha-branched" or " α,α -disubstituted". That nomenclature is used to indicate that the usually present alpha-carbon of the acceptor molecule is itself bonded to at least two atoms other than hydrogen, which also means that the alpha-carbon is bonded to no more than one hydrogen atom. Thus, acetaldehyde and aldehyde are not acceptor molecules in a reaction contemplated by this embodiment as each as at least two hydrogen atoms bonded to the alpha-carbon.

Thus, in this reaction, the donor, acceptor and product molecules have the structures shown below in Scheme 3.

Scheme 3



Here, R^1 , R^2 and R^4 all preferably hydrido (H-), and the R^3 substituent, in addition to including the α -carbon that itself contains one or no hydrogen atoms, further contains one to 29 carbon atoms and is a substituent selected from the group consisting of:

- a branched chain hydrocarbyl,
- a cyclic hydrocarbyl,
- a cyclic hydrocarbyl containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,
- an aryl group as discussed previously,
- a substituted aryl group wherein the substituent is selected from the group consisting of C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C_1 - C_8 -hydrocarbyloxy and hydroxyl, and
- a straight chain hydrocarbyl substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C_1 - C_8 -hydrocarbyloxy group, (c) an aryl group as above, or (d) a substituted aryl group as above.

If desired, the beta-hydroxy alpha-(diprotectedamino) aldehyde product can be converted directly into a beta-hydroxy alpha-amino acid without prior isolation or can be isolated (recovered), purified further if desired and thereafter converted into the amino acid. That conversion can take place by oxidation of the aldehyde to a carboxylic acid using a common oxidation reagent such as $NaClO_2$, and deprotection of the amine using a usual reagent for that purpose such as hydrazine for phthalimides, succinimides and maleimides, or acid in the case of

t-BOC group. These methods of oxidation and deprotection are well known in this art.

Using easily accessible reagents and inexpensive chiral catalysts, a simple, scalable, and environmentally safe synthetic route to highly enantiomerically enriched anti- β -hydroxy- α -amino acid derivatives has been developed. Although asymmetric aldol reactions of glycinate Schiff base and its silicon enolate using chiral quaternary ammonium salt catalysts [(3)(c) Ooi et al., *Angew. Chem. Int. Ed.* **2002**, 41, 4542. (h) Ooi et al., *J. Am. Chem. Soc.* **2004**, 126, ASAP (ja048865q)] and chiral zirconium catalysts [(3)(g) Kobayashi et al., *J. Am. Chem. Soc.* **2004**, 126, 9192.] have provided excellent results for providing β -hydroxy- α -amino acid derivatives, when α -monosubstituted aldehyde acceptors and arylaldehyde acceptors were used, respectively, the synthetic method described herein that utilizes an aldol reaction of aldehyde donor Compound 1 was efficient to afford γ -branched- β -hydroxy- α -amino acid derivatives using α,α -disubstituted aldehyde acceptors. Of note, the use of a glycyl aldehyde is versatile from a synthetic perspective because the aldehyde functionality resident in the products can be readily transformed through oxidation or reduction or can serve as an electrophilic handle for a wide variety of other transformations. [(9)(b) Notz et al., *J. Org. Chem.* **2003**, 68, 9624. (11)Palucki et al., *Tetrahedron Lett.* **2001**, 42, 6811.]

In another embodiment of an aldol reaction, the invention contemplates the reaction of an excess of an α -(diprotectedamino)aldehyde acceptor is reacted with an α -unsubstituted (or α -non-

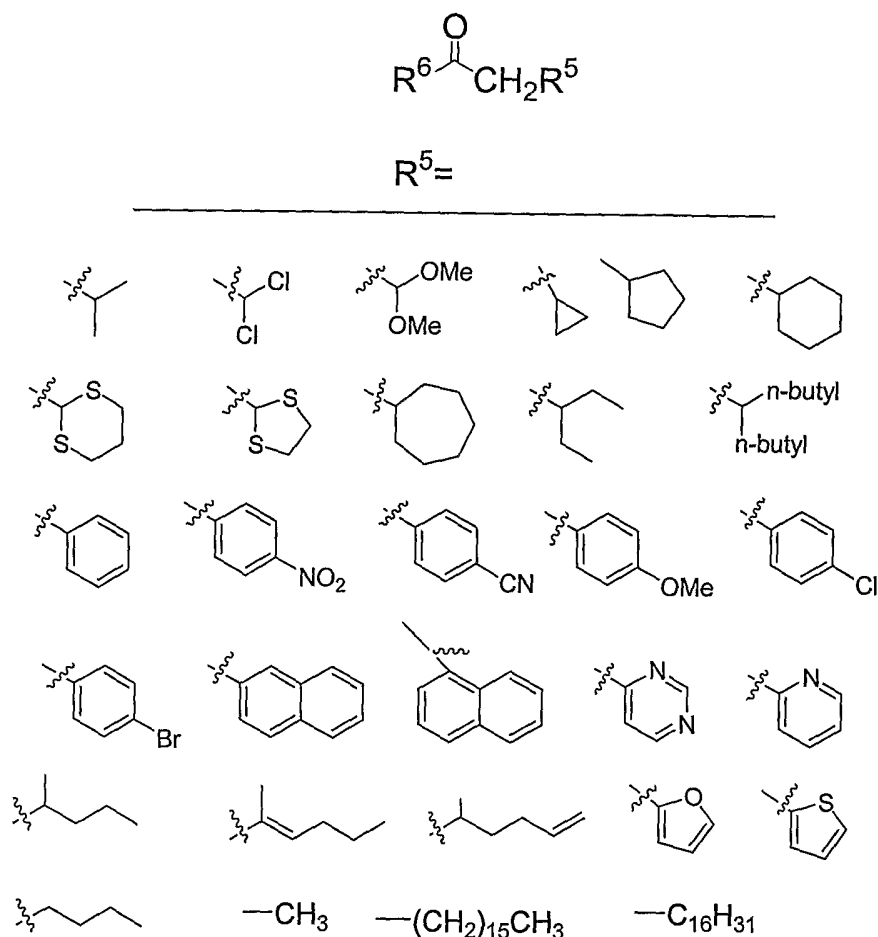
branched) aldehyde or ketone donor dissolved or dispersed in a solvent and in the presence of an optically active amine catalyst that contains up to about 25 carbon atoms such as D- or L-pyrrolidine to form a reaction medium. That reaction medium is maintained for a time sufficient to form a β -hydroxy- γ -(diprotectedamino)aldehyde or -ketone. As above, the β -hydroxy- γ -(diprotectedamino)aldehyde can be converted directly into a β -hydroxy- γ -amino acid without prior isolation or can be isolated, purified further if desired and thereafter converted into the amino acid.

In this embodiment, the acceptor aldehyde molecule can be the same as the donor aldehyde molecule used in the method of preparing a β -hydroxy- α -(diprotectedamino)aldehyde, and the acceptor molecule here can be a ketone or aldehyde that contains at least two hydrogen atoms on a carbon α to the carbonyl group. Structural formulas for the acceptor molecules in this embodiment are those discussed for a donor molecule in a before-discussed aldol reaction embodiment, whereas the donor molecules have structural formulas that correspond to those shown below in Table 4. In those structures, a donor contemplated in this embodiment can contain up to about 18 carbon atoms, preferably 2 to about 6 carbon atoms, and is preferably an aldehyde so that substituent R^6 is preferably a hydrido group.

A donor here can also be a ketone in which case the donor's R^6 substituent can be the same as those shown for R^5 below. However, when a donor is a ketone, it is preferred that the R^6 substituent contain no more than one α -hydrogen atom; i.e.,

be α,α -disubstituted, and have structure such as those shown for the R^3 group of an acceptor used in the first embodiment as is shown in Table 2.

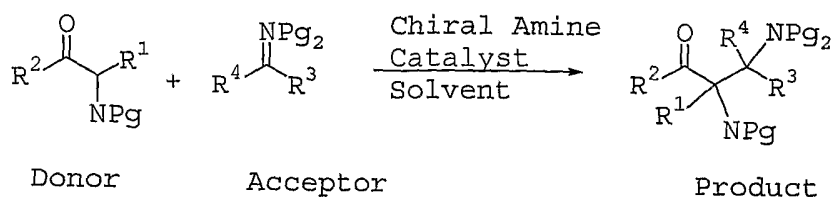
Table 4



Another more specific aspect of the present invention contemplates a Mannich reaction using a before-described donor molecule and an unsaturated acceptor molecule that is present as an imine and the product is an α,β -(protected-diamino)aldehyde or -ketone. The generalized reaction scheme is illustrated in the Scheme 4 below, wherein Pg and Pg₂

are nitrogen protecting groups that are usually different.

Scheme 4



The R¹, R² and R⁴ groups are as described before. However, it is again preferred that R¹, R² and R⁴ groups each be hydrido (H-). The R³ substituent is as before-described and can contain one to 29 carbon atoms and is a substituent selected from the group consisting of:

- a branched chain hydrocarbyl,
- a cyclic hydrocarbyl,
- a cyclic group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,
- an aryl group as discussed before,
- a sulfonylaryl group as previously discussed,
- a nitro group, and
- a C₁-C₈-hydrocarbyloxycarbonyl [-C(=O)-O-C₁-C₈] group,
- a substituted aryl group wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic

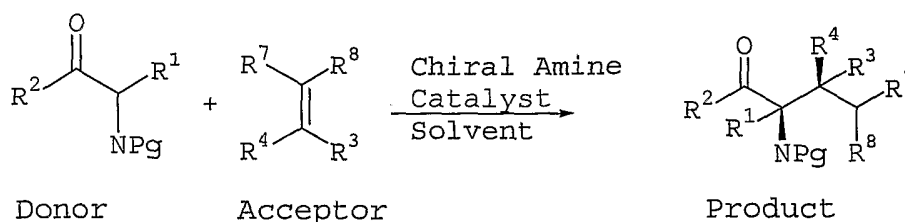
hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈ hydrocarbyloxy and hydroxyl, and

a straight chain hydrocarbyl substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C₁-C₈-hydrocarbyloxy group, (c) an aryl group as above, or (d) a substituted aryl group as above.

Where the R³ group is an N-protected imidazolyl group, a chiral pyrrolidine aldehyde analogue or pyrrolidone aldehyde analogue of Sch 50971,1 can be prepared by reaction of N-phthalimidoglycine aldehyde with an acceptor in which the R³ group is N-protected imidazolyl (as in an N-trityl-imidazolyl group) and the R⁴ group is hydrido, followed by removal of the two nitrogen blocking groups and reaction with formaldehyde or dimethyl carbonate to close the pyrrolidine or pyrrolidone ring, respectively.

A further specific embodiment of the invention contemplates a Michael addition reaction. Here, a before-describe donor molecule is used and an addition reaction occurs across the double bond of the ethylenically unsaturated acceptor molecule to form an α -(diprotectedamino)aldehyde or -ketone. The number of carbon atoms in each of the donor and acceptor, exclusive of those in protecting groups, is as before discussed, but the can be arrayed differently here because of the two additional "R" groups. This reaction is illustrated in Scheme 5, below.

Scheme 5



The R¹, R² and R⁴ groups are as described before, and each is again preferably hydrido. The R³ substituent can be hydrido, but preferably contains 1 about 29, and more preferably 1 to about 20 carbon atoms, and is a substituent selected from the group consisting of:

a branched chain hydrocarbyl,
a cyclic hydrocarbyl,
a cyclic group containing 1 to 3
heteroatoms in the ring, wherein the heteroatoms are
oxygen, sulfur and trisubstituted nitrogen atoms, or
two of the three heteroatoms,
an aryl group as discussed before,
a substituted aryl group wherein the
substituent is selected from the group consisting of
C₁-C₈ straight chain, branched chain or cyclic
hydrocarbyl group, halogen, cyano, trifluoromethyl,
nitro, C₁-C₈ hydrocarbyloxy and hydroxyl, and
a straight chain hydrocarbyl substituted
with 1, 2 or 3 substituents selected from the group
consisting of (a) a halogen, (b) a C₁-C₈-
hydrocarbyloxy group, (c) an aryl group as above, or
(d) a substituted aryl group as above. It is
preferred that the R³ substituent be an aryl or
substituted aryl group in many embodiments,
particularly where one of R⁷ and R⁸ is a nitro group

One or both of R⁷ and R⁸ is an electron withdrawing substituent such as:

- a sulfonylaryl group as discussed before,
- a nitro group, and
- a C₁-C₈-hydrocarbyloxycarbonyl [-C(=O)-O-C₁-C₈] group.

An R⁷ or R⁸ group that is not an electron withdrawing group can be a hydrido group, a substituent containing one to about 20 carbon atoms that is selected from the group consisting of:

- a branched chain hydrocarbyl,
- a cyclic hydrocarbyl,
- a cyclic group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,
- an aryl group as described before,
- a substituted aryl group as discussed above wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈ hydrocarbyloxy and hydroxyl, and

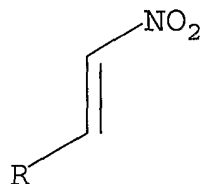
- a straight chain hydrocarbyl substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C₁-C₈ hydrocarbyloxy group, (c) an aryl group as above, or (d) a substituted aryl group as above. When both of R⁷ and R⁸ are not electron withdrawing substituent, it is preferred that the non-electron withdrawing substituent be hydrido.

It is preferred in several embodiments that that the R³ substituent be an aryl or substituted

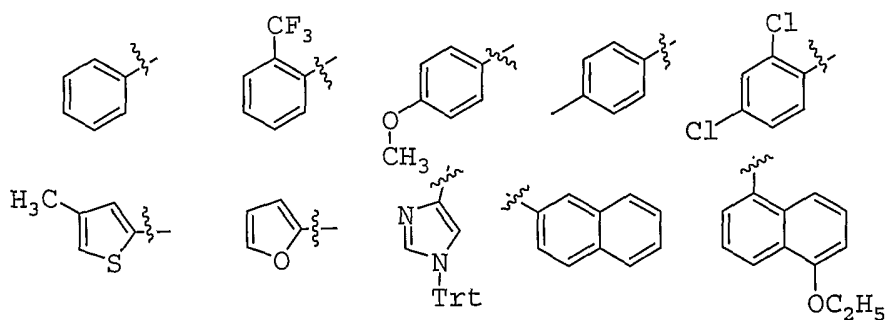
aryl group, particularly where one of R^7 and R^8 is a nitro group. Thus, preferred Michael addition acceptor molecules are *cis*- and *trans*- β -nitro-styrene and their derivatives and analogues.

A β -nitro-styrene derivative has one, two or three substituent groups on the phenyl ring, whereas an analogue compound contains an aryl group as discussed previously herein instead of a phenyl group. *trans*- β -Nitro-styrene, some illustrative derivatives and analogues are shown in Table 5, below, wherein "Trt" is trityl and the wavy line indicates the position of the bond. The derivatives can be substituted with one through three substituents selected from the group consisting of C_1 - C_8 -hydrocarbyl, C_1 - C_8 -hydrocarbyloxy, trifluoromethyl and halo.

Table 5



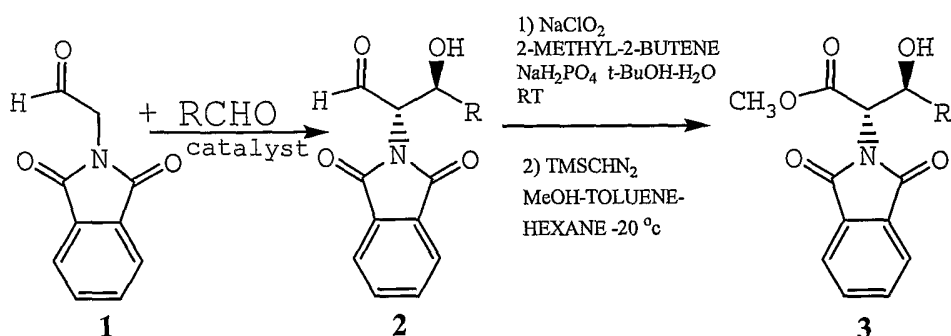
R =



Results

Scheme 6 below, illustrates direct asymmetric aldol reactions of an α -(diprotectedamino)substituted aldehyde Compound **1** to afford a corresponding β -hydroxy- α -aminoaldehyde Compound **2** and the conversion of **2** to a β -hydroxy- α -amino acid ester Compound **3**.

Scheme 6

**2a, 3a:** $R=CHMe$ **2b, 3b:** $R=CHEt_2$ **2c, 3c:** $R=CH(nBu)_2$ **2d, 3d:** $R=c-C_6H_{11}$ **2e, 3e:** $R=c-C_5H_9$ **2f, 3f:** $R=CH(OMe)_2$

First, the aldol reaction of Compound **1** with isobutyraldehyde was explored under various conditions (Table 6 hereinafter). A mixture of donor aldehyde **1** (2 mmol), acceptor isobutyraldehyde (5 equivalents to **1**), and L-proline (30 mol% to **1**) in DMSO (4 mL) was stirred at room temperature (rt) for 16 hours (entry 1). The desired aldol product **2a** was obtained in 62% yield with high diastereoselectivity (dr = 10:1) and enantioselectivity (95% ee); side products were the dehydration product of **2a** and the self-aldol product of donor aldehyde **1**.

It was previously demonstrated that α,α -disubstituted aldehydes were less reactive than

α -monosubstituted aldehydes as donors in the L-proline-catalyzed aldol reactions. [(8)(b) Mase et al., *Org. Lett.* **2003**, 5, 4369.] In the reaction of Compound **1** and isobutyraldehyde, only Compound **1** acted as the donor. No formation of self-aldol product of isobutyraldehyde and of α,α -dimethyl- β -hydroxy- γ -amino aldehyde was observed.

The reactions in DMF and in N-methylpyrrolidone (NMP) also gave good results in terms of yield, dr, and ee (entries 2 and 3). The same reaction in NMP afforded a higher yield (86%) of **2a** than did the reaction in DMSO primarily as a consequence of suppression of side products formation. Although a longer reaction time was required, the reaction performed in NMP at 4 °C provided excellent diastereoselectivity (dr = >100:1) and enantioselectivity (>99.5% ee) (entry 4). When higher concentrations were used, a shorter reaction time afforded the same yield with excellent diastereo- and enantioselectivities (entries 5 and 6).

Aldehyde **2a** could be used without purification in additional transformations. Oxidation of the crude aldol product **2a** with NaClO₂ and then esterification afforded **3a** (Scheme 2) in good yield with high diastereo- and enantioselectivities (73% from **1**, dr = >100:1, >99.5% ee) (entry 7). The reaction in the presence of (S)-5-pyrrolidine-2-yl-1H-tetrazole (**4**) [(6)(b) Torii et al., *Angew. Chem. Int. Ed.* **2004**, 43, 1983. (c) Hartikka et al., *Tetrahedron: Asymmetry* **2004**, 15, 1831. (i) Momiyama et al., *Proc. Natl. Acad. Sci. U.S.A.* **2004**, 101, 5374. (j) Cobb et al., *Synlett* **2004**, 558.] also afforded product **2a** in excellent yield with excellent diastereo- and

enantioselectivities (entry 8), whereas reaction with another aldol catalyst, (S)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine/(S)-(+)-camphorsulphonic acid [(b) Mase et al., *Org. Lett.* **2003**, 5, 4369. (e) Sakthivel et al., *J. Am. Chem. Soc.* **2001**, 123, 5260.], gave **2a** in low yield when the same reaction time was used, albeit with >99% ee for anti-**2a**.

Table 6

entry	solvent	conc. ^a	temp.	Time (h)	yield (%) ^b	dr (anti:syn) ^c	ee ^d
1	DMSO	0.5 M	rt	16	62 (2a)	10:1 (2a)	95 (2a)
2	DMF	0.5 M	rt	48	75 (2a)	5:1 (2a)	88 (2a)
3	NMP	0.5 M	rt	72	86 (2a)	>10:1 (2a)	94 (2a)
4	NMP	0.5 M	4 °C	144	93 (2a)	>100:1 (2a)	>99 (2a)
5	NMP	1.0 M	4 °C	72	91 (2a)	>100:1 (2a)	>99 (2a)
6	NMP	2.0 M	4 °C	36	87 (2a)	>100:1 (2a)	>99.5 (2a)
7	NMP	2.0 M	4 °C	36	73 (3a)	>100:1 (3a)	>99.5 (3a)
8 ^e	NMP	2.0 M	rt	16	76 (3a)	>100:1 (3a)	99.5 (3a)

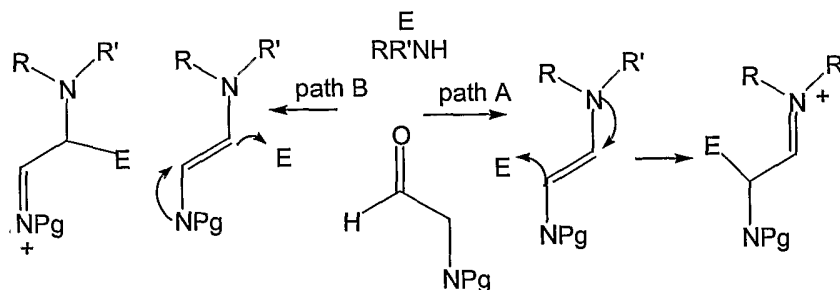
^a Concentration of aldehyde Compound **1** in the reaction mixture. ^b Yield of product **2a** or of product **3a** (from Compound **1**) as indicated in parentheses. See Scheme 2 ^c Diastereomeric ratio of **2a** without purification or of purified **3a**. The dr was determined by ¹H NMR. anti-Isomer = (2S*,3S*)-isomer. ^d Enantiometric excess of (2S,3S)-**2a** or of (2S,3S)-**3a**. The ee of (2S,3S)-**2a** was determined by chiral-phase HPLC analysis of the corresponding oxime prepared with O-benzylhydroxylamine. The ee of (2S,3S)-**3a** was determined by chiral-phase HPLC analysis. ^e Catalyst = L-Proline except for entry 8 where the catalyst was (**4**) = (S)-5-pyrrolidine-2-yl-1H-tetrazole.

Slow addition of the donor aldehyde was not required to obtain **2a** in good yield when 5-10 equivalents of the acceptor aldehyde to the donor aldehyde Compound **1** were used in the reaction with L-proline or **4**; the formation of the self-aldol product of aldehyde Compound **1** was minimized. This result stands in contrast to the aldol reactions of α -oxyaldehydes: Aldol reactions of α -oxyaldehydes

with isobutyraldehyde afforded the desired aldol products in moderate yields (along with a significant amount of the self-aldol product of α -oxyaldehyde), even after slow addition (over 36 hours) of the donor α -oxyaldehyde. [(6)(a) Northrup et al., *Angew. Chem. Int. Ed.* **2004**, 43, 2152.]

The use of a di-N-protected (diprotected) amino group such as that of phthalimidoacetaldehyde of Compound (1) was a key for this reaction. The enamine intermediates in the reactions of N-protected glycine aldehydes can react via one or both pathways shown in Scheme 7, wherein R and R' are hypothetical substituents on the chiral catalyst molecule and Pg is a double protecting group such as phthalimido or two N-acetyl groups.

Scheme 7



Protection of the α -amino group of glycine aldehyde as phthalimide permitted the selective reaction via path A. Aldehyde Compound 1 can be synthesized in large scale in two steps; reaction of allylamine with phthalic anhydride [See (1) hereinbefore] followed by ozonolysis provides a crystalline product that is stable for at least several months at room temperature. *t*-Butyloxy-

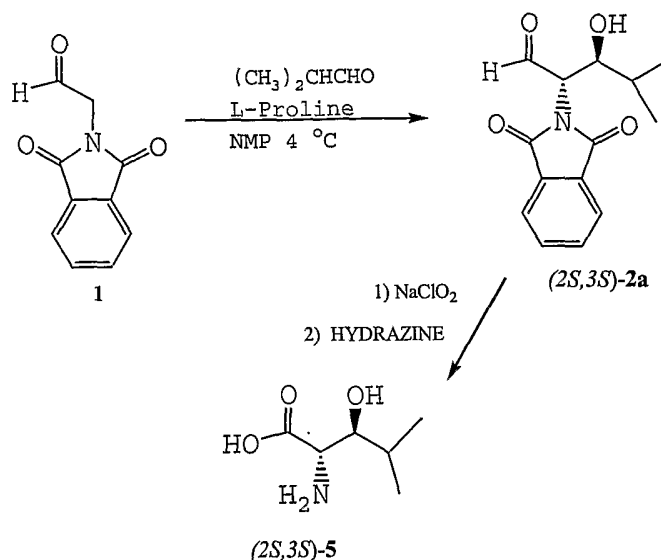
carbonyl- (Boc) and benzoyl-protected glycine aldehyde derivatives were less optimal as donors in this reaction as compared to phthalimidoacetaldehyde (1). Succinimido or maleimido derivatives are similar to the phthalimido derivatives.

To determine the relative stereochemistry and absolute configuration, aldol product Compound **2a** was transformed into 3-hydroxyleucine (Compound 5) via oxidation of the aldehyde with NaClO₂ and deprotection of the phthalimide with hydrazine. Aldol product **2a** obtained from the L-proline-catalyzed reaction afforded (2S,3S)-Compound 5, [(2)(c) Laib, et al., *J. Org. Chem.* **1998**, 63, 1709. (d) Nagamitsu et al., *J. Am. Chem. Soc.* **1996**, 118, 3584. (e) Panek et al., *J. Org. Chem.* **1998**, 63, 2382; (12)(a) Makino et al., *Tetrahedron: Asymmetry* **2001**, 12, 1757. (b) Williams et al., *Tetrahedron* **1996**, 52, 11673. (c) Hale et al., *Tetrahedron* **1994**, 50, 9181. (d) Kanemasa et al., *Tetrahedron Lett.* **1993**, 34, 8293. (e) Corey et al., *Tetrahedron Lett.* **1992**, 33, 6735. (f) Caldwell et al., *Synthesis* **1990**, 34.] as determined by ¹H-NMR spectra and by optical rotation, and the data were identical with the literature values. The stereochemical course of the aldol reaction to afford (2S,3S)-Compound **2a** is in accordance with the transition states suggested for other L-proline-catalyzed aldol reactions. [(8)(e) Sakthivel et al., *J. Am. Chem. Soc.* **2001**, 123, 5260. (13) Bahmanyar, *Org. Lett.* **2003**, 5, 1249.] Procedures developed here were easily performed on a semi-preparative scale.

The aldol reaction to afford Compound **2a** was performed on a 10.5 mmol scale (2 g of aldehyde 1) and the resulting aldol products were further

transformed to (2*S*,3*S*)-Compound **5** (940 mg, 60 % from **1**). This reaction is shown more specifically in Scheme 8 hereinbelow.

Scheme 8



A series of acceptor aldehydes was used to study the scope of the reaction. Results of reactions with α,α -disubstituted aldehyde acceptors are shown in Table 7, hereinafter.

Reactions with 2-ethylbutyraldehyde, cyclohexanecarboxaldehyde ($\text{c-C}_6\text{H}_{11}\text{CHO}$), and cyclopentanecarboxaldehyde ($\text{c-C}_5\text{H}_9\text{CHO}$), provided aldol products at $4\text{ }^\circ\text{C}$ and these product aldehydes were transformed to the corresponding methyl esters in good yields (62-75 % from Compound **1**) with high enantioselectivities (94-98% ee) (entries 1, 3, and 4). The diastereoselectivities of the aldol reactions were also high (dr = >10:1 to 15:1). The diastereomeric ratio of the aldol products decreased by epimerization at C2 when the compounds were stored or when they were purified by silica gel column.

chromatography. [See (9) (b) Notz et al., *J. Org. Chem.* **2003**, 68, 9624. (c) Cordova et al., *J. Am. Chem. Soc.* **2002**, 124, 1866.] The column chromatography did not completely separate the anti- and syn-isomers of Compound 3 from each other.

The reaction with di-n-butylacetaldehyde, an aldehyde bearing a bulky group, was slow at 4 °C and was performed at room temperature (rt; entry 2). This case also provided the desired product with high enantioselectivity (93% ee). The reaction with α -dimethoxy acetaldehyde, available in aqueous solution, afforded the desired aldol product with low diastereoselectivity, but 86% ee in the presence of water (entry 5).

Thus, the aldol reaction of Compound 1 was efficient for the synthesis of a broad range of enantiomerically enriched γ -branched- β -hydroxy- α -amino acid derivatives. Results for reactions illustrated in Scheme 2 are shown in Table 7, again only Compound 1 acted as the donor.

Table 7^a

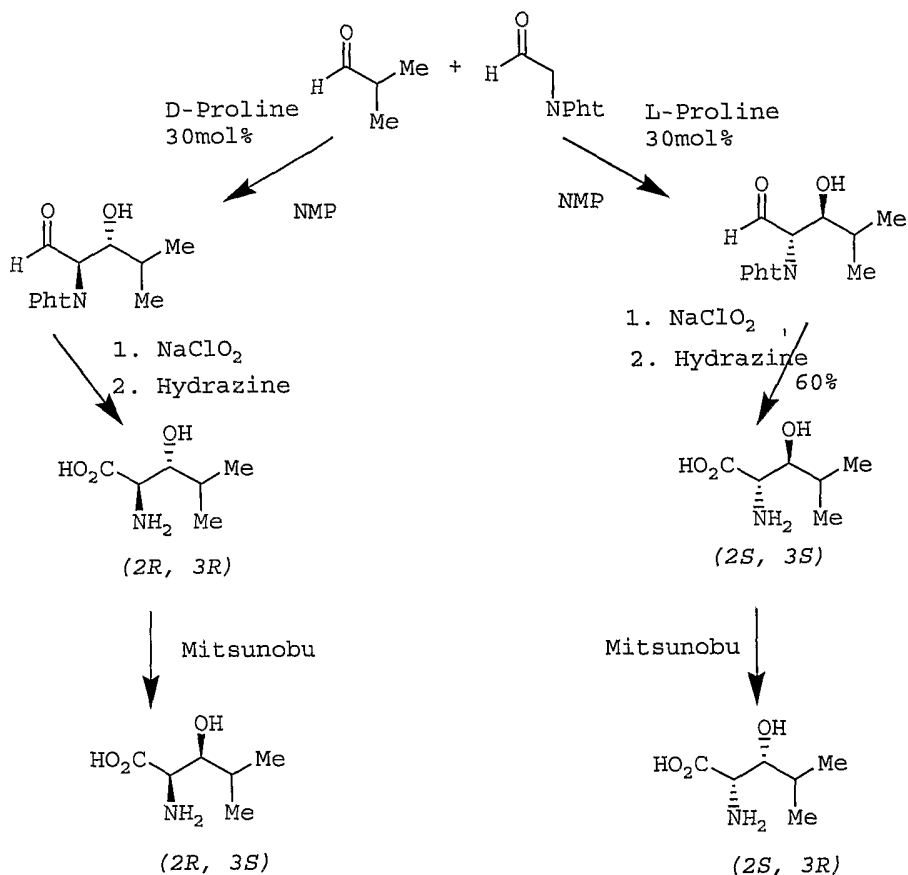
entry	R	Compound 2		ee (%) ^e	Yield (%) ^c
		product	dr (anti:syn) ^b		
1	CHEt ₂	2b	>10:1	--	--
2 ^f	CH(nBu) ₂	2c	10:1	--	--
3	c-C ₆ H ₁₁	2d	15:1	--	--
4	c-C ₅ H ₉	2e	14:1	--	--
5 ^h	CH(OMe) ₂	2f	5:1	--	--
Compound 3					
entry	R	product	dr (anti:syn) ^b	ee (%) ^e	Yield (%) ^c
1	CHEt ₂	3b	>10:1	94	75
2 ^f	CH(nBu) ₂	3c	7:1	93	68
3	c-C ₆ H ₁₁	3d	5:1	98	73
4	c-C ₅ H ₉	3e	16:1	98 ^g	62
5 ^h	CH(OMe) ₂	3f	1:1	86 (syn, 68)	69

^a Unless otherwise noted, a mixture of Compound 1 (2 mmol), acceptor aldehyde (10-20 mmol), and L-proline

(0.6 mmol) in N-methylpyrrolidone (NMP) (1 mL) was stirred at 4 °C for 16-48 hours for the aldol reaction. See Scheme 2. ^b Diastereomeric ratio of Compound 2 determined by ¹H NMR analysis of the reaction mixture without purification. ^c Isolated yields of Compound 3 (from Compound 1). ^d Diastereomeric ratio of Compound 3 after purification using silica gel column chromatography, determined by ¹H NMR analysis. ^e Enantiomeric excess of anti-Compound 3 determined by chiral-phase HPLC analysis, except noted. ^f The reaction was performed at rt. ^g The ee of anti-Compound 2e was determined by HPLC analysis of the corresponding oxime prepared with O-benzylhydroxylamine. ^h The reaction mixture included water.

It is seen that following the teachings laid out herein, a skilled worker can selectively prepare both enantiomers and both diastereomers of a desired α -amino- β -hydroxy acid. An illustrative synthetic reaction scheme for those preparations is laid out below in Scheme 9, wherein "Pht" is phthalimido. The last steep in each sequence involves an inversion in configuration of the β -hydroxyl group. That change is accomplished using a Mitsunobu Reaction as illustrated in Hughes, *Org. Reactions*, **1992**, 42, 335-656.

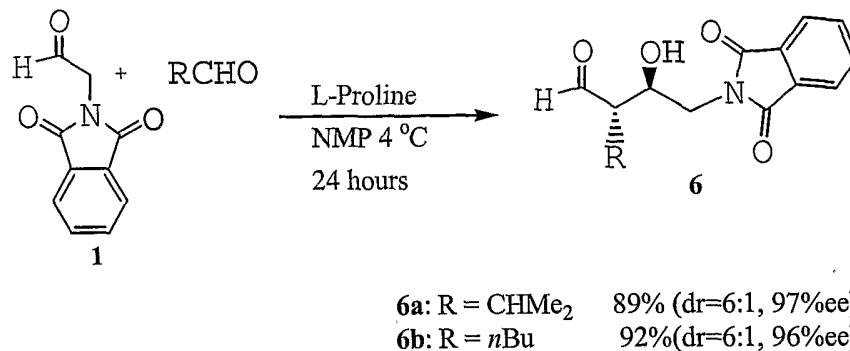
Scheme 9



Aldehyde reaction partner selection was key in order to assign donor and acceptor roles to aldehydes in the previously discussed aldol reaction. Aldol reactions between Compound 1 and α -non-branched aldehydes such as isovaleraldehyde and hexanal afforded β -hydroxy- γ -(diprotected)amino aldehydes Compounds 6 under identical conditions to those used in Table 5 (see, Scheme 10, hereinbelow, wherein R is a non-branched substituent containing at least two hydrogen atoms). No formation of β -hydroxy- α -amino aldehydes was detected. In these instances, aldehyde Compound 1 acted as the acceptor. Slow addition of aldehyde Compound 1 to isovaleraldehyde in the

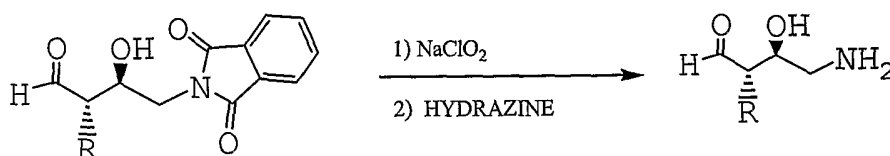
presence of the catalyst did not change the outcome of the reaction.

Scheme 10



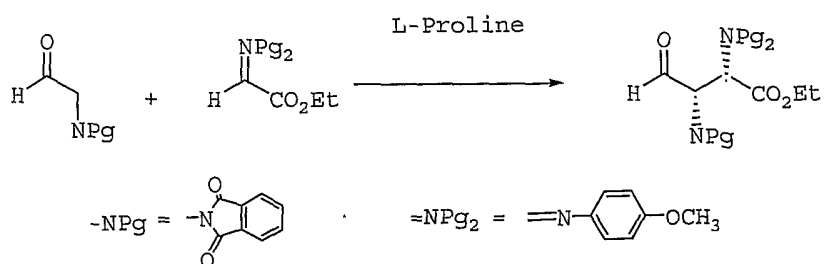
A β -hydroxy- γ -(diprotected)amino aldehyde of Scheme 10 can be deprotected and oxidized as discussed elsewhere herein to form the corresponding β -hydroxy- γ -amino acid as is shown in Scheme 10a, below.

Scheme 10a



An illustrative Mannich reaction utilized N-phthalimidoglycine aldehyde as the donor and ethyl α -(N-p-methoxyphenylimino)glyoxylate as acceptor with L-proline as catalyst to form a Mannich product having a 98% enantiomeric excess. This reaction is shown below in Scheme 11.

Scheme 11



A series of illustrative Michael reactions was carried out using *trans*- β -nitrostyrene as the acceptor and N-phthalimidoglycinealdehyde as the donor. Several solvents were utilized as were several chiral amine catalysts to achieve enantiomeric excess of up to about 90%.

An illustrative reaction is shown below in Scheme 12, wherein "NPg" is a phthalimido group and "Ph" is phenyl. The reaction was carried out at room temperature (rt) and using 20 mole percent catalyst. Results using this reaction system and two solvents (chloroform and dimethyl sulfoxide) are shown in Table 8 hereinafter.

Scheme 12

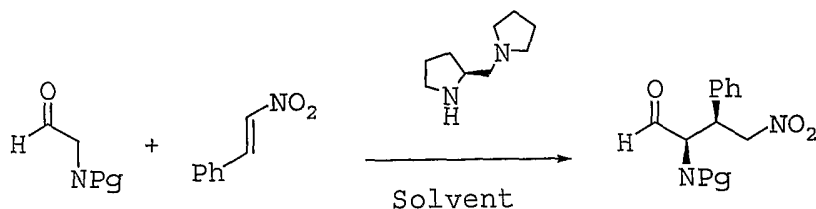
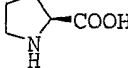
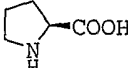
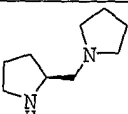
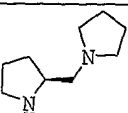


Table 8

Entry	Solvent	Time (Hours)	dr	ee (%)
1	DMSO+CHCl ₃ (5:5)	16	2.3:1	53:10
2	DMSO+CHCl ₃ (6:4)	24	1.7:1	61:5
3	DMSO+CHCl ₃ (7:3)	24	2:1	63:7
4	DMSO+ CHCl ₃ (8:2)	24	2:1	64:0
5	DMSO+ CHCl ₃ (9:1)	48	2.4:1	65:27
6	DMSO+ CHCl ₃ (1:9)	16	1.8:1	52:1
7	DMSO+ CHCl ₃ (2:8)	16	1.9:1	54:9
8	DMSO+ CHCl ₃ (3:7)	16	2:1	55:3
9	DMSO+ CHCl ₃ (4:6)	16	1.8:1	63:10
10	DMSO (100%)	48	2.7:1	65:19
11	CHCl ₃ (100%)	16	2:1	67:2

The same reaction was studied using different catalysts, times and an additive, -sparteine. The results of that study are shown in Table 9, below.

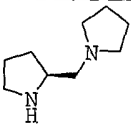
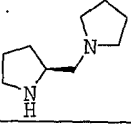
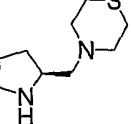
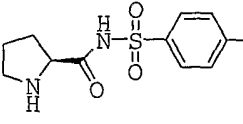
Table 9

Entry	Catalyst	Solvent	Time (Hours)	Ratio	ee (%)
1		DMSO	2	Messy	--
2		CHCl ₃	1	2:1	18
3		DMSO	1	Messy	--
4		CHCl ₃	48	10:1	95

The same Michael addition was studied further by varying the catalyst used while maintaining the use of chloroform as solvent and

using 10 mole % -sparteine as an additive alone and with tetrazole as a further additive in one instance. Those results are shown in Table 10, below

Table 10

Entry	Catalyst	Additive	Time (Hours)	Ratio	ee (%)
1		Tetrazole	1	1.2:1	55:8
2		--	About 18	1:1	55:--
3		--	24	1.5:1	80:0
4		--	48	1.4:1	8:68

A further study of the same reaction was carried out by varying the amount of the -sparteine additive. Those results are shown in Table 11, below.

Table 11

Entry	Additive (mol %)	Time (Hours)	dr Ratio	ee (%)
1	5	24	9:1	89
2	10	24	10:1	95
3	20	24	11:1	85

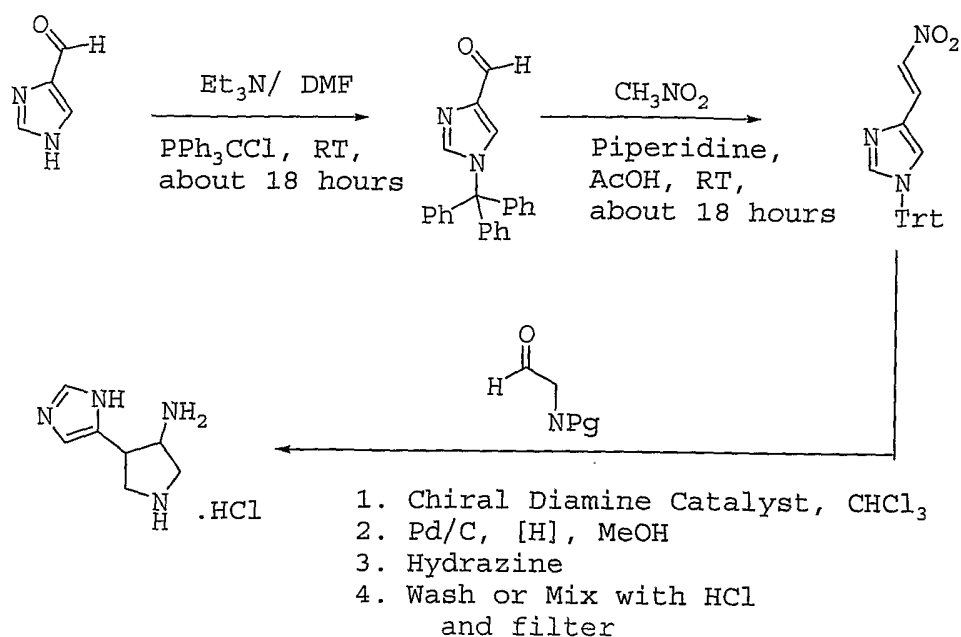
Results of a study of the same Michael reaction using a diamine catalyst as a function of added amine additive are shown in Table 12, below.

Table 12

Entry	Additive	Time (Hours)	dr Ratio	ee (%)
1	(+)-Cinchonine	24	1.6:1	60:0
2	(-)-Cinchonidine	24	1.8:1	66:0
3	Quinine	16	2:1	85:27
4	Quinindine	24	1.2:1	74:22
5	Quinuclidine	24	2:1	85:0
6	Hydroquinine	24	1:1	85:0
7	(DHQ) ₂ PHAL	24	1.3:1	63:8
8	(DHQD) ₂ PHAL	24	1.2:1	61:14
9	(-)-Nicotine	24	1.4:1	60:0
10	Brucine Hydrate	24	1.6:1	73:0
11	1,4-Dimethylpiperazine	24	1.5:1	65:0
12	DABCO	24	2:1	78:22
13	DBU	48	~10:1	86:--
14	(R)-(-)Quinuclidinol .HCl	24	2.3:1	68:7
15	(-)-Sparteine	48	10:1	91:--

Scheme 13, below, wherein "Pg" is phthalimido, "Ph" is phenyl and "rt" is room temperature, illustrates a synthesis for an analogue of the histamine H3 receptor agonist Sch 50971,1.

Scheme 13



Each of the patents and articles cited herein is incorporated by reference. The use of the article "a" or "an" is intended to include one or more.

The foregoing description and the examples are intended as illustrative and are not to be taken as limiting. Still other variations within the spirit and scope of this invention are possible and will readily present themselves to those skilled in the art.

WHAT IS CLAIMED:

1. A method for asymmetrically forming an α -(diprotectedamino)aldehyde or -ketone product having a chiral center and in which one enantiomer is in excess over the other comprising the steps of:

(a) reacting an enolizable α -(diprotectedamino)aldehyde or -ketone donor molecule with an excess of an unsaturated acceptor molecule that has one or no hydrogen atoms bonded to a carbon atom alpha to the carbon of the unsaturation, wherein the donor and acceptor molecules are dissolved or dispersed in a liquid solvent and are in the presence of a chiral amine catalyst to form an addition product reaction medium; and

(b) maintaining the reaction medium for a time sufficient to form an α -(diprotectedamino)-aldehyde or -ketone product having a chiral center formed at a carbon atom bonded to the α -(diprotectedamino) group and in which one enantiomer is in excess over the other.

2. The method according to claim 1 wherein said donor molecule contains 2 to about 28 carbon atoms exclusive of any carbon atoms that may be present in the diprotectedamino group.

3. The method according to claim 1 wherein said acceptor molecule contains 2 to about 30 carbon atoms exclusive of any carbon atoms that may be present in an amine protecting group.

4. The method according to claim 1 wherein said chiral amine catalyst contains up to about 25 carbon atoms.

5. The method according to claim 1 wherein said chiral amine catalyst is present in an amount of about 1 to about 50 mole percent based on the amount of donor molecule.

6. The method according to claim 1 wherein said solvent is liquid at a temperature of about -50°C to about 150°C.

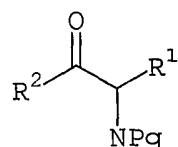
7. A method for asymmetrically forming an α -(diprotectedamino)aldehyde or -ketone product having a chiral center and in which one enantiomer is in excess over the other comprising the steps of:

(a) reacting (i) an enolizable α -(diprotectedamino)-aldehyde or -ketone donor molecule that contains 2 to about 28 carbon atoms exclusive of any carbon atoms that may be present in the diprotectedamino group with (ii) an excess of an unsaturated acceptor molecule that contains 2 to about 30 carbon atoms exclusive of any carbon atoms that may be present in an amine protecting group, wherein the donor and acceptor molecules are (iii) dissolved or dispersed in a liquid solvent that is liquid at a temperature of about -50°C to about 150°C. and are (iv) in the presence of a chiral amine catalyst that contains up to about 25 carbon atoms and is present in an amount of about 5 to about 50 mole percent based on the amount of donor molecule to form an addition product reaction medium; and

(b) maintaining the reaction medium for a time sufficient to form an α -(diprotectedamino)-aldehyde or -ketone product having a chiral center formed at a carbon atom bonded to the α -(diprotectedamino) group and in which one enantiomer is in excess over the other.

8. The method according to claim 7 including the further step of recovering the α -(diprotectedamino)aldehyde or -ketone product.

9. The method according to claim 7 wherein said donor molecule corresponds in structure to the formula



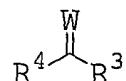
wherein -NPg is nitrogen and its protecting group;

R^1 is selected from the group consisting of hydrido, C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl, halogen, cyano and trifluoromethyl groups; and

R^2 is selected from the group consisting of hydrido, a C_1 - C_{18} straight chain, branched chain or cyclic hydrocarbyl group, an aryl group, and an aryl group substituted with a substituent selected from the group consisting of C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, hydroxyl, and a $-\text{CO}_2\text{R}^a$

group, wherein R^a is a C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group.

10. The method according to claim 7 wherein said acceptor molecule corresponds in structure to the formula



wherein W is an oxygen atom, a protected nitrogen atom or a carbon atom that is substituted with two substituents, R⁷ and R⁸, one or both of is an electron withdrawing substituent, and wherein the R⁷ or R⁸ group that is not an electron withdrawing group is selected from the group consisting of be a hydrido group, a substituent containing one to about 20 carbon atoms that is selected from the group consisting of:

- a branched chain hydrocarbyl,
- a cyclic hydrocarbyl,
- a cyclic group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,
- an aryl group,
- a substituted aryl group wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈ hydrocarbyloxy and hydroxyl, and
- a straight chain hydrocarbyl substituted with 1, 2 or 3 substituents selected from the group

consisting of (a) a halogen, (b) a C₁-C₈ hydrocarbyloxy group, (c) an aryl group, or (d) a substituted aryl group,

the R³ substituent contains one to about 29 carbon atoms and is selected from the group consisting of:

- a branched chain hydrocarbyl,
- a cyclic hydrocarbyl,
- a cyclic group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,

- an aryl group,
- a sulfonylaryl group,
- a nitro group,
- a C₁-C₈-hydrocarbyloxycarbonyl group,
- a substituted aryl group wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈-hydrocarbyloxy and hydroxyl, and

- a straight chain hydrocarbyl group substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C₁-C₈-hydrocarbyloxy group, (c) an aryl group, or (d) a substituted aryl group, and

the R⁴ substituent is hydrido or contains one to about 29 carbon atoms and is selected from the group consisting of:

- a branched chain hydrocarbyl,
- a cyclic hydrocarbyl,
- a cyclic group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are

oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,

an aryl group,

a sulfonylaryl group,

a nitro group,

a C₁-C₈-hydrocarbyloxycarbonyl group,

a substituted aryl group wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈-hydrocarbyloxy and hydroxyl, and

a straight chain hydrocarbyl group substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C₁-C₈-hydrocarbyloxy group, (c) an aryl group, or (d) a substituted aryl group.

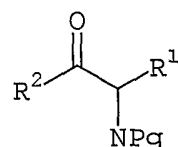
11. The method according to claim 7 wherein the donor and acceptor react in an aldol addition reaction, a Mannich reaction or a Michael addition reaction.

12. A method of asymmetrically forming a beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone that comprises the steps of:

(a) reacting an alpha-(diprotectedamino)-aldehyde or -ketone donor molecule with an excess of an alpha-disubstituted aldehyde acceptor molecule dissolved or dispersed in a solvent and in the presence of a chiral amine catalyst to form a reaction medium; and

(b) maintaining said reaction medium for a time sufficient to form a beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone.

13. The method according to claim 12 wherein said alpha-(diprotectedamino)-aldehyde or -ketone donor has a formula that corresponds in structure to



in which -NPg is a nitrogen protecting group selected from the group consisting of phthalimido, succinimido, maleimido, dibenzylimino, diacetylimido, ditrifluoroacetylimido, di-*t*-butyloxycarbonylimido, di-*p*-toluenesulfonimido, dicarbobenzyloxycarbonylimido and azido,

R¹ is selected from the group consisting of hydrido, C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl, halogen, cyano and trifluoromethyl groups; and

R² is selected from the group consisting of hydrido, C₁-C₁₈ straight chain, branched chain or cyclic hydrocarbyl, aryl or aryl substituted with a substituent selected from the group consisting of a C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, hydroxyl, and a -CO₂R³ group, wherein R³ is a C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group.

14. The method according to claim 12 wherein the acceptor aldehyde molecule contains 2 to about 20 carbons, and one or no hydrogen atoms are bonded to the alpha-carbon.

15. The method according to claim 14 wherein said alpha-carbon of said acceptor aldehyde molecule further contains a substituent that has one to 18 carbon atoms that is selected from the group consisting of

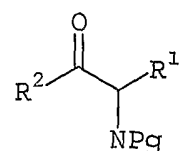
- a branched chain hydrocarbyl group,
- a cyclic hydrocarbyl group,
- a cyclic hydrocarbyl group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,
- a straight chain hydrocarbyl group substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C₁-C₈ alkoxy group, (c) an aryl group, or (d) a substituted aryl group wherein the substituent is selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C₁-C₈ alkoxy and hydroxyl,
- an aryl group, and
- a substituted aryl group.

16. The method according to claim 12 wherein said chiral amine catalyst contains up to about 25 carbon atoms.

17. A method of asymmetrically forming a beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone that comprises the steps of:

(a) reacting an alpha-(diprotectedamino)-aldehyde or -ketone donor molecule with an excess of an alpha-disubstituted aldehyde acceptor molecule dissolved or dispersed in a solvent that is free of aldehydic, ketonic, acidic and ester carbonyl groups and in the presence of a chiral amine catalyst that contains up to about 25 carbon atoms to form a reaction medium, wherein

said alpha-(diprotectedamino)aldehyde or -ketone donor has a formula that corresponds in structure to



in which -NPg is a nitrogen protecting group selected from the group consisting of phthalimido, succinimido, maleimido, dibenzylimino, diacetylimido, ditrifluoroacetylimido, di-*t*-butyloxycarbonylimido, di-*p*-toluenesulfonimido, dicarbobenzyloxycarbonylimido and azido,

R^1 is selected from the group consisting of hydrido, C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl, halogen, cyano and trifluoromethyl groups; and

R^2 is selected from the group consisting of hydrido, C_1 - C_{18} straight chain, branched chain or cyclic hydrocarbyl, aryl and aryl substituted with a substituent selected from the group consisting of a C_1 - C_8 straight chain, branched chain or cyclic

hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, hydroxyl, and a $-\text{CO}_2\text{R}^a$ group, wherein R^a is a C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group,

said alpha-disubstituted aldehyde acceptor molecule is present in about 1- to about 20-fold molar excess over the donor molecule; and

said the acceptor aldehyde molecule contains 2 to about 20 carbons, and one or no hydrogen atoms are bonded to the alpha-carbon, and the alpha-carbon of said acceptor aldehyde molecule further contains a substituent that has one to 18 carbon atoms that is selected from the group consisting of

a branched chain hydrocarbyl group,

a cyclic hydrocarbyl group,

a cyclic hydrocarbyl group containing 1 to 3 heteroatoms in the ring, wherein the heteroatoms are oxygen, sulfur and trisubstituted nitrogen atoms, or two of the three heteroatoms,

a straight chain hydrocarbyl group substituted with 1, 2 or 3 substituents selected from the group consisting of (a) a halogen, (b) a C_1 - C_8 alkoxy group, (c) an aryl group, or (d) a substituted aryl group wherein the substituent is selected from the group consisting of C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, C_1 - C_8 alkoxy and hydroxyl,

an aryl group, and

a substituted aryl group, and

(b) maintaining said reaction medium for a time sufficient to form a beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone.

18. The method according to claim 12 wherein an aldehyde is formed and R² is hydrido.

19. The method according to claim 12 wherein said solvent that is a liquid at a temperature of about -50°C to about 150°C.

20. The method according to claim 12 including the further step of recovering the beta-hydroxy-alpha-(diprotectedamino)aldehyde or -ketone.

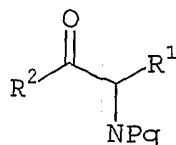
21. A method of preparing a β -hydroxy- α -amino butyric acid that comprises the steps of oxidizing and deprotecting a beta-hydroxy-alpha-(diprotectedamino)aldehyde of claim 12.

22. A method of asymmetrically forming an α,β -(protected-diamino)aldehyde or -ketone that comprises the steps of:

(a) reacting an alpha-(diprotectedamino)-aldehyde or -ketone donor molecule with an excess of an unsaturated acceptor molecule that is present as an imine dissolved or dispersed in a solvent and in the presence of a chiral amine catalyst to form a reaction medium; and

(b) maintaining said reaction medium for a time sufficient to form an α,β -(protected-diamino)aldehyde or -ketone.

23. The method according to claim 22 wherein said donor molecule corresponds in structure to the formula



wherein -NPg is nitrogen and its protecting group;

R¹ is selected from the group consisting of hydrido, C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl, halogen, cyano and trifluoromethyl groups; and

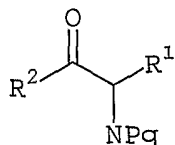
R² is selected from the group consisting of hydrido, a C₁-C₁₈ straight chain, branched chain or cyclic hydrocarbyl group, an aryl group, and an aryl group substituted with a substituent selected from the group consisting of C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, hydroxyl, and a -CO₂R^a group, wherein R^a is a C₁-C₈ straight chain, branched chain or cyclic hydrocarbyl group.

24. A method of asymmetrically forming an α-(diprotectedamino)aldehyde or -ketone that comprises the steps of:

(a) reacting an alpha-(diprotectedamino)-aldehyde or -ketone donor molecule across the double bond of an excess of an ethylenically unsaturated acceptor molecule that is present dissolved or dispersed in a solvent and in the presence of a chiral amine catalyst to form a reaction medium; and

(b) maintaining said reaction medium for a time sufficient to form an α -(diprotectedamino)-aldehyde or -ketone.

25. The method according to claim 24 wherein said donor molecule corresponds in structure to the formula



wherein -NPg is nitrogen and its protecting group;

R^1 is selected from the group consisting of hydrido, C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl, halogen, cyano and trifluoromethyl groups; and

R^2 is selected from the group consisting of hydrido, a C_1 - C_{18} straight chain, branched chain or cyclic hydrocarbyl group, an aryl group, and an aryl group substituted with a substituent selected from the group consisting of C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group, halogen, cyano, trifluoromethyl, nitro, hydroxyl, and a $-\text{CO}_2\text{R}^a$ group, wherein R^a is a C_1 - C_8 straight chain, branched chain or cyclic hydrocarbyl group.

26. In the method of reacting an enolizable donor aldehyde or ketone molecule with an unsaturated acceptor molecule in a carbon-to-carbon bond-forming addition reaction, the improvement that comprises reacting an α -(diprotectedamino)-

aldehyde or -ketone as the enolizable donor molecule with an excess of said acceptor molecule in the presence of a chiral amine catalyst dissolved or dispersed in a solvent to form an alpha-(diprotectedamino)aldehyde or -ketone product in which one enantiomer is in excess over the other.

27. The method of claim 26 wherein said carbon-to-carbon bond-forming addition reaction is an aldol, Michael or Mannich reaction.

28. The method according to claim 26 including the further step of removing the protecting group.

29. The method according to claim 26 wherein the product is an aldehyde and including the further step of oxidizing the product aldehyde to form an acid.

30. The method according to claim 29 wherein said oxidation is carried out prior to removing said protecting group.

31. The method according to claim 26 wherein said alpha-(diprotectedamino)-aldehyde donor molecule is diprotected-glycine aldehyde.

32. The method according to claim 31 wherein said diprotecting group is a phthalimido group.