PROCESS OF MAKING α-AMINOXYKETONE/α-AMINOXYALDEHYDE AND α-HYDROXYKETONE/α-HYDROXYALDEHYDE COMPOUNDS AND A PROCESS OF MAKING REACTION PRODUCTS FROM CYCLIC α,β-UNSATURATED KETONE SUBSTRATES AND NITROSO SUBSTRATES

The present invention is directed to a process of making α-aminoxyketone and α-hydroxyketone compounds. The synthetic pathway generally involves reacting an aldehyde or ketone substrate and a nitroso substrate in the presence of a catalyst of formula (IV), wherein X¹-X¹ represent independently nitrogen, carbon, oxygen or sulfur and Z represents a 4 to 10-membered ring with or without a substituent and optionally a further step to convert the α-aminoxyketone compound formed to the α-hydroxyketone compound. The present invention results in α-aminoxyketone and α-hydroxyketone compounds with high enantiomer/electivity and high purity. The present invention is also directed to a catalytic asymmetric O-nitroso Aldol / Michael reaction. The substrates of this reaction are generally cyclic α,β-unsaturated ketone substrate and a nitroso substrate. This methodology generally involves reacting the cyclic α,β-unsaturated ketone substrate and the nitroso substrate in the presence of a proline-based catalyst, to provide a heterocyclic product.
TITLE OF THE INVENTION
PROCESS OF MAKING α-AMINOXYKETONE/α-AMINOXYALDEHYDE AND α-HYDROXYKETONE/α-HYDROXYALDEHYDE COMPOUNDS AND A PROCESS OF MAKING REACTION PRODUCTS FROM CYCLIC α,β-UNSATURATED KETONE SUBSTRATES AND NITROSO SUBSTRATES

INCORPORATION BY REFERENCE
This application claims benefit of Japanese patent application Serial No. ________ filed February 20, 2004 and U.S. Provisional Application Serial No. 60/564,048 filed April 20, 2004.

The foregoing applications, and all documents cited therein or during their prosecution ("appln cited documents") and all documents cited or referenced in the appln cited documents, and all documents cited or referenced herein ("herein cited documents"), and all documents cited or referenced in herein cited documents, together with any manufacturer’s instructions, descriptions, product specifications, and product sheets for any products mentioned herein or in any document incorporated by reference herein, are hereby incorporated herein by reference, and may be employed in the practice of the invention.

STATEMENT OF FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT
The subject matter of this application was in part funded by the National Institutes of Health (GM068433-01). The government may have certain rights in this invention.

FIELD OF THE INVENTION
This invention relates to a process of making α-aminoxyketones or α-hydroxyketones with high enantioselectivity and high purity and also describes the catalytic methods involves in the process of making α-aminoxyketones or α-hydroxyketones. The invention is also directed to a catalytic asymmetric O-nitroso Aldol/Michael reaction. The substrates of this reaction are generally a cyclic α,β-unsaturated ketone substrate and a nitroso substrate. This methodology generally involves reacting the cyclic α,β-unsaturated ketone substrate and the nitroso substrate in the presence of a proline-based catalyst, to provide a heterocyclic product.

BACKGROUND OF THE INVENTION
α-Hydroxyketone compounds are found in natural products and frequently in the molecule framework of pharmaceutical compounds. They are synthetic equivalents for aldose compounds, e.g. pentoses and hexoses, and are very important synthetic building...
blocks which can lead to various physiologically active materials, medicines and intermediates in the synthesis of liquid crystalline materials.

\( \alpha \)-Hydroxyketones can be obtained readily with high purity by asymmetric oxidation of carbonyl compounds. However, asymmetric oxidation of the \( \alpha \)-position of the carbonyl group by the usual methods requires a two-step process. First, the preparation and isolation of an enolate, and second, the use of a relatively expensive oxygen-introducing reagent, which have the problem of low atom efficiency.

Other methods for direct preparation of chiral \( \alpha \)-hydroxyketones without isolation of an enolate have been reported.


However, many problems remain unsolved with this method, including a lack of catalytic efficiency (10 to 20 mol % catalyst are needed) and an inability to consistently reproduce results. Moreover, it is known that a second unwanted oxygen atom may be introduced via a side reaction with a second equivalent of nitrosobenzene.

Alternatively, it was reported that \( \alpha \)-aminoxyketone could be obtained in high yield from an alkylsilyl ether and nitrosobenzene with alkylsilyl triflate as a Lewis Acid catalyst (see e.g. Momiyama, N., Yamamoto, H. (2002) Angew. Chem. Int. Ed. 41, 2986-2987) and also from an alkyltin enolate and nitrosobenzene with Ag-BINAP as a catalysis (see e.g. Momiyama, N., Yamamoto, H. (2003) J. Am. Chem. Soc. 125, 6038-6039).

Additionally, other methods have been disclosed to produce aldol products from the condensation reaction of carbonyl compounds by: (1) using a substrate with an ether or alcohol unit in the molecule with liquid CO\(_2\), or supercritical CO\(_2\) as a solvent (see e.g. Japanese Patent 2002- No. 284729); (2) running the reaction in water using boronic acid or a phase transfer catalyst or Brönsted acid (see e.g. Japanese Patent 2002-No. 275120); or (3) using a lanthanide triflate with a chiral crown ether (see e.g. Japanese Patent 2002-No. 200428).

Despite these numerous methods for synthesizing \( \alpha \)-aminoxyketone or \( \alpha \)-hydroxyketone compounds, there is still a need in the art for a process which can produce \( \alpha \)-aminoxyketone or \( \alpha \)-hydroxyketone compounds with sufficient enantioselectivity,
purity and/or reproducibility of results to enable these compounds to be suitable for use as synthetic building blocks or intermediates in a synthetic process.

One of the most intensely studied areas in chemical synthesis at present is the development of new catalytic and highly enantioselective processes. Especially, hetero Diels–Alder reactions have been one of the most powerful synthetic constructions to date. By using proline-based catalyst, we have also discovered a reaction process which provides a method for the catalytic asymmetric synthesis of bicyclo ketones which contain nitrogen and oxygen heteroatoms when reaction an α,β-unsaturated cyclic ketone with a nitroso compound, where the regiochemistry of this product is opposite that of the normal nitroso Diels-Alder reaction.

Citation or identification of any document in this application is not an admission that such document is available as prior art to the present invention.

SUMMARY OF THE INVENTION

The invention is based, in part, on applicants’ development of a process of making α-aminoxyketones or α-hydroxyketones with high enantioselectivity and high purity and method of preparing bicyclo ketones which contain nitrogen and oxygen heteroatoms when reacting an α,β-unsaturated cyclic ketone with a nitroso compound, where the regiochemistry of this product is opposite that of the normal nitroso Diels-Alder reaction.

The object of the invention provides a method to prepare α-aminoxyketone (which are precursors of α-hydroxyketones) and to develop new synthetic routes for making saccharide related compounds or glycosylation of compounds, especially those compounds with anti-cancer or anti-HIV effects.

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Another object of the invention is to provide a method of preparing bicyclo ketones which contain nitrogen and oxygen heteroatoms when reacting an α,β-unsaturated cyclic ketone with a nitroso compound, where the regiochemistry of this product is opposite that of the normal nitroso Diels-Alder reaction.

It is noted that in this disclosure and particularly in the claims and/or paragraphs, terms such as “comprises”, “comprised”, “comprising” and the like can have the meaning attributed to it in U.S. Patent law; e.g., they can mean “includes”, “included”, “including”, and the like; and that terms such as “consisting essentially of” and “consists essentially of”
have the meaning ascribed to them in U.S. Patent law, e.g., they allow for elements not explicitly recited, but exclude elements that are found in the prior art or that affect a basic or novel characteristic of the invention.

These and other embodiments are disclosed or are apparent from and encompassed by, the following Detailed Description.

**DETAILED DESCRIPTION**

This invention provides a method to prepare α-aminoxyketone (which are precursors of α-hydroxyketones) which comprises reacting an aldehyde of formula (I) or ketone of formula (II):

(I) \[ \text{R} \]

(II) \[ \text{R}^1 \text{R}^2 \]

with a nitroso compound of formula (IIIa) or (IIIb):

(IIIa) \[ \text{R}^3_n \]

(IIIb) \[ \text{R}^4 \]

in the presence of a solvent and a catalyst of formula (IV):

(IV) \[ \text{Z} \]

wherein:

R, R¹ and R² independently represent either hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted alkoxy group; a substituted or unsubstituted alkoxy carbonyl group; a substituted or unsubstituted aryl group; or

R¹ and R² together form a cycloalkyl ring;

R³ is each independently selected from the group consisting of:

consisting of hydrogen, halogen, -OR⁴, -OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NO₂, -NR⁴R⁵, -NRC(O)R⁴, -NR⁴CO₂R⁵, -NR⁴S(O)₂R⁵, -SR⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NR⁴R⁵, C₁₈ alkyl, C₂₈ alkenyl, C₂₈ alkynyl, C₃₈
cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; wherein
each R¹ and R² may be independently selected from the group consisting of
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-members heteroaryl, and 3- to 10-membered heterocyclyl;

n is an integer from 0-5;
R⁴ is substituted or unsubstituted alkyl;
X¹, X² and X³ independently represent oxygen; sulfur; substituted or unsubstituted nitrogen; or substituted or unsubstituted carbon; and
Z represents a substituted or unsubstituted 4 to 10-membered ring which optionally contain up to three additional heteroatoms.

Another embodiment of the invention is where:
R, R¹ and R² independently represent either hydrogen; a substituted or unsubstituted

C₁-C₈ alkyl group; a substituted or unsubstituted C₁-C₈ alkoxy group; a substituted or unsubstituted C₁-C₈ alkoxy carbonyl group; a substituted or unsubstituted aryl group, wherein the groups when substituted are substituted by the group consisting of of hydrogen, halogen, -OR⁴,
-OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NO₂, -NR⁴R⁵,
-NRC(O)R⁴, -NR⁴CO₂R⁵, -NR⁴S(O)₂R⁵, -SR⁴, -S(O)R⁴, -S(O)₂R⁴,
-S(O)₂NR⁴R⁵, C₁₋₈ alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; or
R¹ and R² together form a C₃₋₈ cycloalkyl ring;
R³ is each independently selected from the group consisting of:
consisting of hydrogen, halogen, -OR⁴, -OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴,
-C(O)NR⁴R⁵, -NO₂, -NR⁴R⁵, -NRC(O)R⁴, -NR⁴CO₂R⁵, -NR⁴S(O)₂R⁵, -SR⁴,
-S(O)R⁴, -S(O)₂R⁴, -S(O)₂NR⁴R⁵, C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; wherein
each R⁴ and R⁵ may be independently selected from the group consisting of
C₁₋₈ alkyl, C₂₋₈ alkenyl, C₂₋₈ alkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;
R⁴ is a substituted or unsubstituted C₁-C₈ alkyl, wherein when substituted are
substituted by the group consisting of halogen, -OR\textsuperscript{4}, -OC(O)R\textsuperscript{4}, -CN, -
C(O)R\textsuperscript{4}, -CO\textsubscript{2}R\textsuperscript{4}, -C(O)NR\textsuperscript{4}R\textsuperscript{5}, -NO\textsubscript{2}, -NR\textsuperscript{4}R\textsuperscript{5}, -NRC(O)R\textsuperscript{4}, -NR\textsuperscript{4}CO\textsubscript{2}R\textsuperscript{5},
-NR\textsuperscript{4}S(O)\textsubscript{2}R\textsuperscript{5}, -SR\textsuperscript{4}, -S(O)R\textsuperscript{4}, -S(O)\textsubscript{2}R\textsuperscript{4}, -S(O)\textsubscript{2}NR\textsuperscript{4}R\textsuperscript{5}, C\textsubscript{1-8} alkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-8} alkynyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{6-10} aryl, 5- to 10-membered
heteroaryl, and 3- to 10-membered heterocyclyl; wherein
each R\textsuperscript{4} and R\textsuperscript{5} may be independently selected from the group consisting of
C\textsubscript{1-8} alkyl, C\textsubscript{2-8} alkenyl, C\textsubscript{2-8} alkynyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{6-10} aryl, 5- to 10-
membered heteroaryl, and 3- to 10-membered heterocyclyl;
n is an integer from 0-3;

X\textsuperscript{1}, X\textsuperscript{2} and X\textsuperscript{3} independently represent oxygen; sulfur; substituted or unsubstituted
nitrogen; or substituted or unsubstituted carbon wherein the groups when
substituted are substituted by the group consisting of hydrogen, halogen
and C\textsubscript{1-8} alkyl; and

Z represents a substituted or unsubstituted C\textsubscript{4}-C\textsubscript{10} membered ring, wherein the ring
contains one additional heteroatom selected from the group consisting of oxygen
and nitrogen and the groups when substituted are substituted by the group
consisting of hydrogen, halogen, C\textsubscript{1-8} alkyl and C\textsubscript{1-8} alkoxy.

In another embodiment of the invention, advantageous alkyl group for R\textsuperscript{1}, R\textsuperscript{2}
include linear or cyclic alkyl groups with 1-30 carbons which include but are not limited to
methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, n-decyl,
cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, or cyclodecyl.

In another embodiment of the invention, advantageous alkoxy group,
alkoxycarbonyl group and aryl group for R, R\textsuperscript{1}, R\textsuperscript{2} are alkoxy groups with 1-30 carbons
which include but are not limited to methoxy, ethoxy, n-propoxy, n-butoxy, n-pentyloxy,
n-hexyloxy, cyclohexyloxy, phenoxy; alkoxy carbonyl group with 1-30 carbons which
include but are not limited to methoxy-carbonyl, ethoxy-carbonyl, butoxy-carbonyl,
pentyloxy-carbonyl and the aryl group with 6-30 carbon atoms which include but are not
limited to phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 2-anthryl, 9-anthryl, 1-phenanthryl, 2-
phenanthryl, benzyl, or phenyl.

In another embodiment of the invention, advantageous alkyl groups, alkoxy
groups, alkoxy-carbonyl groups and aryl groups for R, R\textsuperscript{1} and R\textsuperscript{2} include but are not
limited to methyl, ethyl, n-propyl, n-butyl, cyclohexyl, cycloheptyl, as a alkyl group;
phenyl, 1-naphthyl, 2-naphthyl, 1-anthryl, 1-phenanthryl, benzyl as an aryl group; and
advantageous substituents include but are not limited to F, Cl, or Br as a halogen group;
methoxy, ethoxy, propoxy, butoxy as an alkoxy group; or hydroxyl, carboxyl, acyl, amino, thio, or nitro group.

In another embodiment of the invention, advantageous ring systems for $R^1$, $R^2$ include but are not limited to cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, cyclodecane as an alkyl group; or benzene, naphthalene, anthracene, as an aromatic; or pyridine, pyrroldidine, piperidine, furan, pyran, tetrahydrofuran, tetrahydropyran as heteroaromatics.

In another embodiment of the invention, advantageous aldehydes of formula (I) include but are not limited to acetaldehyde, propionaldehyde, isobutyaldehyde, valeraldehyde, isovaleraldehyde, caproaldehyde, heptaldehyde, caprylic aldehyde, caprylic aldehyde, undecylaldehyde, lauraldehyde, tridecylaldehyde, pentadecylaldehyde, palmitic aldehyde, stearic aldehyde, squaric aldehyde.

In another embodiment of the invention, advantageous ketones of formula (II) include but are not limited to acetone, ethylmethylketone, propylmethylketone, isopropylmethylketone, butylmethylketone, diethylketone, diisopropylketone, 2-undecanone, fluoroacetone, chloroacetone, 2,4-pentadione, cyclobutanone, cyclopentanone, 2-methylcyclohexanone, cyclohexancanone, 2-norbornanone, 2-adamantanone, tetrahydropryane-4-one, spiro[4,5]-1,4-dioxy-decane-8-one, 1-benzylcarbonylpyperidine-4-one, 1-indanone, 2-indanone, $\alpha$-tetralone, $\beta$-tetralone, 7-methoxy-2-tetralone, acetophenone, propiophenone, benzylphenone, dibenzylketone, 3,4-dimethylacetophenone, 2-acetophenone, 2-choroacetophenone.

In an advantageous embodiment of the invention, the aldehyde (formula (I)) or ketone (formula (II)) are selected from the group consisting of:

![Chemical Structures]

In another embodiment of the invention, advantageous nitroso compounds of formula (III) include but are not limited to alkyl nitroso compounds wherein nitroso substitution is at the tertiary carbon, e.g. 2-nitroso-isobutane, 2-nitroso-2-methylpentane.

Advantageous substituted aryl nitroso compounds include but are not limited to substituted nitrosobenzenes or 2-nitrosonaphthalene. Advantageous substituents for alkyl nitroso
catalysts include but are not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, alkoxyl groups like methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, s-butoxy, isobutoxy, t-butoxy, phenoxy, benzyloxy, phenethyloxy, or halogens like F, Cl, Br, I. Advantageous substituents for nitrosobenzene include but are not limited to o-nitrosotoluene, m-nitrosotoluene, p-nitrosotoluene, 3,5-dimethylnitrosobenzene, o-nitrosoethylbenzene, o-nitrosostyrene, o-nitrosoanisole, p-nitrosoanisole, o-nitrosophenol, m-nitrosophenol, o-fluoronitrosobenzene, m-fluoronitrosobenzene, p-fluoronitrosobenzene, o-chloronitrosobenzene, m-chloronitrosobenzene, p-chloronitrosobenzene, o-bromonitrosobenzene, m-bromonitrosobenzene, p-bromonitrosobenzene.

In an advantageous embodiment of the invention, the nitroso compounds is Ph-N=O.

In another embodiment of the invention, the catalyst of formula (IV) is a N-H acid-N-H base combined catalyst where the NH group at the α position of the heterocycle acts as an acid and the NH group at the α position of the alkyl heterocycle compound acts as a base. The 5-membered ring heterocycle (which acts as an acid) includes but is not limited to tetrazole, 1,2,3-triazole, 1,2,4-triazole, pyrazole, pyrazoline, imidazole, imidazoline, thiotriazoline, oxatriazoline. Advantageously, the five-membered ring is a tetrazole as disclosed in formula (IVa) below:

![Diagram of (IVa)](image)

The 5-10 membered heterocycle (which acts as a base) includes but is not limited to pyrrolidine, piperidine, hexamethyleneimine, heptamethyleneimine, oxazoline, oxazole, and substituents for these heterocycles includes but is not limited to alkyl groups like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or t-butyl groups, or alkoxyl groups like methoxy or ethoxy. Smaller substituents are advantageous since a bulky ones would lower the yield of the process.

Advantageously, the catalyst of formula (IV) includes but is not limited to 5-(2'-pyrrolidinyl)-1H-1,2,3,4-tetrazole, 5-(4H, 5H-2'-oxazolyl)-1H-1,2,3,4-tetrazole, 5-(2'-piperidinyl)-1H-1,2,3,4-tetrazole, 5-benzo[c]-2'-piperidinyl-1H-1,2,3,4-tetrazole, 5-2'-(pyrrolidinyl)-1H-1,2,3,4-triazole, 5-2'-pyrrolidinyl1H-1,2,4-triazole, 2-2'-pyrrolidinyl-1H-imidazole, 5-2'-pyrrolidinyl-1H-imidazole, 5-2'-pyrrolidinyl-1H, 4H, 5H-1,2,3,4-thiotriazoline, 5-2'pyrrolidinyl-4H, 5H-pyrazoline. Most advantageous is 5-(2'-pyrrolidinyl)-1H-1,2,3,4-tetrazole as shown in structure(IVb):
In another embodiment of the invention, the enantioselectivity of the α-aminooxyketones and α-aminooxyaldehydes compounds produced by the process of the invention is greater than about 90% ee. Advantageously, enantioselectivity is greater than about 95% ee. More advantageously, enantioselectivity is greater than 99% ee.

In another embodiment of the invention, the purity of the α-aminooxyketones and α-aminooxyaldehydes compounds produced by the process of the invention is greater than about 90%. Advantageously, purity is greater than about 95%. More advantageously, purity is greater than 99%.

In another embodiment of the invention, the product yield of the α-aminooxyketones and α-aminooxyaldehydes compounds produced by the process of the invention is greater than about 80%. Advantageously, product yield is greater than about 85%. More advantageously, product yield is greater than 90%.

In another embodiment of the invention, the amount of catalyst of formula (IV) used in the process of the invention is less than about 10 mol. % but greater than 0 mol. %. Advantageously, the amount of catalyst of formula (IV) is the range of from about 2 mol. % to about 5 mol. %. More advantageously, the amount of catalyst of formula (IV) is about 5 mol. %.

In another embodiment of the invention, the molar equivalent ratio of aldehyde (compound of formula (I)) or ketone (compound of formula (II)) starting material to nitroso compound of formula (IIIa) or (IIIb) is between about 10: 1 to about 1:2. Advantageously, the molar equivalent ratio of aldehyde (compound of formula (I)) or ketone (compound of formula (II)) starting material to nitroso compound of formula (IIIa) or (IIIb) is between about 5: 1 to about 1:1. More advantageously, the molar equivalent ratio of aldehyde (compound of formula (I)) or ketone (compound of formula (II)) starting material to nitroso compound of formula (IIIa) or (IIIb) is about 3:1.

In another embodiment of the invention, the solvent used in the process of the invention may be any solvent which facilitates the reaction of the aldehyde or ketone starting material and the nitroso compound in the presence of the catalyst of formula (IV). Advantageous examples include but are not limited to dimethylsulfoxide (DMSO), acetonitrile (MeCN), pyridine (Py) and dimethylformamide (DMF).

In another embodiment of the invention, corresponding α-Hydroxyketones based on the α-aminooxyketones and aldehydes of the invention may be synthesized by
treatment of an α-aminoxyketones or aldehydes with CuSO₄ to in solution using known methods. Possible solvents include alcohols like methanol and ethanol. The reaction temperature can be about 0°C - 25 °C, and the reaction time can be about 3 - 10 hours.

The invention to synthesize α-aminoxyketones comprises reacting a carbonyl compound and a nitroso compound in the presence of the catalyst which is shown in general structure (I) or preferably tetrazole derivative (III). The amount of nitroso compound could be in a range of 2-4 equivalents and is preferably 2.5-3.5 equivalents versus the carbonyl compound and the amount of catalyst which is shown in scheme (III) could be 1-10 mol% and preferably 2-20 mol%. The solvent could be water, chloroalkane like dichloromethane, chloroform, dichloroethane, chlorobenzene, hydrocarbon aromatics like benzene, toluene, xylene, aliphatic hydrocarbons like cyclohexane, n-hexane, n-heptane, esters like ethylacetate, nitriles like acetonitrile or dimethylsulfoxide and preferably dimethysulfoxide or acetonitrile. The amount of the solvent could be 15-30 volumes but the reaction can be done without solvent. The reaction temperature could be 0-50°C and preferably 20-30°C but the reaction can be done at room temperature. The reaction time can be 30 minutes to 3 hours, and for example the reaction can be done in open air with stirring for 1 hour. The reaction is very mild and furthermore, water will not inhibit the reaction, so there is no need for dehydrating the starting material and catalyst and the reaction is easy to control. After the reaction is complete, the product can be extracted with ethylacetate and then dried and purified through known methods.

Except where otherwise indicated, the variables, formula numbers, table and figure numbers below refer to the process of making reaction products from cyclic α,β-unsaturated ketone substrates and nitroso substrates only.

The process of making reaction products from cyclic α,β-unsaturated ketone substrates and nitroso substrates (also referred to as a catalytic asymmetric O-nitroso Aldol / Michael Reaction) may be represented as follows:
This reaction provides a method for the catalytic asymmetric synthesis of heterocyclic product VII, where the regiochemistry of this product is opposite that of the normal nitroso Diels-Alder reaction, as shown below by formula VIIa.

![Formula VIIa](image)

In one embodiment, the cyclic α,β-unsaturated ketone substrate may be represented by formulae (I), (II), (IIa), (III), (IV), or (XII):

![Formulae (I), (II), (IIa), (III), (IV), (XII)](image)

and

![Formula XII](image)

where \( R_b, R^1, R^4, R^7, R^{10}, R^{18}, X^1, X^2, X^3, X^4, X^5, X^6, X^7, X^8, X^{15}, X^{16} \) and \( n \) are as defined below.

In one embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure (I):

![Structure (I)](image)

where:

- each \( R^1 \) may represent a substituent independently selected from the group consisting of hydrogen, halogen, -OR, -OC(O)R, -CN, -C(O)R, -CO₂R, -
-C(O)NR'\text{I}^{ii}, -NO_2, -NR'\text{I}^{ii}, -NR'\text{C}(O)R', -NR'\text{CO}_2R', -SR', -S(O)R', -S(O)_2R', -C_{1-8} \text{ alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, C6-10 aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;}

each X^1 may independently represent -CR'\text{R'}^{ii}, -NR'\text{R'}, -O-, or -S-;

R^2 and R^3 may represent substituents independently selected from the group consisting of hydrogen, halogen, -OR', -OC(O)R', -CN, -C(O)R', -CO_2R', -C(O)NR'\text{R'}^{ii}, -NO_2, -NR'\text{R'}^{ii}, -NR'\text{C}(O)R', -NR'\text{CO}_2R', -NR'\text{S(O)}_2R', -SR', -S(O)R', -S(O)_2R', -S(O)_2NR'\text{R'}^{ii}, C_{1-8} \text{ alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, C6-10 aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;}

each R^2 and R^3, together with the atom to which they are attached, may form a 5-, 6- or 7-membered heterocyclic ring; and

X^2 may represent -C- or -S-;

each R'^i and R'^{ii} may independently selected from the group consisting of hydrogen, C_{1-8} \text{ alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, C6-10 aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.}

In another embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure (I) wherein:

each R'^1 may represent a substituent independently selected from the group consisting of hydrogen, C_{1-8} \text{ alkyl, C}_6 \text{ aryl and 5-membered heterocyclyl,}

each X'^1 may independently represent -CR'^2R'^3-;

R'^2 and R'^3 may represent a substituent independently selected from the group consisting of hydrogen, C_{1-8} \text{ alkyl, C}_6 \text{ aryl and 5-membered heterocyclyl,}

X'^2 may represent -C-.

In one embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure (II):

\[ \text{II} \]

where:
each R⁴ may represent a substituent independently selected from the group consisting of hydrogen, halogen, -OR³, -OC(O)R³, -CN, -C(O)R³, -CO₂R³, -C(O)NR³R⁴, -NO₂, -NR³R⁴, -NR³C(O)R⁴, -NR³CO₂R⁴, -NR³S(O)₂R⁴, -SR³, -S(O)R³, -S(O)₂R³, -S(O)₂NR³R⁴, C₁-₈ alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, C₃-₈

cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclic;

each X³ may independently represent -CR⁵R⁶, -NR⁵, -O-, or -S-;

R⁵ and R⁶ represent substituents independently selected from the group consisting of hydrogen, halogen, -OR³, -OC(O)R³, -CN, -C(O)R³, -CO₂R³, -C(O)NR³R⁴, -NO₂, -NR³R⁴, -NR³C(O)R⁴, -NR³CO₂R⁴, -NR³S(O)₂R⁴, -SR³, -S(O)R³, -S(O)₂R³, -S(O)₂NR³R⁴, C₁-₈ alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclic;

each R³ and R⁴, together with the atom to which they are attached, may form a 5-, 6- or 7-membered heterocyclic ring; and

X⁴ may represent C or S;

each R³ and R⁴ may be independently selected from the group consisting of hydrogen, C₁-₈ alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclic.

In another embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure (II) wherein:

each R⁴ may represent a substituent independently selected from the group consisting of hydrogen, C₁-₈ alkyl, C₆ aryl and 5-membered heterocycyl,

each X³ may independently represent -CR⁵R⁶-;

R⁵ and R⁶ may represent a substituent independently selected from the group consisting of hydrogen, C₁-₈ alkyl, C₆ aryl and 5-membered heterocycyl,

X⁴ may represent -C-. 

In one embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure (IIa):
where,

each \( R^b \) may represent a substituent independently selected from the group consisting of hydrogen, halogen, -OR\(^c\), -OC(O)R\(^c\), -CN, -C(O)R\(^c\), -CO₂R\(^c\),
-\( \text{C(O)NR}^d \text{R}^d \), -NO₂, -\( \text{NR}^d \text{R}^d \), -\( \text{NR}^d \text{C(O)R}^d \), -\( \text{NR}^d \text{CO₂R}^d \), -\( \text{NR}^d \text{S(O)₂R}^d \), -SR\(^c\),
-\( \text{S(O)R}^c \), -\( \text{S(O)₂R}^c \), -\( \text{S(O)₂NR}^d \text{R}^d \), \( \text{C}_{1-8} \) alkyl, \( \text{C}_{2-8} \) alkenyl, \( \text{C}_{2-8} \) alkynyl, \( \text{C}_{3-8} \) cycloalkyl, \( \text{C}_{6-10} \) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

\( n \) may be 0, 1, 2, or 3; and

each \( R^e \) and \( R^d \) may be independently selected from the group consisting of hydrogen, \( \text{C}_{1-8} \) alkyl, \( \text{C}_{2-8} \) alkenyl, \( \text{C}_{2-8} \) alkynyl, \( \text{C}_{3-8} \) cycloalkyl, \( \text{C}_{6-10} \) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

In another embodiment, the cyclic \( \alpha,\beta \)-unsaturated ketone substrate may have a structure (IIa) wherein:

each \( R^b \) may represent a substituent independently selected from the group consisting of hydrogen, \( \text{C}_{1-8} \) alkyl, \( \text{C}_{6} \) aryl and 5-membered heterocyclyl; and

\( n \) is 0 or 1.

In one embodiment, the cyclic \( \alpha,\beta \)-unsaturated ketone substrate may have a structure (III):

\[ \text{III} \]

where:

each \( R^7 \) may represent a substituent independently selected from the group consisting of hydrogen, halogen, -\( \text{OR}^y \), -\( \text{OC(O)R}^y \), -CN, -C(O)R\(^y\), -CO₂R\(^y\),
-\( \text{C(O)NR}^v \text{R}^v \), -NO₂, -\( \text{NR}^v \text{R}^v \), -\( \text{NR}^v \text{C(O)R}^v \), -\( \text{NR}^v \text{CO₂R}^v \), -\( \text{NR}^v \text{S(O)₂R}^v \), -SR\(^y\),
-\( \text{S(O)R}^v \), -\( \text{S(O)₂R}^v \), -\( \text{S(O)₂NR}^v \text{R}^v \), \( \text{C}_{1-8} \) alkyl, \( \text{C}_{2-8} \) alkenyl, \( \text{C}_{2-8} \) alkynyl, \( \text{C}_{3-8} \) cycloalkyl, \( \text{C}_{6-10} \) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each \( X^5 \) independently represents -\( \text{CR}^8 \text{R}^9 \), -\( \text{NR}^8 \), -\( \text{O} \), or -\( \text{S} \);

\( R^8 \) and \( R^9 \) may represent substituents independently selected from the group consisting of hydrogen, halogen, -\( \text{OR}^x \), -\( \text{OC(O)R}^x \), -CN, -C(O)R\(^x\), -
CO₂R³, -C(O)NR³R⁶, -NO₂, -NR³R⁶, -NR³C(O)R⁶, -NR³CO₂R⁶,
-NR³S(O)₂R⁶, -SR³, -S(O)R³, -S(O)₃R³, -S(O)₂NR³R⁶, C₁₈ alkyl, C₂-8
alkenyl, C₂-8 alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered
heteroaryl, and 3- to 10-membered heterocyclgł;
each R³ and R⁶, together with the atom to which they are attached, may
form a 5-, 6- or 7-membered heterocyclic ring; and
X⁶ may represent C or S;
each R³ and R⁶ may be independently selected from the group consisting of
hydrogen, C₁₈ alkyl, C₂-8 alkenyl, C₂-8 alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to
10-membered heteroaryl, and 3- to 10-membered heterocyclglob.

In another embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure
(III) wherein:
each R⁷ may represent a substituent independently selected from the group
consisting of hydrogen, C₁₈ alkyl, C₆ aryl and 5-membered heterocyclgl,
each X⁵ may independently represent -CR³R⁶-;
R³ and R⁶ may represent a substituent independently selected from the
group consisting of hydrogen, C₁₈ alkyl, C₆ aryl and 5-membered
heterocyclgl,
X⁶ may represent -C-.

In one embodiment, the cyclic α,β-unsaturated ketone substrate may have a structure (IV):

where:
R¹⁰ may represent a substituent independently selected from the group consisting
of hydrogen, halogen, -OR⁸, -OC(O)R⁸, -CN, -C(O)R⁸, -CO₂R⁸,
-C(O)NR³R⁶, -NO₂, -NR³R⁶, -NR³C(O)R⁶, -NR³CO₂R⁶, -NR³S(O)₂R⁶,
-SR³, -S(O)R³, -S(O)₃R³, -S(O)₂NR³R⁶, C₁₈ alkyl, C₂-8 alkenyl, C₂-8
alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-
membered heterocyclglo;
each $X^7$ independently represents $-\text{CR}^{11}R^{12}$, $-\text{NR}^{13}$, $-\text{O}$, or $-\text{N}$;

$R^{11}$ and $R^{12}$ may represent substituents independently selected from the

- group consisting of hydrogen, halogen, $-\text{OR}^{vi}$, $-\text{OC(O)}R^{vii}$, $-\text{CN}$, $-\text{C(O)}R^{vii}$,
- $\text{CO}_2R^{vii}$, $-\text{C(O)NR}^{vii}R^{viii}$, $-\text{NO}_2$, $-\text{NR}^{vii}R^{viii}$, $-\text{NR}^{vii}C(O)R^{viii}$, $-\text{NR}^{vii}\text{CO}_2R^{viii}$,
- $-\text{NR}^{vii}S(O)R^{vii}$, $-\text{SR}^{vii}$, $-\text{S(O)}R^{vii}$, $-\text{S(O)}_2R^{vii}$, $-\text{S(O)}_2\text{NR}^{vii}R^{viii}$, $C_{1-8}$ alkyl,
- C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, C6-10 aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocycl;

each $R^{11}$ and $R^{12}$, together with the atom to which they are attached, may
form a 5-, 6- or 7-membered heterocyclic ring; and

$X^8$ may represent $-\text{C}$- or $-\text{S}$-;

each $R^{vii}$ and $R^{viii}$ may be independently selected from the group consisting of
hydrogen, $C_{1-8}$ alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, C6-10 aryl, 5- to
10-membered heteroaryl, and 3- to 10-membered heterocycl.

In another embodiment, the cyclic $\alpha,\beta$-unsaturated ketone substrate may have a structure

(IV) wherein:

- each $R^{10}$ may represent a substituent independently selected from the group
consisting of hydrogen, $C_{1-8}$ alkyl, $C_6$ aryl and 5-membered heterocycl,

- each $X^7$ may independently represent $-\text{CR}^{11}R^{12}$;

- $R^2$ and $R^3$ may represent a substituent independently selected from the

- group consisting of hydrogen, $C_{1-8}$ alkyl, $C_6$ aryl and 5-membered
heterocycl,

$X^8$ may represent $-\text{C}$-

In one embodiment, the cyclic $\alpha,\beta$-unsaturated ketone substrate may have a structure

(XII):

where:

each $R^{18}$ may represent a substituent independently selected from the group
consisting of hydrogen, halogen, $-\text{OR}^{xi}$, $-\text{OC(O)}R^{xi}$, $-\text{CN}$, $-\text{C(O)}R^{xi}$, $-\text{CO}_2R^{xi}$,
- $\text{C(O)NR}^{xi}R^{xii}$, $-\text{NO}_2$, $-\text{NR}^{xi}R^{xii}$, $-\text{NR}^{xii}C(O)R^{xii}$, $-\text{NR}^{xi}\text{CO}_2R^{xii}$, $-\text{NR}^{xi}S(O)R^{xii}$, $-\text{SR}^{xi}$,
-S(O)R\textsuperscript{xi}, -S(O)\textsubscript{2}R\textsuperscript{xi}, -S(O)\textsubscript{2}NR\textsuperscript{xi}R\textsuperscript{xii}, C\textsubscript{1-8} alkyl, C2-8 alkenyl, C2-8 alkynyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{6-10} aryl, 5- to 10-membered heteroaroyl, and 3- to 10-membered heterocyclcycl;

each X\textsuperscript{15} independently represents \(-\text{CR}^{19}\text{R}^{20}\), \(-\text{NR}^{19}\), \(-\text{O}\), or \(-\text{S}\);

R\textsuperscript{19} and R\textsuperscript{20} may represent substituents independently selected from the group consisting of hydrogen, halogen, \(-\text{OR}^{\text{xii}}\), \(-\text{OC(O)R}^{\text{xii}}\), \(-\text{CN}\), \(-\text{C(O)R}^{\text{xii}}\), \(-\text{CO}_{2}\text{R}^{\text{xii}}\), \(-\text{C(O)}\text{NR}^{\text{xii}}\text{R}^{\text{xii}}\), \(-\text{NO}_{2}\), \(-\text{NR}^{\text{xii}}\text{R}^{\text{xii}}\), \(-\text{NR}^{\text{xii}}\text{C(O)R}^{\text{xii}}\), \(-\text{NR}^{\text{xii}}\text{CO}_{2}\text{R}^{\text{xii}}\), \(-\text{NR}^{\text{xii}}\text{S(O)}\text{R}^{\text{xii}}\), \(-\text{SR}^{\text{xii}}\), \(-\text{S(O)R}^{\text{xii}}\), \(-\text{S(O)}\text{R}^{\text{xii}}\text{R}^{\text{xii}}\), \(-\text{S(O)}\text{NR}^{\text{xii}}\text{R}^{\text{xii}}\), C\textsubscript{1-8} alkyl, C2-8 alkenyl, C2-8 alkynyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{6-10} aryl, 5- to 10-membered heteroaroyl, and 3- to 10-membered heterocyclcycl;

each R\textsuperscript{19} and R\textsuperscript{20}, together with the atom to which they are attached, may form a 5-, 6-, or 7-membered heterocyclic ring; and

X\textsuperscript{16} may represent C or S;

each R\textsuperscript{\text{xii}} and R\textsuperscript{\text{xii}} may be independently selected from the group consisting of hydrogen, C\textsubscript{1-8} alkyl, C2-8 alkenyl, C2-8 alkynyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{6-10} aryl, 5- to 10-membered heteroaroyl, and 3- to 10-membered heterocyclcycl.

In another embodiment, the cyclic \(\alpha,\beta\)-unsaturated ketone substrate may have a structure (XII) wherein:

each R\textsuperscript{18} may represent a substituent independently selected from the group consisting of hydrogen, C\textsubscript{1-8} alkyl, C\textsubscript{6} aryl and 5-membered heterocycyclycl,

each X\textsuperscript{15} may independently represent \(-\text{CR}^{19}\text{R}^{20}\);

R\textsuperscript{19} and R\textsuperscript{20} may represent a substituent independently selected from the group consisting of hydrogen, C\textsubscript{1-8} alkyl, C\textsubscript{6} aryl and 5-membered heterocyclcycl,

X\textsuperscript{16} may represent \(-\text{C}-\).

In one embodiment, the cyclic \(\alpha,\beta\)-unsaturated ketone substrate may be selected from the group consisting of:

\[
\begin{align*}
\text{O} \\
\text{Me} & \quad \text{Me} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O} \\
& \quad \text{and} \\
\end{align*}
\]

In one embodiment, the nitroso substrate may be represented by the structure (V):
where:

$R^{13}$ may represent 1 to 5 substituents each independently selected from the group consisting of hydrogen, halogen, $-OR^{ix}$, $-OC(O)R^{ix}$, $-CN$, $-C(O)R^{ix}$, $-CO_2R^{ix}$, $-C(O)NR^{ix}R^{x}$, $-NO_2$, $-NR^{ix}R^{x}$, $-NR^{ix}C(O)R^{j}$, $-NR^{ix}CO_2R^{x}$, $-NR^{ix}S(O)_2R^{x}$, $-SR^{ix}$, $-S(O)R^{ix}$, $-S(O)_2R^{ix}$, $-S(O)NR^{ix}R^{x}$, C$_{1-8}$ alkyl, C$_{2-8}$ alkenyl, C$_{2-8}$ alkynyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each $R^{ix}$ and $R^{x}$ may be independently selected from the group consisting of C$_{1-8}$ alkyl, C$_{2-8}$ alkenyl, C$_{2-8}$ alkynyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

In another embodiment of the invention, the nitroso substrate may be represented by the structure (V) wherein:

$R^{13}$ may represent 1 to 5 substituents each independently selected from the group consisting of hydrogen, halogen and C$_{1-8}$ alkyl.

In another embodiment of the invention, the nitroso substrate may be selected from the group consisting of:

![Chemical Structures]

In one embodiment, the proline-based catalyst may be represented by the following structure (VI):

![Proline Structure]

The $R^{14}$ substituent may be selected from the group consisting of:
The R\textsuperscript{15} may be a substituent selected from the group consisting of hydrogen, C\textsubscript{1-8} alkyl, C2-8 alkenyl, C2-8 alkynyl, C\textsubscript{3-8} cycloalkyl, C\textsubscript{6-10} aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

In another embodiment of the invention, the catalyst of formula is a N-H acid-N-H base combined catalyst where the NH group at the α position of the heterocycle acts as an acid and the NH group at the α position of the alkyl heterocycle compound acts as a base. The 5-membered ring heterocycle (which acts as an acid) includes but is not limited to tetrazole, 1,2,3-triazole, 1,2,4-triazole, pyrazole, pyrazoline, imidazole, imidazoline, thiotriazoline, oxatriazoline. Advantageously, the five-membered ring is a tetrazole as disclosed in formula:\n
\[
\begin{array}{c}
\text{N} \\
\text{Z} \\
\text{N} \\
\text{NH} \\
\text{N}
\end{array}
\]

The 5-10 membered heterocycle (which acts as a base) includes but is not limited to pyrrolidine, piperidine, hexamethylenimine, heptamethylenimine, oxazoline, oxazole, and substituents for these heterocycles includes but is not limited to alkyl groups like methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, or t-butyl groups, or alkoxy groups like methoxy or ethoxy. Smaller substituents are advantageous since a bulky ones would lower the yield of the process.

Advantageously, the catalyst of formula (IV) includes but is not limited to 5-(2'-pyrrolidinyl)-1H-1,2,3,4-tetrazole, 5-(4H, 5H-2'-oxazolyl)-1H-1,2,3,4-tetrazole, 5-(2'-piperidinyl)-1H-1,2,3,4-tetrazole, 5-benzo[c]-2'-piperidinyl-1H-1,2,3,4-tetrazole, 5-2'-pyrrolidinyl-1H-1,2,3,4-tetrazole, 5-2'-pyrrolidinyl1H-1,2,4-triazole, 2-2'-pyrrolidinyl-1H-imidazole, 5-2'-pyrrolidinyl-1H-imidazole, 5-2'-pyrrolidinyl-1H-4H, 5H-pyrazoline. Most advantageous is 5-(2'-pyrrolidinyl)-1H-1,2,3,4-tetrazole as shown in structure:

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{NH} \\
\end{array}
\]

In an advantageous embodiment of the invention, the proline-base catalyst may be selected from the group consisting of:
The proline-based catalysts of the invention may be obtained via the methods and processes described above in the “Detailed Description for the Process of Making α-aminoxyketone/α-aminoxyaldehyde and α-hydroxyketone/α-hydroxyaldehyde” and “Examples for the Process of Making α-aminoxyketone/α-aminoxyaldehyde and α-hydroxyketone/α-hydroxyaldehyde” which is incorporated herein by reference.

In one embodiment, the heterocyclic product may be represented by the following structure (VII):

\[
\text{VII}
\]

In another embodiment, the heterocyclic product may be represented by the following structure (VIII):

\[
\text{VIII}
\]

In another embodiment, the heterocyclic product may be represented by the following structure (VIIIa):

\[
\text{VIIIa}
\]
In another embodiment, the heterocyclic product may be represented by the following structure (IX):

![Structure IX]

In another embodiment, the heterocyclic product may be represented by the following structure (X):

![Structure X]

In another embodiment of the invention, the enantioselectivity of the \( \alpha \)-aminoxyketones and \( \alpha \)-aminoxyaldehydes compounds produced by the process of the invention is greater than about 90% ee. Advantageously, enantioselectivity is greater than about 95% ee. More advantageously, enantioselectivity is greater than 99% ee.

In another embodiment of the invention, the amount of proline-base catalyst used in the process of the invention is less than about 40 mol. % but greater than 0 mol. %. Advantageously, the amount of proline base catalyst is the range of from about 10 mol. % to about 30 mol. %. More advantageously, the amount of proline base catalyst is about 20 mol. %.

In another embodiment of the invention, the molar ratio of the amount of nitroso compound to \( \alpha,\beta \)-unsaturated cyclic ketone (enone) is from about 10:1 to about 0.5:1. Advantageously, the molar ratio of the amount of nitroso compound to \( \alpha,\beta \)-unsaturated cyclic ketone (enone) is from about 4:1 to about 1:1. More advantageously, the molar ratio of the amount of nitroso compound to \( \alpha,\beta \)-unsaturated cyclic ketone (enone) is from about 2:1.
The invention also encompasses pharmaceutical compositions that may comprise the α-aminoxyketones, α-hydroxyketones and cyclic α, β unsaturated ketones described herein. In an advantageous embodiment, the invention encompasses anti-cancer or antiviral compositions that may comprise α-aminoxyketones, α-hydroxyketones and cyclic α, β unsaturated ketones, or derivatives thereof, and methods for administering the same.

In one embodiment, the α-aminoxyketones of the present invention may be substituted for its natural equivalent. Such substitutions will be apparent to one of skill in the art. In another embodiment, the α-aminoxyketones of the present invention may be substituted for α-hydroxyketones and their equivalents thereof. Such substitutions will be apparent to one of skill in the art. In another embodiment, the α-hydroxyketones of the present invention may be substituted for its natural aldose equivalent. Such substitutions will be apparent to one of skill in the art.

The compounds of the invention may be useful for treating or preventing a variety of cancers, including, but not limited to, leukemias, including but not limited to acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, myeloblastic, promyelocytic, myelomonocytic, monocytic, erythroleukemia, chronic leukemia, chronic myelocytic, (granulocytic) leukemia, chronic lymphocytic leukemia, Polycythemia vera, Lymphomas including but not limited to Hodgkin's disease, non-Hodgkin's disease, Multiple myeloma, Waldenstrom's macroglobulinemia, Heavy chain disease, Solid tumors including but not limited to sarcomas and carcinomas, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synoviomia, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, uterine cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, and neuroblastomaretinoblastoma.

The compounds of the invention may be useful for treating or preventing a variety of viral infections, including, but not limited to those caused by infection with
hepatitis B, hepatitis C, rotavirus, human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), human T-cell lymphotropic virus type I (HTLV-I), human T-cell lymphotropic virus type II (HTLV-II), AIDS, DNA viruses such as hepatitis type B and hepatitis type C virus; paroviruses, such as adeno-associated virus and cytomegalovirus; papovaviruses such as papilloma virus, polyoma viruses, and SV40; adenoviruses; herpes viruses such as herpes simplex type I (HSV-I), herpes simplex type II (HSV-II), and Epstein-Barr virus; poxviruses, such as variola (smallpox) and vaccinia virus; and RNA viruses, such as human immunodeficiency virus type I (HIV-I), human immunodeficiency virus type II (HIV-II), human T-cell lymphotropic virus type I (HTLV-I), human T-cell lymphotropic virus type II (HTLV-II), influenza virus, measles virus, rabies virus, Sendai virus, picornaviruses such as poliomyelitis virus, coxsackieviruses, rhinoviruses, reoviruses, togaviruses such as rubella virus (German measles) and Semliki forest virus, arboviruses, and hepatitis type A virus.

In an advantageous embodiment, the compounds of the present invention, or a derivative thereof, may be useful as an antiviral against against orthopox viruses, such as, but not limited to, smallpox, monkeypox and cowpox (see, e.g., Chu et al., Bioorg Med Chem Lett. 2003 Jan 6;13(1):9-12). In another advantageous embodiment, the cyclic α, β unsaturated ketones of the present invention, or a derivative thereof, may be used in the synthesis of nucleosides, nucleotides or derivatives thereof that may be used as antiviral therapeutic agents (see, e.g., Jin & Chu, Nucleosides Nucleotides Nucleic Acids. 2003 May-Aug;22(5-8):771-3).

The compounds of the invention may be useful for treating or preventing several types of inflammation, including, but not limited to, eczema, inflammatory bowel disease, rheumatoid arthritis, asthma, psoriasis, ischemia/reperfusion injury, ulcerative colitis and acute respiratory distress syndrome. In an advantageous embodiment, the compounds of the present invention, or a derivative thereof, may be used as an inhibitor of interleukin-1 biosynthesis (see, e.g., Batt et al., J Med Chem. 1993 May 14;36(10):1434-42).

In another embodiment, the compounds of the invention are useful for treating or preventing ulcers. For example, urease inhibitors have recently attracted much attention as potential new anti-ulcer drugs (see, e.g., Amtul et al., Curr Med Chem. 2002 Jul;9(14):1323-48). Accordingly, the compounds of the invention may be used as an inhibitor of urease activity (see, e.g., Tanaka et al., Bioorg Med Chem. 2004 Jan 15;12(2):501-5).
In another embodiment, the compounds of the invention are useful for treating or preventing Alzheimer’s disease. Accordingly, the compounds of the invention may be used as an inhibitor of amyloid-beta (Abeta) protein production, and accordingly as a potential treatment for Alzheimer’s disease (see, e.g., Wallace et al., Bioorg Med Chem Lett. 2003 Mar 24;13(6):1203-6).

In another embodiment, the compounds of the invention may be useful as analgesics. For example, heterocyclic bicyclo[3.3.1]nonan-9-ones were found to have a high affinity to kappa opioid receptors (see, e.g., Brandt et al., Arch Pharm (Weinheim). 1996 Jun;329(6):311-23). In another example, 2,4-di-2-pyridyl- substituted 7-methyl-3,7-diazabicyclo[3.3.1] nonan-9-one-1,5-diester was found to have a reasonable kappa-agonistic activity (see, e.g., Holzgrabe & Erciyas, Arch Pharm (Weinheim). 1992 Oct;325(10):657-63).

In another embodiment, the compounds of the present invention may be useful in preventing or treating cardiovascular diseases, such as, but not limited to, hypertension, heart failure, pulmonary hypertension and renal diseases. For example, bosentan, an endothelin receptor antagonist, has received approval by the Food and Drug Administration (FDA) for use in pulmonary artery hypertension (see, e.g., Vatter et al., Methods Find Exp Clin Pharmacol. 2004 May;26(4):277-86). The compounds of the present invention, or a derivative thereof, may be used as an endothelin receptor antagonist (see, e.g., Niyama et al., Bioorg Med Chem. 2002 Nov;10(11):3437-44).

Due to their activity, the compounds of the invention are advantageously useful in veterinary and human medicine.

When administered to a patient, a compound of the invention is preferably administered as component of a composition that optionally comprises a pharmaceutically acceptable vehicle. The present compositions, which comprise a compound of the invention, are preferably administered orally. The compositions of the invention may also be administered by any other convenient route, for example, by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal, and intestinal mucosa, etc.) and may be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, e.g., encapsulation in liposomes, microparticles, microcapsules, capsules, etc., and can be used to administer the compounds of the invention.

In certain embodiments, the present compositions may comprise one or more compounds of the invention.
Methods of administration include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The mode of administration is left to the discretion of the practitioner. In most instances, administration will result in the release of a compound of the invention into the bloodstream.

In specific embodiments, it may be desirable to a compound of the invention locally. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers.

In certain embodiments, it may be desirable to introduce a compound of the invention into the central nervous system by any suitable route, including intraventricular, intrathecal and epidural injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the compounds of the invention can be formulated as a suppository, with traditional binders and vehicles such as triglycerides.

In another embodiment, the compounds of the invention can be delivered in a vesicle, in particular a liposome (see Langer, 1990. Science 249:1527-1533; Treat et al, in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, N.Y., pp. 353-365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid).

In yet another embodiment, the compounds of the invention can be delivered in a controlled release system (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, Science 249:1527-1533) may be used. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201; Buchwald et al., 1980, Surgery 88:507 Saudek et al., 1989, N. Engl. J. Med. 321:574). In another embodiment, polymeric materials can be used (see Medical Applications of

The present compositions can optionally comprise a suitable amount of a pharmaceutically acceptable vehicle so as to provide the form for proper administration to the patient.

In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, mammals, and more particularly in humans. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier with which a compound of the invention is administered. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. When administered to a patient, the pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when the compound of the invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the pharmaceutically acceptable vehicle is a capsule (see e.g., U.S. Pat. No. 5,698,155). Other examples of suitable pharmaceutical vehicles are
described in Remington's Pharmaceutical Sciences, Alfonso R. Gennaro ed., Mack
reference.

In a preferred embodiment, the compounds of the invention are formulated in
accordance with routine procedures as a pharmaceutical composition adapted for oral
administration to human beings. Compositions for oral delivery may be in the form of
tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules,
syrups, or elixirs, for example. Orally administered compositions may contain one or more
agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring
agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving
agents, to provide a pharmaceutically palatable preparation. Moreover, where in tablet or
pill form, the compositions can be coated to delay disintegration and absorption in the
gastrointestinal tract thereby providing a sustained action over an extended period of time.
Selectively permeable membranes surrounding an osmotically active driving compound
are also suitable for orally administered compositions. In these later platforms, fluid from
the environment surrounding the capsule is imbibed by the driving compound, which
swells to displace the agent or agent composition through an aperture. These delivery
platforms can provide an essentially zero order delivery profile as opposed to the spiked
profiles of immediate release formulations. A time delay material such as glycerol
monostearate or glycerol stearate may also be used. Oral compositions can include
standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium
saccharine, cellulose, magnesium carbonate, etc. Such vehicles are preferably of
pharmaceutical grade. Typically, compositions for intravenous administration comprise
sterile isotonic aqueous buffer. Where necessary, the compositions may also include a
solubilizing agent.

In another embodiment, the compounds of the invention can be formulated for
intravenous administration. Compositions for intravenous administration may optionally
include a local anesthetic such as lignocaine to lessen pain at the site of the injection.
Generally, the ingredients are supplied either separately or mixed together in unit dosage
form, for example, as a dry lyophilized powder or water free concentrate in a hermetically
sealed container such as an ampoule or sachette indicating the quantity of active agent.
Where the compounds of the invention are to be administered by infusion, they can be
dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade
water or saline. Where the compounds of the invention are administered by injection, an
ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The amount of a compound of the invention that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for oral administration are generally about 0.001 milligram to about 200 milligrams of a compound of the invention or a pharmaceutically acceptable salt thereof per kilogram body weight per day. In specific preferred embodiments of the invention, the oral dose is about 0.01 milligram to about 100 milligrams per kilogram body weight per day, more preferably about 0.1 milligram to about 75 milligrams per kilogram body weight per day, more preferably about 0.5 milligram to 5 milligrams per kilogram body weight per day. The dosage amounts described herein refer to total amounts administered; that is, if more than one compound of the invention is administered, or if a compound of the invention is administered with a therapeutic agent, then the preferred dosages correspond to the total amount administered. Oral compositions preferably contain about 10% to about 95% active ingredient by weight.

Suitable dosage ranges for intravenous (i.v.) administration are about 0.01 milligram to about 100 milligrams per kilogram body weight per day, about 0.1 milligram to about 35 milligrams per kilogram body weight per day, and about 1 milligram to about 10 milligrams per kilogram body weight per day. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight per day to about 1 mg/kg body weight per day. Suppositories generally contain about 0.01 milligram to about 50 milligrams of a compound of the invention per kilogram body weight per day and comprise active ingredient in the range of about 0.5% to about 10% by weight.

Recommended dosages for intradermal, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual, intracerebral, intravaginal, transdermal administration or administration by inhalation are in the range of about 0.001 milligram to about 200 milligrams per kilogram of body weight per day. Suitable doses for topical administration are in the range of about 0.001 milligram to about 1 milligram, depending on the area of administration. Effective doses may be extrapolated from dose-response curves derived
from in vitro or animal model test systems. Such animal models and systems are well known in the art.

The invention also provides pharmaceutical packs or kits comprising one or more vessels containing one or more compounds of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In a certain embodiment, the kit contains more than one compound of the invention. In another embodiment, the kit comprises a therapeutic agent and a compound of the invention.

The compounds of the invention are preferably assayed in vitro and in vivo, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays can be used to determine whether it is preferable to administer a compound of the invention alone or in combination with another compound of the invention and/or a therapeutic agent. Animal model systems can be used to demonstrate safety and efficacy.

Other methods will be known to the skilled artisan and are within the scope of the invention.

In certain embodiments of the present invention, a compound of the invention can be used in combination therapy with at least one other therapeutic agent. The compound of the invention and the therapeutic agent can act additively or, more preferably, synergistically. In a preferred embodiment, a composition comprising a compound of the invention is administered concurrently with the administration of another therapeutic agent, which can be part of the same composition as or in a different composition from that comprising the compound of the invention. In another embodiment, a composition comprising a compound of the invention is administered prior or subsequent to administration of another therapeutic agent. As many of the disorders for which the compounds of the invention are useful in treating are chronic, in one embodiment combination therapy involves alternating between administering a composition comprising a compound of the invention and a composition comprising another therapeutic agent, e.g., to minimize the toxicity associated with a particular drug. The duration of administration of the compound of the invention or therapeutic agent can be, e.g., one month, three months, six months, a year, or for more extended periods. In certain embodiments, when a compound of the invention is administered concurrently with another therapeutic agent that potentially produces adverse side effects including, but not limited to, toxicity, the
therapeutic agent can advantageously be administered at a dose that falls below the threshold at which the adverse side is elicited.

The therapeutic agent can be an anti-cancer agent. Useful anti-cancer agents include, but are not limited to, methotrexate, taxol, mercaptopurine, thioguanine, hydroxyurea, cytarabine, cyclophosphamide, ifosfamide, nitrosoureas, cisplatin, carboplatin, mitomycin, dacarbazine, procarbazine, etoposides, camptothecins, bleomycin, doxorubicin, idarubicin, daunorubicin, dactinomycin, plicamycin, mitoxantrone, asparaginase, vinblastine, vincristine, vinorelbine, paclitaxel, and docetaxel, gamma-radiation, alkylating agents including nitrogen mustard such as cyclophosphamide, ifosfamide, trofosfamide, Chlorambucil, nitrosoureas such as carmustine (BCNU), and Lomustine (CCNU), alkylsulphonates such as busulfan, and Treosulfan, triazenes such as Dacarbazine, platinum containing compounds such as Cisplatin and carboplatin, plant alkaloids including vinca alkaloids, vincristine, Vinblastine, Vindesine, and Vinorelbine, taxoids including paclitaxel, and Docetaxol, DNA topoisomerase inhibitors including Epipodophyllins such as etoposide, Teniposide, Topotecan, 9-aminocamptothecin, campto irinotecan, and crsintol, mytomycins such as mytomycin C, and Mytomycin C, antimitabolites, including anti-folates such as DHFR inhibitors, methotrexate and Trimetrexate, IMP dehydrogenase inhibitors including mycophenolic acid, Tiazofurin, Ribavirin, EICAR, Ribonucleotide reductase Inhibitors such as hydroxyurea, deferoxamine, pyrimidine analogs including uracil analogs 5-Fluorouracil, Floxuridine, Doxifluridine, and Ratitrexed, cytosine analogs such as cytarabine (ara C), cytosine arabinoside, and fludarabine, purine analogs such as mercaptopurine, thioguanine, hormonal therapies including receptor antagonists, the anti-estrogens Tamoxifen, Raloxifene and megestrol, LHRH agonists such as goscrelin, and Leuprolide acetate, anti-androgens such as flutamide, and bicalutamide, retinoids/deltoids, Vitamin D3 analogs including EB 1089, CB 1093, and KH 1060, photodynamic therapies including verteporfin (BPD-MA), Phthalocyanine, photosensitizer Pc4, Demethoxy-hypocrellin A, (2BA-2-DMIA), cytokines including Interferon-alpha, Interferon-gamma, tumor necrosis factor, as well as other compounds having anti-tumor activity including Isoprenylation inhibitors such as Lovastatin, Dopaminergic neurotoxins such as 1-methyl-4-phenylpyridinium ion, Cell cycle inhibitors such as staurosporine, Actinomycins such as Actinomycin D and Dactinomycin, Bleomycins such as bleomycin A2, Bleomycin B2, and Peplomycin, anthracyclines such as daunorubicin, Doxorubicin (adriamycin), Idarubicin, Epirubicin,
Pirubicin, Zorubicin, and Mitoxantrone, MDR inhibitors including verapamil, and Ca\(^{2+}\) ATPase inhibitors such as thapsigargin.

The therapeutic agent can be an antiviral agent. Useful antiviral agents include, but are not limited to, nucleoside analogs, such as zidovudine, acyclovir, gancyclovir, vidarabine, idoxuridine, trifluridine, and ribavirin, as well as foscarnet, amantadine, rimantadine, saquinavir, indinavir, ritonavir, and the alpha-interferons.

The therapeutic agent can be an anti-inflammatory agent. Useful anti-inflammatory agents include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, diclofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxican, pivoxidam, teroxicam, nabumetone, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide; leukotriene antagonists including, but not limited to, zileuton, aurothioglucone, gold sodium thiomalate and auranofin; and other anti-inflammatory agents including, but not limited to, colchicine, allopurinol, probenecid, sulfonpyrazone and benzbromarone.

The invention will now be further described by way of the following non-limiting examples.

**EXAMPLES**

The catalyst of formula (IV) can be synthesized using previously known methods in the art. The heterocyclic compound could be synthesized from natural or synthesized proline. The tetrazole derivative shown in formula (IVa) could be synthesized by a reported method (*Tetrahedron Lett.*, vol. 36, 7115-7118, (1995); and *J. Med. Chem.*, vol. 28, 1067-1071, (1985)). Thus, commercially available N-(benzyloxy carbonyl)-L-proline is converted to an amide via a reaction with ammonia and dehydrated with phosphorous oxychloride to give nitrile. The obtained nitrile is treated with sodium azide to give a tetrazole and the Cbz (benzyloxy carbonyl) group is deprotected with HBr/AcOH or Pd/C, H\(_2\) to give the tetrazole derivative which is shown in formula (IVa). An example of this preparative scheme is described in detail below:

**Preparation of L-Pyrrolidine-2-yl-1H-tetrazole (catalyst of formula (IVa))**

**Preparation of N-benzyloxy carbonyl-L-prolinamide**

The ammonium hydrogen carbonate (1.26 equiv) was added to the stirred solution
of carbobenzyloxy-L-proline (1 equiv), pyridine and Boc₂O (1.30 equiv) in acetonitrile and stirred for 20 h. The solvent was removed, and the residue was diluted with ethyl acetate, washed with water, extracted with ethyl acetate, dried over MgSO₄ and evaporated in vacuo to afford N-benzylxocarbonyl-L-prolinamide as colorless crystals. ¹H NMR (CDCl₃, 400 MHz) δ7.36 (m, 5H, Ar-H), 6.71 (s, 1H, NH-H), 5.81 (s, 1H, NH-H), 5.20 (d, 1H, J = 12 Hz, OCH₂H), 5.15 (d, 1H, J = 12 Hz, OCH₂H), 4.32 (m, 1H, NCH), 3.53 (m, 2H, NCH₂), 1.91-2.33 (m, 4H, CH₂CH₂);  

**Preparation of N-benzylxocarbonyl-L-proline nitrile.**

The phosphorus oxychloride in dichloromethane was added over 10 min to the solution of N-benzylxocarbonyl-L-prolinamide in dry pyridine at −5 to −10 °C under N₂. The mixture was stirred at −5 to −10 °C for 1 h and then it was poured on ice and extracted with saturated cupric sulfate solution and saturated sodium chloride solution, dried over MgSO₄ and evaporated in vacuo to afford N-benzylxocarbonyl-L-proline nitrile as a pale yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ7.96 (d, 2H, J = 7.2 Hz, Ar-H), 7.90 (t, 1H, J = 7.2 Hz, Ar-H), 7.77 (t, 2H, J = 8.0 Hz, Ar-H), 4.80 (t, 1H), 3.28-3.36 (m, 2H), 2.34-2.52 (m, 1H), 2.04-2.20 (m, 3H);  

**Preparation of N-benzylxocarbonyl pyrroline-L-2-y1-1H-tetrazole.**

The mixture of N-benzylxocarbonyl-L-prolinamide (1 equiv), sodium azide (1.04 equiv), ammonium chloride (1.1 equiv), and dry DMF was stirred at 90–95 °C under N₂ for 6 h. The mixture was poured onto ice, acidified to pH 2 with diluted HCl, and extracted with CHCl₃. The CHCl₃ layer was washed with water and saturated sodium chloride, dried over Na₂SO₄ and evaporated in vacuo to afford crude material. This crude material was purified with silicagel chromatography to pure N-benzylxocarbonyl
pyrrolidine-L-2-yl-1H-tetrazole. \(^{1}\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) 7.37 (s, 5H), 5.20 (m, 3H), 3.55 (m, 2H), 2.06-2.34 (m, 4H).

**Preparation of L-pyrrolidine-2-yl-1H-tetrazole.**

\[
\text{Cbz} \xrightarrow{\text{Pd/H\_2}} \begin{array}{c}
\text{AcOH-H\_2O (9:1)} \\
\text{r.t., 4 h}
\end{array}
\]

Scheme 4

\(N\)-benzyloxycarbonyl pyrrolidine-L-2-yl-1H-tetrazole, and 10 % palladium on charcoal in acetic acid/water (9:1) was stirred under H\(_2\) at room temperature for 4 h. The mixture was filtered through Celite and the filtrate was evaporated in vacuo to afford crude L-pyrrolidine-2-yl-1H-tetrazole, which was recrystallized from acetic acid and diethyl ether. \([\alpha]_D^{25}+14.1^\circ\) (c = 0.12, MeOH); \(^{1}\)H NMR (CD\(_3\)OD, 400 MHz) \(\delta\) 4.82 (m, 2H), 3.33 (m, 2H), 2.39 (m, 1H), 2.02-2.41 (m, 3H); \(^{13}\)C NMR (CD\(_3\)OD, 100 MHz) \(\delta\) 159.6, 56.2, 46.6, 31.1, 24.8.

The tetrazole derivative of formula (IV) could also be prepared by following the reported method from *Organic Letters*, 2001, Vol.3, No.25, 4091-4094; *Organic Letters*, 2002, Vol. 4 No. 15, 2525-2527.

**Example 1 (General Procedure for the O-Nitroso Aldol Reaction of Ketone to Nitrosobenzene Using L-Pyrrolidine-based Tetrazole Catalyst (formula (IVa)))**

To a room temperature solution of pyrrolidine-based tetrazole catalyst (5 mol%) and ketone (1.5 mmol, 3 eq) in DMSO (1 ml) was added the solution of nitrosobenzene (0.5 mmol, 1 eq) in DMSO (1 mL) dropwise for 1 h. The resulting mixture was stirred at this temperature until the nitrosobenzene was completely consumed (1 h), as determined by TLC (hexane/ethyl acetate=3/1). The reaction mixture was then poured into iced saturated NH\(_4\)Cl solution. The aqueous layer was extracted with ethyl acetate (20 mLx3). The combined organic extracts were washed with brine, dried over Na\(_2\)SO\(_4\) with cooling and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on a two-layered column filled with Florisil\textsuperscript{®} (upper layer) and silica gel (lower layer) using a mixture of ethyl acetate and hexane as the eluant to give the product.

**Example 2 (General procedure for the O-nitroso aldol reaction of aldehyde to nitrosobenzene using L-pyrrolidine-based tetrazole catalyst (formula IVa))**

To a room temperature solution of pyrrolidine-based tetrazole catalyst (10 mol%) in acetonitrile (1 mL) was added nitrosobenzene (1 equiv, 0.5 mmol) in one portion and stirred at room temperature for 10 min. To this green heterogeneous solution was then
added aldehyde (3 equiv, 1.5 mmol) in one portion. The resulting mixture was stirred at this temperature until the nitrosobenzene was completely consumed (15–30 min), as determined by TLC (hexane/ethyl acetate=2/1). Then, the reaction was transferred to a methanol suspension of NaBH₄ at 0 °C. After 20 min, the reaction mixture was then poured into saturated NH₄Cl solution. The aqueous layer was extracted with diethyl ether (20 mL x 3). The combined organic extracts were dried over Na₂SO₄ with cooling and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on column filled with silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

Example 3 (General procedure for the synthesis of α-hydroxy cyclohexanone)

To a room temperature solution of pyrrolidine-based tetrazole catalyst (5 mol%) and cyclohexanone (3 equiv, 1.5 mmol) in DMSO (1 mL) was added the solution of nitrosobenzene (1 equiv, 0.5 mmol) in DMSO (1 mL) dropwise for 1 h. The resulting mixture was stirred at this temperature until the nitrosobenzene was completely consumed (1 h), as determined by TLC (hexane/ethyl acetate=3/1). After cooling to 0 °C, CuSO₄ (0.3 eq) and MeOH (3 mL) were added and stirred at 0°C for 10 h. The reaction mixture was quenched by cooled brine (20 mL) and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄ with cooling and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on a silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

Example 4 (General procedure for the synthesis of 1,2-cyclohexanediol)

The solution of α-hydroxy cyclohexanone 8a (1 equiv, 0.8 mmol) in MeOH (1 mL) was added to a methanol suspension of NaBH₄ at 0 °C and stirred at this temperature for 1 h. Then, the reaction mixture was poured into saturated NH₄Cl solution. The aqueous layer was extracted with diethyl ether (20 mL x 3). The combined organic extracts were dried over Na₂SO₄ with cooling and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on column filled with silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

General procedure for the synthesis of 3-phenyl-propane-1,2-diol, 9f. The solution of 2-N-phenylaminoxy-3-phenylpropan-1-ol 8f (1 equiv) MeOH (1 mL) was added to a methanol suspension of CuSO₄ (0.3 equiv) at 0 °C and stirred at this temperature for 3 h. The reaction mixture was quenched by cooled brine (20 mL) and the aqueous layer was extracted with ethyl acetate (10 mL x 3). The combined organic extracts were washed with

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brine, dried over Na₂SO₄ with cooling and concentrated under reduced pressure after filtration. The residual crude product was chromatographed on a silica gel using a mixture of ethyl acetate and hexane as the eluant to give the product.

Additional of the O-nitroso aldol reaction was further investigated using other ketones and aldehydes (Figure 1 and Examples 5a – 12a below). Optimal results were obtained with 5 mol% of L-pyrroolidine-tetrazole (formula (IVA)) in the reaction of nitroso benzene with an excess of cyclohexanone (Example 5a: 94 %, >99 % ee). The other substituted cyclohexanone (Examples 6a, 6b and 6c) also reacted smoothly in the presence of the catalyst of formula (IVA) (5 mol%), to afford O-adducts 1a in 87-97 % yield and in >99 % ee. When the acyclic ketone (Examples 9a and 9b) and aldehydes (Examples 10a – 12a) were used, the enantioselectivities were still maintained in excellent level, but, yields of O-nitroso aldol products were moderate due to production of the N-adduct (see Example 9b) and azoxy dimer byproduct (see compound 5c in Table 3 below). The use of 10-20 mol% catalyst, however, afforded 67-75 % yield.

**Figure 1. General Reaction Scheme for Examples 5a – 12a**

![Chemical Structure](image)

**Example 5a - 2-(N-Phenyl aminooxy) cyclohexanone**

Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish powder. TLC Rf = 0.30 (3:1 hexane: ethyl acetate); [α]D²⁷ + 122.0° (c = 2.83, CHCl₃); IR (CHCl₃) 3021, 2951, 2872, 1722, 1603, 1495, 1132, 1100, 1073, 1028, 928 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.82 (s, 1H, NH), 7.25 (t, 2H, J = 8.4 Hz, Ar-H), 6.94 (t, 3H, J = 8.1 Hz, Ar-H), 4.35 (q, 1H, J = 6.0 Hz, CH₂), 2.34 – 2.48 (m, 2H, CH₂), 2.00 – 2.02 (m, 2H, CH₂),
1.71 – 1.79 (m, 4H, CH₂); 13C NMR (CDCl₃, 75 MHz) δ 209.9, 148.0, 128.8 (2C), 122.0, 114.3 (2C), 86.2, 40.8, 32.5, 27.2, 23.7; Anal. Calc'd for C₁₂H₁₅NO₂: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.22; H, 7.42; N, 6.91. Enantiomeric excess was determined by HPLC with a Chiralcel AD column (40:1 hexane:2-propanol), 1.0 mL/min; major enantiomer tᵣ = 34.3 min, minor enantiomer tᵣ = 28.1 min.

**Example 6a - 2-(N-Phenyl aminooxy) tetrahydro-4H-pyran-4-one**

Purification by flash column chromatography with elution by hexane:ethyl acetate (5:1) provided as yellowish powder. TLC Rₓ = 0.079 (5:1 hexane:ethyl acetate); [α]D²⁷⁺63.0° (c = 0.2, CHCl₃); IR (CHCl₃) 3262, 2990, 2886, 1708, 1659, 1587, 1478, 1273, 1125, 1081, 988, 968, 860 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 7.77 (s, 1H, NH), 7.26 (t, 2H, J = 7.8 Hz, Ar-H), 6.97 (t, 1H, J = 7.4 Hz, Ar-H), 6.92 (d, 2H, J = 7.8 Hz, Ar-H), 4.48 – 4.52 (m, 1H, CH₂), 4.40 – 4.45 (m, 1H, CH₂) 4.16 – 4.19 (m, 1H, CH), 3.66 – 3.74 (m, 2H, CH₂), 2.66 – 2.71 (m, 1H, CH₂), 2.57 (td, 1H, J = 2.9, 14.3 CH₂); ¹³C NMR (CDCl₃, 100 MHz) δ 205.4, 147.7, 128.9 (2C), 122.5, 114.7 (2C), 83.5, 70.0, 68.1, 42.3; MS (Cl) Exact Mass Calc'd for C₁₁H₁₃NO₃ (M+H)+: 208.1. Found: 208.1. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (9:1 hexane:2-propanol), 1.0 mL/min; major enantiomer tᵣ = 19.8 min, minor enantiomer tᵣ = 26.5 min.

**Example 7a - 7-(N-Phenyl aminooxy) 1,4-dioxa-spiro[4.5]decan-8-one**

Purification by flash column chromatography with elution by hexane:ethyl acetate (7:1) provided as yellowish powder. TLC Rₓ = 0.18 (3:1 hexane:ethyl acetate); [α]D²⁷⁺40.6° (c = 2.3, CHCl₃); IR (CHCl₃) 3164, 2989, 1855, 1764, 1580, 1382, 861 cm⁻¹; ¹H NMR (CDCl₃, 400 MHz) δ 87.84 (s, 1H, NH), 7.24 (t, 2H, J = 7.5 Hz, Ar-H), 6.92 (t, 3H, J = 8.1 Hz, Ar-H), 4.64 (q, 1H, J = 5.7 Hz, CH), 4.05 (s, 4H, CH₂), 2.65 – 2.81 (m, 1H, CH₂), 2.42 – 2.50 (m, 4H, CH₂), 1.99 – 2.05 (m, 1H, CH₂); ¹³C NMR (CDCl₃, 100 MHz) δ 210.3, 147.9, 128.8 (2C), 122.0, 114.3 (2C), 107.5, 82.6, 64.6, 64.5, 39.6, 35.9, 34.3; MS (Cl) Exact Mass Calc'd for C₁₄H₁₇NO₄ (M+H)+: 264.0. Found: 264.10. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (9:1 hexane:2-propanol), 0.5 mL/min; major enantiomer tᵣ = 20.2 min, minor enantiomer tᵣ = 23.2 min.
Example 8a - 1-Phenylacetyl-3-(N-phenyl aminooxy) piperidin-4-one

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N}^\text{Ph} & \quad \text{S}^\text{Ph}
\end{align*}
\]

(5d, entry 4, Table 2). Purification by flash column chromatography with elution by hexane:ethyl acetate (3:1) provided as yellowish oil. TLC \( R_f = 0.10 \) (2:1 hexane:ethyl acetate); \([\alpha]_D^{20} +25.7^\circ \) (c = 0.7, CHCl₃); IR (neat) 3269, 3033, 2954, 1710, 1649, 1547, 1480, 1411, 1365, 1277, 1110, 986, 910 cm⁻¹; \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta 7.75 \) (bs, 1H, NH), 7.25 – 7.37 (m, 8H, Ar-H), 7.22 (t, 2H, J = 7.5 Hz, Ar-H), 6.94 (t, 2H, J = 7.4 Hz, Ar-H), 4.36 (b, 1H, CH), 3.75 (t, 2H, CH₂), 3.55 (q, 1H, CH₂), 3.37 – 3.44 (m, 1H, CH₂), 2.55 (b, 2H, CH₂), 2.41 (b, 2H, CH₂); \(^{13}\)C NMR (CDCl₃, 100 MHz) \( \delta 205.4, 155.1, 136.4, 128.8 \) (3C), 128.4, 128.2, 127.9 (2C), 122.3, 114.5 (2C), 82.9, 67.9, 64.4, 47.9, 43.7, 42.9, 40.8; MS (EI) Exact Mass Calcd for C₁₉H₂₀N₂O₃ (M-H)\(^{+}\): 323.1. Found: 323.1. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (9:1 hexane:2-propanol), 1.0 mL/min; major enantiomer \( t_r = 36.5 \) min, minor enantiomer \( t_r = 26.0 \) min.

Example 9a - 3-(N-phenyl aminooxy) butan-2-one

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N}^\text{Ph} & \quad \text{Ph}
\end{align*}
\]

Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish oil. TLC \( R_f = 0.20 \) (5:1 hexane:ethyl acetate); \([\alpha]_D^{25} +57.4^\circ \) (c = 3.8, CHCl₃); IR (neat) 3572, 1815, 1765, 1711, 1582, 1484, 1382, 837, 780 cm⁻¹; \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta 7.37 \) (s, 1H, NH), 7.26 (t, 2H, J = 7.4 Hz, Ar-H), 6.96 (t, 3H, J = 8.5 Hz, Ar-H), 4.43 (q, 1H, CH), 2.20 (s, 3H, CH₃), 1.42 (d, 3H, J = 7.0 Hz, CH₃); \(^{13}\)C NMR (CDCl₃, 100 MHz) \( \delta 209.6, 148.2, 129.3 \) (2C), 122.7, 114.8 (2C), 84.8, 25.9, 15.8; MS (EI) Exact Mass Calcd for C₁₉H₁₃N₂O₂ (M): 179. Found: 179. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 0.5 mL/min; major enantiomer \( t_r = 45.2 \) min, minor enantiomer \( t_r = 47.6 \) min.

Example 9b - 3-(N-phenyl hydroxyamino) butan-2-one

\[
\begin{align*}
\text{O} & \quad \text{N}^\text{Ph} \\
\text{OH} & \quad \text{Ph}
\end{align*}
\]

Purification by flash column chromatography with elution by hexane:ethyl acetate (10:1) provided as yellowish oil. TLC \( R_f = 0.15 \) (5:1 hexane:ethyl acetate); \([\alpha]_D^{25} -6.3^\circ \) (c = 0.12, CHCl₃); IR (neat) 3623, 3141, 1855, 1659, 1580, 1468, 1291, 1161, 852 cm⁻¹; \(^1\)H NMR (CDCl₃, 400 MHz) \( \delta 7.32 \) (t, 2H, J = 7.4 Hz, Ar-H), 7.10 (d, 2H, J = 7.7 Hz, Ar-H), 6.97 (t, 1H, J = 7.6 Hz, Ar-H), 5.80 (s, 1H, N-OH), 3.7
4.24 (q, 1H, J = 7.6 Hz, CH), 2.26 (s, 3H, CH₃), 1.31 (d, 3H, J = 6.7 Hz, CH₃); ¹³C NMR (CDCl₃, 100 MHz) δ 209.4, 150.7, 129.3 (2C), 122.3, 116.5 (2C), 69.98, 27.4, 10.8; MS (EI) Exact Mass Calcd for C₁₀H₁₃NO₂ (M): 179. Found: 179. Enantiomeric excess was determined by HPLC with a Chiralcel AD-H column (40:1 hexane:2-propanol), 0.5 mL/min; major enantiomer tₑ = 28.9 min, minor enantiomer tᵣ = 25.9 min.

Example 10a - 3-Phenyl-2-(N-phenyl aminooxy)-propan-1-ol

```
OH
O\N\Ph
```
Purification by flash column chromatography with elution by hexane:ethyl acetate (6:1) provided as yellowish oil. TLC Rₛ = 0.27 (2:1 hexane:ethyl acetate); [α]ᵣ<sup>20</sup> +26.0 (c = 1.07, CHCl₃); IR (neat) 3314, 2976, 2862, 1599, 1491, 1452, 1402, 1250, 1105, 1039, 910.5; ¹H δ 87.40 - 7.12 (m, 8H), 6.94 (t, J = 7.2 Hz, 1H), 6.82 (dd, J = 0.9, 8.7 Hz, 1H), 4.13 (dddd, J = 2.7, 6.9, 6.3, 6.3 Hz, 1H), 3.85 (dd, J = 2.7, 12 Hz, 1H), 3.71 (dd, J = 5.7, 12 Hz, 1H), 3.04 (dd, J = 6.9, 13.8 Hz, 1H), 2.84 (dd, J = 6.9, 13.8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 148.2, 137.7, 129.4, 128.9, 128.4, 126.4, 122.3, 114.5, 84.9, 64.1, 36.3; HRMS exact mass calcd for (C₁₂H₁₇NO₂) requires m/z 243.1259, found m/z 243.1251. Enantiomeric excess was determined by HPLC with a Chiralcel AD column (95:5 hexane:ethanol), 1.0 mL/min; major enantiomer tₑ = 42.8 min, minor enantiomer tᵣ = 40.1 min.

Example 11a - 3-Methyl-2-(N-phenyl aminooxy)-butan-1-ol

```
OH
O\N\Ph
```
Purification by flash column chromatography with elution by hexane:ethyl acetate (4:1) provided as yellowish oil. TLC Rₛ = 0.22 (2:1 hexane:ethyl acetate); [α]ᵣ<sup>20</sup> +18.3 (c = 1.03, CHCl₃); IR (neat) 3400, 3269, 3047, 2963, 2878, 1599, 1491, 1468, 1412, 1238, 1051, 1024, 978.0, 908.6, 771.6, 735.0, 694.5 cm⁻¹; ¹H NMR (300 MHz) δ 7.38 - 7.20 (m, 3H), 7.10 - 6.95 (m, 3H), 3.92 - 3.85 (m, 2H), 3.80 - 3.70 (m, 1H), 2.65 (t, J = 5.7 Hz, 1H), 2.12 - 1.95 (m, 1H), 1.05 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 148.2, 128.9, 122.3, 114.8, 88.5, 63.4, 28.6, 18.7, 18.5; HRMS exact mass calcd for (C₁₁H₁₇NO₂) requires m/z 195.1259, found m/z 195.1239. Enantiomeric excess was determined by HPLC with a Chiralcel AD column (95:5 hexane:ethanol), 1.0 mL/min; major enantiomer tₑ = 16.2 min, minor enantiomer tᵣ = 14.8 min.
Example 12a - 2-(N-Phenyl aminoxy)-hexan-1-ol

Purification by flash column chromatography with elution by hexane:ethyl acetate (6:1) provided as yellowish oil. TLC Rf = 0.36 (2:1 hexane:ethyl acetate); [α]D20 = +14.1 (c = 1.08, CHCl3; IR (neat) 3377, 3144, 2955, 1601, 1493, 1464, 1377, 1240, 1030, 902.8, 769.7; 1H NMR (300 MHz, CDCl3) 8.73-8.20 (m, 2H), 7.04-6.94 (m, 3H), 3.96 (dddd, J = 2.4, 6.6, 6.6, 6.6 Hz, 1H), 3.91-3.72 (m, 2H), 2.48 (m, 1H), 1.80-1.20 (m, 7H), 0.92 (t, J = 6.6 Hz, 3H); 13C NMR (75 MHz, CDCl3) 8148.3, 128.8, 122.1, 114.5, 83.8, 64.9, 29.5, 27.8, 22.7, 13.8; HRMS exact mass calcd for (C12H19NO2) requires m/z 209.1416, found m/z 209.1401. Enantiomeric excess was determined by HPLC with a Chiracel AD column (95:5 hexane:ethanol), 1.0 mL/min; major enantiomer tR = 19.5 min, minor enantiomer tR = 17.9 min.

Table 1. Additional O-nitroso aldol reactions*

<table>
<thead>
<tr>
<th>entry</th>
<th>I or II</th>
<th>Ex.</th>
<th>yield, %f</th>
<th>Ia/Ib**</th>
<th>ee of I or II</th>
<th>%g+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>5a</td>
<td>94</td>
<td>&gt;99 / -</td>
<td>&gt;99</td>
<td>(S)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>6a</td>
<td>87</td>
<td>&gt;99 / -</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>7a</td>
<td>97</td>
<td>&gt;99 / -</td>
<td>&gt;99</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>8a</td>
<td>95</td>
<td>&gt;99 / -</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>5†</td>
<td></td>
<td>9a/9b</td>
<td>75</td>
<td>72 / 28</td>
<td>&gt;99</td>
<td></td>
</tr>
<tr>
<td>6²</td>
<td></td>
<td>10a</td>
<td>67*</td>
<td>&gt;99 / -</td>
<td>98</td>
<td>(R)</td>
</tr>
<tr>
<td>7²</td>
<td></td>
<td>11a</td>
<td>65*</td>
<td>&gt;99 / -</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>8²</td>
<td></td>
<td>12a</td>
<td>69*</td>
<td>&gt;99 / -</td>
<td>98</td>
<td></td>
</tr>
</tbody>
</table>
* Reactions were conducted with 5 mol% of IVa, 1.0 equiv of nitrosobenzene, and 3 equiv of 4 in DMSO at room temperature.

† Reaction was conducted with 20 mol% of IVa in DMSO at room temperature.

‡ Reactions were conducted with 10 mol% of IVa in MeCN at room temperature.

§ Reaction was conducted with 20 mol% of IVa in MeCN at room temperature.

¶ Isolated yield.

* Determined by isolated yield of corresponding primary alcohol obtained after reduction of product.

** Determined by yield of isolated each isomer.

†† Determined by HPLC (Supporting Information).

§§ Determined after conversion to the corresponding diol (Supporting Information).

Reaction of nitrosobenzene with pyrrolidine enamine in benzene at 0 °C generated a new intermediate 1, which was converted to the second intermediate 2 by the exposure of acetic acid. The intermediate 2 was able to be transformed to the aminooxy ketone after usual work-up (Fig. 1). Various solvents and temperature combination were examined for this transformation, and DMSO emerged as the most suitable solvent to afford aminooxy ketone without production of azoxy dimer byproduct. ¹H NMR study in DMSO-d₆ revealed a downfield shift of enamine olefin proton (J = 3.9 Hz) from δ 4.1 to 4.4 ppm, one proton broad singlet at δ 8.2 ppm due to the aminooxy NH, and one proton triplet (J = 4.5 Hz) at pyrrolidine α-position at δ 4.3 ppm, which indicate the formation of the intermediate 1 (32). After treatment with acetic acid, complete conversion to a single new species is observed. This is assigned as the iminium salt 2 (33, 34); the significant downfield shift from δ 4.3 to 5.3 ppm (α-proton of iminium group) and disappearance of δ 4.4 ppm triplet (35). After work-up, the iminium salt 2 can be hydridized to α-aminooxy ketone.

Fig. 2. Plausible structure of intermediate

This information, together with the reported proline catalyzed reactions of nitrosobenzene with aldehydes, prompted us to test the possible enantioselective O-nitroso aldo synthesis of cyclohexanone using pyrrolidine-based Brønsted acid catalysts. The results with various catalysts are summarized in Table 2. The several kinds of substituted pyrrolidine-
TFA (IVb-IVd) were unable to catalyze nitroso aldol process after 1 day at room temperature. The diamine-protonic acid catalyst (IVe) afforded O-adduct with R configuration, but not provide catalyst turnover. The proline (IVf) and pyrrolidine-based tetrazole (IVA) afforded promising level of regioselection and enantiorecognition with S configuration for O-nitroso aldol adduct. Especially, the tetrazole catalyst was shown to be more attractive from the higher reactivity. The difference of reactivity is clearly demonstrated by the following comparison experiments with taking advantage of the complete enantiorecognition for aminooxy ketone: under the 3 mol% L-pyrrolidine-based tetrazole and D-proline as a mixed catalyst, the O-nitroso aldol product was isolated in 81% yield with 32% ee mainly from the tetrazole catalyst (S/R = 66:34) – see Figure 4 below.

**Figure 3. Comparison of effects of different catalysts of formula (IV)**
Table 2. Catalyst survey of O-nitroso aldol reaction*

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (mol%)</th>
<th>time</th>
<th>yield, %</th>
<th>5a / 5c / 5b</th>
<th>ee of 5a, %</th>
<th>(conf.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IVb (5)</td>
<td>1 day</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>IVc (5)</td>
<td>1 day</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>IVd (5)</td>
<td>1 day</td>
<td>&lt;1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>IVe (5)</td>
<td>1 h</td>
<td>4</td>
<td>&gt;99 / - / -</td>
<td>37 (R)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>IVf (5)</td>
<td>1 h</td>
<td>35</td>
<td>98 / 2 / -</td>
<td>&gt;99 (S)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>IVa (5)</td>
<td>1 h</td>
<td>94</td>
<td>&gt;99 / - / -</td>
<td>&gt;99 (S)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>IVa (3)</td>
<td>1 h</td>
<td>72</td>
<td>&gt;99 / - / -</td>
<td>&gt;99 (S)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>IVa (2)</td>
<td>1 h</td>
<td>50</td>
<td>&gt;99 / - / -</td>
<td>&gt;99 (S)</td>
<td></td>
</tr>
</tbody>
</table>

*Reactions were conducted with catalytic amount of IV, 1.0 equiv of nitrosobenzene, and 3 equiv. of cyclohexanone in DMSO at room temperature.

† Isolated yield.

‡ Determined by yield of isolated each isomer.

§ Determined by HPLC, CHIRALPAK AD.

¶ Determined after conversion to the corresponding diol.

**Figure 4. Effect of mixed catalysts on product formation**

![Diagram](image_url)

The absolute configuration of α-aminoxy compounds were determined by reduction to the corresponding diols (Figure 5 - eq 9, 10), which revealed opposite absolute configuration from ketone and aldehyde products. This observation indicated the different transition states depending on the choice of starting carbonyl compounds. These results can be explained as follows: because of steric (and/or electronic) stability of pyrrolidine enamines, the most stable enamine conformer derived from ketone or aldehyde can be assigned as shown in Fig. 6. While not wishing to be bound by theory, the reaction of nitrosobenzene may proceed from the same side of tetrazole (or carboxylic acid) by
either direct activation of nitrosobenzene by acidic proton (10a, 10b) or indirect route via amine-nitrosobenzene complexation followed by rearrangement (10a', 10b').

**Figure 5. Process to determine absolute configuration of α-aminoxy compounds**

![Chemical structures and reactions](image)

**Figure 6. Plausible transition states in O-nitroso aldol process.**

![Chemical structures](image)

The O-nitroso aldol synthesis has been developed using pyrrolidine-tetrazole catalyst not only for aldehydes but also ketones. With the appropriate of Brensted acidity in tetrazole catalyst, both high enantiomeric excesses and reactivity was realized in catalytic reaction. Identification of clean and regioselective transformation of O-nitroso aldol adducts furnished from pyrrolidine enamine gave the essential information to achieve catalytic enantioselective route using chiral amine catalyst. It is believes that this
O-nitroso aldol synthesis offers a new entry into pyrrolidine-based organic catalysis and deliver valuable information about relationship between small amines and nitroso compounds.

Examples of the α-aminoxyaldehydes which can be obtained by this invention include but are not limited to:

1. (N-isobutylaminooxy)acetaldehyde,
2. [N-(1,1-dimethylbutyl)]aminooxyacetaldehyde,
3. (N-phenylaminooxy)acetaldehyde,
4. 2-(N-isobutylaminooxy)propanal,
5. 2-[N-(1,1-dimethylbutyl)aminooxy]propanal,
6. 2-N-phenylaminooxypropanal,
7. 2-(N-isobutylaminooxy)butanal,
8. 2-[N-(1,1-dimethylbutyl) aminooxy]-2-methylpropanal,
9. 2-(N-phenylaminooxy)2-methylpropanal,
10. 2-(N-isobutylaminooxy)-4-methylbutanal,
11. 2-[N-(1,1-dimethylbutyl)aminooxy-4-methylbutanal,
12. 2-(N-phenylaminooxy)-4-methylbutanal 2-(N-isobutylaminooxy)hexanal,
13. 2-[N-(1,1-dimethylbutyl)aminooxyhexanal,
14. 2-(N-phenylaminooxy)hexanal, 2-(N-isobutylaminooxy)heptanal,
15. 2-[N-(1,1-dimethylbutyl)aminooxyheptanal,
16. 2-(N-phenylaminooxy)heptanal,
17. 2-(N-isobutylaminooxy)octanal,
18. 2-[N-(1,1-dimethylbutyl)aminooxyoctanal,
19. 2-(N-phenylaminooxy)octanal,
20. 2-(N-isobutylaminooxy)nonanal,
21. 2-[N-(1,1-dimethylbutyl)aminooxynonanal,
22. 2-(N-phenylaminooxy)nonanal,
23. 2-(N-isobutylaminooxy)decanal,
24. 2-[N-(1,1-dimethylbutyl)aminooxydecanal,
25. 2-(N-phenylaminooxy)decanal,
26. 2-(N-isobutylaminooxy)undecanal,
27. 2-[N-(1,1-dimethylbutyl)aminooxyundecanal,
28. 2-(N-phenylaminooxy)undecanal,
29. 2-(N-isobutylaminooxy)dodecanal,
2-(N-(1,1-dimethylbutyl)aminoxy)dodecanal,
2-(N-phenylaminoxy)dodecanal,
2-(N-isobutylaminoxy)tridecanal,
2-[N-(1,1-dimethylbutyl)aminoxy]tridecanal; and
2-(N-phenylaminoxy)tridecanal.

Examples of compounds which can be obtained as α-aminoxyaldehydes include
but are not limited to:
2,3-bis (N-isobutylaminoxy)butanedial,
2,3-bis[N-1,1-dimethylbutyl]aminoxy]butanedial,
2,3-bis[N-phenylaminoxy]butanedial,
2-N-isobutylaminoxy-2-propanal,
2-N-(1,1-dimethylbutyl)aminoxy-2-propanal,
2-N-phenylaminoxy-2-propanal,
2-N-isobutylaminoxy-2-butenal,
2-N-(1,1-dimethylbutyl)aminoxy-2-butenal,
2-N-phenylaminoxy-2-butenal,
3-phenyl-2-N-isobutylaminoxy-2-propanal,
3-phenyl-2-N-(1,1-dimethylbutyl)aminoxy-2-propanal; and
3-phenyl-2-N-phenylaminoxy-2-propanal.

Examples of the α-aminoxyketones which can be obtained by this invention
include but are not limited to:
(N-isobutylaminoxy)acetone,
[N-(1,1-dimethylbutyl)aminoxy]acetone,
(N-phenylaminoxy)acetone,
3-(N-isobutylaminoxy)butane-2-one,
3-[N-(1,1-dimethylbutyl)aminoxy]butane-2-one,
(N-phenylaminoxy)butane-2-one,
3-(N-isobutylaminoxy)pentane-2-one,
3-[N-(1,1-dimethylbutyl)aminoxy]pentane-2-one,
(N-phenylaminoxy)pentane-2-one,
3-(N-isobutylaminoxy)-4-methylbutane-2-one,
3-[N-(1,1-dimethylbutyl)aminoxy]-4-methylbutane-2-one,
(N-phenylaminoxy)-4-methylbutane-2-one,
3-(N-isobutylaminoxy)hexane-2-one,
3-[N-(1,1-dimethylbutyl)aminooxy]hexane-2-one,
(N-phenylaminooxy)hexane-2-one,
3-(N-isobutylaminooxy)-4-methylpentane-2-one,
3-[N-(1,1-dimethylbutyl)aminooxy]-4-methylpentane-2-one,
(N-phenylaminooxy)-4-methylpentane-2-one,
3-(N-isobutylaminooxy)-pentane-3-one,
3-[N-(1,1-dimethylbutyl)aminooxy]-pentane-3-one,
(N-phenylaminooxy)-pentane-3-one,
3-(N-isobutylaminooxy)-2,4-dimethylpentane-3-one,
3-[N-(1,1-dimethylbutyl)aminooxy]-2,4-dimethylpentane-3-one,
(N-phenylaminooxy)-2,4-dimethylbutane-3-one,
3-(N-isobutylaminooxy)undecane-2-one,
3-[N-(1,1-dimethylbutyl)aminooxy]undecane-2-one; and
(N-phenylaminooxy)undecane-2-one.

Examples of the α-aminooxyketones which can be obtained in this invention include but are not limited to:
3-N-isobutylaminooxy-2-butene-2-one,
3-N-(1,1-dimethylbutyl)aminooxy-3-butene-2-one,
3-N-phenylaminooxy-3-butene-2-one,
3-N-isobutylaminooxy-4-methyl-3-pentene-2-one,
3-N-(1,1-dimethylbutyl)aminooxy-4-methyl-3-pentene-2-one,
3-N-phenylaminooxy-4-methyl-3-pentene-2-one,
1-fluoro-1-(N-isobutylaminooxy)acetone,
1-fluoro-1-[N-(1,1-dimethylbutyl)aminooxy]acetone,
1-fluoro-1-(N-phenylaminooxy)acetone,
1-chloro-1-(N-isobutylaminooxy)acetone,
1-chloro-1-[N-(1,1-dimethylbutyl)aminooxy]acetone,
1-chloro-1-(N-phenylaminooxy)acetone,
3-(N-isobutylaminooxy)-2,4-pentanedione,
3-[N-(1,1-dimethylbutyl)aminooxy]-2,4-pentanedione,
3-(N-phenylaminooxy)-2,4-pentanedione,
3-(N-isobutylaminooxy)cyclobutanone,
3-[N-(1,1-dimethylbutyl)aminooxy]cyclobutanone,
3-(N-phenylaminooxy)cyclobutanone,
3-(N-isobutylaminoxy)cyclopentanone,
3-[N-(1,1-dimethylbutyl)aminoxy]cyclopentanone,
3-(N-phenylaminoxy)cyclopentanone,
3-(N-isobutylaminoxy)cyclohexanone,
5 3-[N-(1,1-dimethylbutyl)aminoxy]cyclohexanone,
3-(N-phenylaminoxy)cyclohexanone,
3-(N-isobutylaminoxy)-2-methylcyclohexanone,
3-[N-(1,1-dimethylbutyl)aminoxy]-2-methylcyclohexanone,
3-(N-phenylaminoxy)-2-methylcyclohexanone,
10 3-(N-isobutylaminoxy) cyclodecanone,
3-[N-(1,1-dimethylbutyl)aminoxy]cyclodecanone,
3-(N-phenylaminoxy)cyclodecanone,
3-(N-isobutylaminoxy)-2-norbornanone,
3-[N-(1,1-dimethylbutyl)aminoxy]-2-norbornanone,
15 3-(N-phenylaminoxy)-2-norbornanone,
3-(N-isobutylaminoxy)-2-adamantanone,
3-[N-(1,1-dimethylbutyl)aminoxy]-2-adamantanone,
3-(N-phenylaminoxy)-2-adamantanone.
2-(N-isobutylaminoxy)-4-tetrahydropyranone,
20 2-[N-(1,1-dimethylbutyl)aminoxy]-4-tetrahydropyranone,
2-(N-phenylaminoxy)-4-tetrahydropyranone,
7-(N-isobutylaminoxy)-spiro[4.5]-1,4-dioxy-decane-8-one,
7-[N-(1,1-dimethylbutyl)aminoxy]spiro[4.5]-1,4-dioxydecane-8-one,
3-(N-isobutylaminoxy)-1-benzylcarbonylpiperidine-4-one,
25 3-[N-(1,1-dimethylbutyl)aminoxy]-1-benzylcarbonylpiperidine-4-one,
3-(N-phenylaminoxy)-1-benzylcarbonylpiperidine-4-one,
3-(N-isobutylaminoxy)-4-phenylbutane-2-one,
3-[N-(1,1-dimethylbutyl)aminoxy]-4-phenylbutane-2-one,
3-(N-phenylaminoxy)-4-phenylbutane-2-one,
30 2-(N-isobutylaminoxy)-1-indanone,
2-[N-(1,1-dimethylbutyl)aminoxy]-1-indanone,
2-(N-phenylaminoxy)-1-indanone,
1-(N-isobutylaminoxy)-2-indanone,
1-[N-(1,1-dimethylbutyl)aminoxy]-2-indanone,
1-(N-phenylaminoxy)-2-indanone,
2-(N-isobutylaminoxy)-1-ketotetrahydronaphthalene,
2’-[N-(1,1-dimethylbutyl)aminoxy]-1-ketotetrahydronaphthalene,
1-(N-phenylaminoxy)-1-ketotetrahydronaphthalene,
1-(N-isobutylaminoxy)-2-ketotetrahydronaphthalene,
1-[N-(1,1-dimethylbutyl)aminoxy]-2-ketotetrahydronaphthalene,
1-(N-phenylaminoxy)-2-ketotetrahydronaphthalene,
1-(N-isobutylaminoxy)-7-methoxy-2-ketotetrahydronaphthalene,
1-[N-(1,1-dimethylbutyl)aminoxy]-7-methoxy-2-ketotetrahydronaphthalene,
1-(N-phenylaminoxy)-7-methoxy-2-ketotetrahydronaphthalene,
2’-(N-isobutylaminoxy)-1’-acetophenone,
2’-[N-(1,1-dimethylbutyl)aminoxy]-1’-acetophenone,
2’-(N-phenylaminoxy)-1’-acetophenone,
2’-(N-isobutylaminoxy)-1’-propiophenone,
2’-[N-(1,1-dimethylbutyl)aminoxy]-1’-propiophenone,
2’-(N-phenylaminoxy)-1’-propiophenone,
2-(N-isobutylaminoxy)-1,2-bisphenylethane-1-one,
2-[N-(1,1-dimethylbutyl)aminoxy]-1,2-bisphenylethane-1-one,
2-(N-phenylaminoxy)-1,2-bisphenylethane-1-one,
1-(N-isobutylaminoxy)-1,2-bisphenylethane-1-one,
1-[N-(1,1-dimethylbutyl)aminoxy]-1,2-bisphenylethane-1-one,
1-(N-phenylaminoxy)-1,2-bisphenylethane-1-one,
6-(N-isobutylaminoxy)-3,4-dimethylacetophenone,
6-[N-(1,1-dimethylbutyl)aminoxy]-3,4-dimethylacetophenone,
6-(N-phenylaminoxy)-3,4-dimethylacetophenone,
3’-(N-isobutylaminoxy)-2’-acetonaphthone,
3’-[N-(1,1-dimethylbutyl)aminoxy]-2’-acetonaphthone,
3’-(N-phenylaminoxy)-2’-acetonaphthone,
3’-(N-isobutylaminoxy)-2’-chloroacetonaphthone,
3’-[N-(1,1-dimethylbutyl)aminoxy]-2’-chloroacetonaphthone; and
3’-(N-phenylaminoxy)-2’-chloroacetonaphthone.

Except where otherwise indicated, the variables, formula numbers, table and figure numbers below refer to the process of making reaction products from cyclic α,β-unsaturated ketone substrates and nitroso substrates only.
The following Table and examples further demonstrate the scope of the present invention. Table 1 demonstrates that the present invention can be performed with a variety of cyclic α,β-unsaturated ketone and nitroso substrates. Furthermore, the results provided in Table 1 reveal that the heterocyclic product can be obtained in good yields with very high enantioselectivities.

**Table 1. Reaction Scope**

<table>
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<tr>
<th>entry</th>
<th>enone</th>
<th>R,R</th>
<th>ArN=O</th>
<th>yield, %</th>
<th>ee, %</th>
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<td>1</td>
<td></td>
<td>1a: Me,Me</td>
<td>2a</td>
<td>64</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1b: H,H</td>
<td>2a</td>
<td>34</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1c: Ph, Ph</td>
<td>2a</td>
<td>56</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1d:--</td>
<td>2a</td>
<td>61</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1a</td>
<td>2b</td>
<td>47</td>
<td>98</td>
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</tr>
<tr>
<td>7</td>
<td></td>
<td>1a</td>
<td>2d</td>
<td>50</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>1e: H,H</td>
<td>2a</td>
<td>14</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>1e: H,H</td>
<td>2a</td>
<td>51</td>
<td>99</td>
</tr>
</tbody>
</table>

* Reaction was conducted with 20 mol% of catalysis, 1 eq. of enone and 2 eq. of nitrosobenzene under N₂ atmosphere at 40°C for 15h. * Isolated yield. * ee value was determined by HPLC (Supporting Information). * L-Proline was used as catalyst.

**Examples—Synthetic and Spectroscopic Data**

**General Procedures**

All non-aqueous reactions were carried out in oven- or flame-dried glassware under an atmosphere of dry nitrogen unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin-layer chromatography using Whatman pre-coated silica gel flexible plates (0.25 mm) with F₂₅₄
indicator or Merck pre-coated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (256 nm), with combination of potassium permanganate and/or Ninhydrin and/or phosphomolybdic acid, and/or ferric chloride solution as a indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (mesh 230-400) supplied by E. Merck. Yields refer to chromatographically and spectrographically pure compounds, unless otherwise noted.

Commercial grade reagents and solvents were used without further purification except as indicated below. Tetrahydrofuran (THF), and Ethylene glycol diethyl ether were distilled from sodium-benzophenone ketyl under an atmosphere of dry argon. 2-

Cycloheptene-1-one was distilled under P_{2}O_{5}. 1,4-Dioxaspiro[4,5]dec-6-en-8-one was prepared according to reported method (Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L. Org. Lett, 2001, 3, 2945-2948).

Infrared spectra were recorded as thin films on sodium chloride plates using a Nicolet 20 SXB FTIR. ^1H NMR and ^13C NMR spectra were recorded on a Bruker Avance 400 (400 MHz ^1H, 100 MHz ^13C), a Bruker Avance 500 (500 MHz ^1H, 125 MHz ^13C). Chemical shift values (δ) are reported in ppm relative to Me_{4}Si (δ 0.0 ppm). The proton spectra are reported as follows δ (multiplicity, number of protons, coupling constant J). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (heptet), m (multiplet) and br (broad).

To the catalyst (0.40 mol) was added enone (2.0 mmol), nitrosobenzene (4.0 mmol) acetonitrile (4.0 mL). The mixture was allowed to warm to 40°C and was stirred at the same temperature for 15 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel chromatography to afford Diels Alder adduct.

**Example 1. Synthesis of 8,8-Dimethyl-3-phenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one**

![Chemical structure image]

Purification by flash column chromatography with elution by (1:9 EtOAc: Hexane) provided as a yellowish oil (64% yield, 99% ee). TLC R_{f} 0.7 (EtOAc/Hexane, 1:5);

\[\alpha\]_{D}^{29}+82.3° (c = 1.10, CHCl_{3}); FTIR (CD_{2}Cl_{2}) ν_{max} 2962, 1743, 1595, 1489, 1028, 992 cm^{-1}; ^1H NMR (400 MHz, CDCl_{3}) δ 7.31 (t, J = 7.4 Hz, 2 H), 7.09 (d, J = 8.7 Hz, 2 H), 7.00 (t, J = 7.3 Hz, 2 H), 4.18 - 4.19 (m, 1 H), 3.51 - 3.53 (m, 1 H), 2.71 (dd, J = 18.7 Hz, J = 2.7 Hz, 1 H), 2.48 (dd, J = 18.7 Hz, J = 3.0 Hz, 1 H), 2.31 (dd, J = 14.5 Hz, J = 3.9 Hz, J = 2.7 Hz, 1 H).
1 H), 1.81 (dd, J = 14.5 Hz, J = 1.8 Hz, 1 H), 1.57 (s, 3 H), 1.47 (s, 3 H); $^{13}$C NMR (100 MHz, CD$_3$Cl) δ 208.1, 149.9, 128.9, 122.4, 116.6, 78.2, 68.4, 39.8, 34.9, 33.1, 28.6, 27.2; MS (Cl) Exact Mass Calcd for C$_4$H$_3$N$_2$O$_4$ (M+H)$^+$: 232.1. Found: 232.1. Enantiomeric excess was determined by HPLC with Chiralcel AD-H column (97:3 hexane:2-propanol), 0.8 mL/min; major enantiomer t$_r$ = 11.1 min, minor enantiomer t$_r$ = 10.6 min. Enantiomer was obtained as a yellowish oil using D-tetrazole catalysis using the same method. (61% yield, 99% ee). [α]$_D^{29}$ -79.7° (c = 0.56, CHCl$_3$).

**Example 2**

![Image](image_url)

Purification by flash column chromatography with elution by (1:19 EtOAc:

CH$_2$Cl$_2$) provided as a yellowish oil (61% yield, 98% ee); TLC R$_f$ 0.6 (EtOAc/ CH$_2$Cl$_2$,

1:19); [α]$_D^{29}$ -5.4° (c = 1.03, CHCl$_3$); FTIR (CD$_3$Cl) ν max 2979, 2892, 1747, 1597, 1489,

1227, 1064 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$Cl) δ 7.31 (t, J = 7.4 Hz, 2 H), 7.13 (d, J = 8.8

Hz, 2 H), 7.02 (t, J = 7.3 Hz, 1 H) 4.32 (dd, J = 3.6 Hz, J = 2.6 Hz, 1 H), 4.10 - 4.15 (m, 1

H), 3.97 - 4.04 (m, 3 H), 3.92 (t, J = 2.9 Hz, 1 H), 2.91 (dd, J = 15.2 Hz, J = 3.9 Hz, 1 H),

2.88 (dd, J = 18.5 Hz, J = 2.9 Hz, 1 H) 2.66 (dd, J = 18.5 Hz, J = 2.9 Hz, 1 H), 2.28 (dd, J

= 15.2 Hz, J = 2.4 Hz, 1 H); $^{13}$C NMR (100 MHz, CD$_3$Cl) δ 204.9, 148.9, 128.8, 122.9,

116.8, 105.5, 77.9, 64.9, 64.8, 64.4, 38.7, 64.5; MS (Cl) Exact Mass Calcd for

C$_{14}$H$_{13}$N$_2$O$_4$ (M+H)$^+$: 262.1. Found: 262.1. Enantiomeric excess was determined by

HPLC with Chiralcel AD-H column (90:10 hexane:2-propanol), 1.0mL/min; major

enantiomer t$_r$ = 20.5 min, minor enantiomer t$_r$ = 17.3 min.

**Example 3** 7-Phenyl-6-oxa-7-aza-bicyclo[3.2.2]nonan-9-one

![Image](image_url)

Purification by flash column chromatography with elution by (1:1 Hexane:

CH$_2$Cl$_2$) provided as a yellowish oil (51% yield, 99% ee); TLC R$_f$ 0.7 (Hexane/ CH$_2$Cl$_2$,

1:19); [α]$_D^{29}$ -186.5° (c = 1.12, CHCl$_3$); FTIR (CD$_3$Cl) ν max 2946, 1736, 1597, 1489, 1204,

1102, 1038, 734 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$Cl) δ 7.31 (t, J = 7.4 Hz, 2 H), 7.04 (d, J =

8.8 Hz, 2 H), 6.92 (t, J = 7.4 Hz, 1 H) 6.60 (br d, J = 5.8 Hz, 1 H), 4.36 - 4.39 (m, 1 H),

2.98 (dd, J = 18.1 Hz, J = 5.5 Hz, 1 H), 2.43 (dd, J = 18.1 Hz, J = 2.1 Hz, 1 H) 2.07 - 2.16

(m, 3 H), 1.86 - 1.96 (m, 1 H), 1.42 - 1.56 (m, 1 H); $^{13}$C NMR (100 MHz, CD$_3$Cl) δ

207.5, 150.0, 129.0, 121.0, 114.7, 83.6, 56.9, 38.8, 30.9, 29.7, 18.9; MS (Cl) Exact Mass

Calcd for C$_{13}$H$_{13}$NO$_2$ (M+H)$^+$: 218.1. Found: 218.1. Enantiomeric excess was
determined by HPLC with Chiralcel AD-H column (90:10 hexane:2-propanol), 1.0mL/min; major enantiomer $t_r = 8.5$ min, minor enantiomer $t_r = 6.9$ min.

**Example 4** 3,8,8-Triphenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one

![Chemical structure]

Purification by flash column chromatography with elution by (1:1 Hexane:
CH$_2$Cl$_2$) provided as a yellowish crystal (56% yield, 99% ee); TLC $R_f$ 0.7 (CH$_2$Cl$_2$);
[$\alpha$]$_D$$^{20}$+288.4° (c = 0.97, CHCl$_3$); FTIR (CD$_3$Cl) $\nu_{\max}$ 3058, 2361, 2337, 1743, 1596, 1449, 1394, 1032, 998, 909 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$Cl) $\delta$ 7.31 (t, $J = 7.4$ Hz, 2 H), 7.04
(d, $J = 8.8$ Hz, 2 H), 6.92 (t, $J = 7.4$ Hz, 1 H) 4.60 (br d, $J = 5.8$ Hz, 1 H), 4.36 – 4.39 (m, 1 H), 2.98 (dd, $J = 18.1$ Hz, $J = 5.5$ Hz, 1 H), 2.43 (dd, $J = 18.1$ Hz, $J = 2.1$ Hz, 1 H) 2.07 –
2.16 (m, 3 H), 1.86 – 1.96 (m, 1 H), 1.42 – 1.56 (m, 1 H); $^{13}$C NMR (100 MHz, CD$_3$Cl) $\delta$
207.5, 150.0, 129.0, 121.0, 114.7, 83.6, 56.9, 38.8, 30.9, 29.7, 18.9; MS (CI) Exact Mass
Caled for C$_{13}$H$_{15}$NO$_2$ (M+H)$^+$: 355.2. Found: 355.1. Enantiometric excess was
determined by HPLC with Chiralcel AD-H column (95:5 hexane:2-propanol), 1.0mL/min;
major enantiomer $t_r = 10.1$ min, minor enantiomer $t_r = 8.8$ min.

**Example 5** 3-Phenyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one

![Chemical structure]

Purification by flash column chromatography with elution by (1:4 EtOAc: Hexane)
provided as a yellowish oil (34% yield, 99% ee); TLC $R_f$ 0.5 (EtOAc/Hexane : 1:3);
[$\alpha$]$_D$$^{27}$-216.9° (c = 0.6, CHCl$_3$); FTIR (CD$_3$Cl) $\nu_{\max}$ 2965, 1745, 1596, 1488, 1306, 1220,
1174, 986 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$Cl) $\delta$ 7.31 (t, $J = 7.4$ Hz, 2 H), 7.12 (d, $J = 8.7$
Hz, 2 H), 7.00 (t, $J = 7.3$ Hz, 1 H) 4.19 – 4.22 (m, 2 H), 3.02 (br d, $J = 18.2$ Hz, 1 H), 2.47
(dd, $J = 18.1$ Hz, $J = 3.1$ Hz, 1 H) 2.26 – 2.40 (m, 2 H), 1.91 – 1.99 (m, 1 H), 1.61 – 1.68
(m, 1 H); $^{13}$C NMR (100 MHz, CD$_3$Cl) $\delta$ 207.1, 150.3, 129.0, 122.2, 116.2, 76.9, 56.1,
41.8, 22.4, 21.5; MS (CI) Exact Mass Caled for C$_{13}$H$_{15}$NO$_2$ (M+H)$^+$: 204.1. Found: 204.1.
Enantiometric excess was determined by HPLC with Chiralcel AD-H column (90:10
hexane:2-propanol), 1.0mL/min; major enantiomer $t_r = 23.4$ min, minor enantiomer $t_r =
10.0$ min.

**Example 6** 3-(4-Bromo-phenyl)-8,8-dimethyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one

![Chemical structure]

52
Solvent system was changed to CH₂Cl₂/MeCN 1:1 (6 mL) was used instead of use of CH₂Cl₂. Purification by flash column chromatography with elution by CH₂Cl₂ provided as a yellowish crystal (50% yield, 99% ee); TLC Rf 0.6 (CH₂Cl₂); [α]D²⁷ +68.1° (c = 2.17, CHCl₃); FTIR (CD₃Cl) ν max 2962, 2871, 1742, 1587, 1485, 1436, 1028, 825 cm⁻¹; ¹H NMR (400 MHz, CD₃Cl) δ 7.33 (d, J = 8.9 Hz, 2 H), 6.90 (d, J = 8.9 Hz, 2 H), 4.10 – 4.12 (m, 1 H), 3.40 – 3.42 (m, 1 H), 2.57 (dd, J = 18.7 Hz, J = 2.7 Hz, 1 H) 2.42 (dd, J = 18.7 Hz, J = 2.9 Hz, 1 H) 2.21 (dd, J = 14.6 Hz, J = 3.9 Hz, 1 H) 1.73 (dd, J = 14.5 Hz, J = 2.3 Hz, 1 H) 1.37 (s, 3 H), 1.01 (s, 3 H); ¹³C NMR (100 MHz, CD₃Cl) δ 207.4, 149.1, 131.8, 118.2, 114.8, 78.3, 68.3, 39.7, 35.0, 33.1, 28.6, 27.2; MS (Cl) Exact Mass Caled for C₁₄H₁₃BrNO₂ (M+H)⁺: 310.0. Found: 310.0. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (98:2 hexane:2-propanol), 1.0 mL/min; major enantiomer tᵣ = 11.3 min, minor enantiomer tᵣ = 15.3 min.

Example 7 8,8-Dimethyl-3-p-tolyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one

\[
\text{\includegraphics{example7.png}}
\]

Purification by flash column chromatography with elution by (1:9 EtOAc: Hexane) provided as a yellowish crystal (46% yield, 98% ee); TLC Rf 0.5 (EtOAc/Hexane 1:5); [α]D²⁷ +44.4° (c = 1.32, CHCl₃); FTIR (CD₃Cl) ν max 2961, 1742, 1506, 1028, 994, 817 cm⁻¹; ¹H NMR (400 MHz, CD₃Cl) δ 7.10 (d, J = 8.1 Hz, 2 H), 6.98 (d, J = 8.5 Hz, 2 H), 4.14 – 4.17 (m, 1 H), 3.42 – 3.45 (m, 1 H), 2.71 (dd, J = 18.7 Hz, J = 2.7 Hz, 1 H) 2.45 (dd, J = 18.7 Hz, J = 3.0 Hz, 1 H) 2.30 (dd, J = 14.4 Hz, J = 4.0 Hz, 1 H), 2.29 (s, 3 H), 1.79 (dd, J = 14.5 Hz, J = 1.8 Hz, 1 H) 1.47 (s, 3 H), 1.07 (s, 3 H); ¹³C NMR (100 MHz, CD₃Cl) δ 208.3, 147.6, 132.0, 129.4, 116.8, 78.2, 68.6, 39.9, 34.7, 33.1, 28.6, 27.3, 20.6; C₁₅H₂₆NO₂ (M+H)⁺: 246.2. Found: 246.1. Enantiometric excess was determined by HPLC with Chiralcel OD-H column x 2 (99:1 hexane:2-propanol), 0.5 mL/min; major enantiomer tᵣ = 38.3 min, minor enantiomer tᵣ = 40.7 min.

Example 8 3-(3,5-Dimethyl-phenyl)-8,8-dimethyl-2-oxa-3-aza-bicyclo[2.2.2]octan-6-one

\[
\text{\includegraphics{example8.png}}
\]

Purification by flash column chromatography with elution by (1:9 EtOAc: Hexane) provided as a yellowish crystal (52% yield, 98% ee); TLC Rf 0.5 (EtOAc/Hexane 1:5); [α]D²⁷ +70.8° (c = 0.67, CHCl₃); FTIR (CD₃Cl) ν max 2961, 2921, 2870, 1742, 1595, 1471,
1028, 1006 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CD\(_3\)Cl) \(\delta\) 6.70 (s, 2 H), 6.64 (s, 1 H), 4.14 - 4.17 (m, 1 H), 3.47 - 3.51 (m, 1 H), 2.72 (dd, \(J = 18.7\) Hz, \(J = 2.7\) Hz, 1 H) 2.47 (dd, \(J = 18.7\)Hz, \(J = 3.0\) Hz, 1 H) 2.29 (dd, \(J = 14.4\) Hz, \(J = 3.9\) Hz, 1 H), 2.29 (s, 6 H), 1.79 (dd, \(J = 14.5\) Hz, \(J = 2.0\)Hz, 1 H) 1.46 (s, 3 H), 1.07 (s, 3 H); \(^{13}\)C NMR (100 MHz, CD\(_3\)Cl) \(\delta\) 208.4, 150.0, 138.5, 124.2, 114.3, 78.2, 68.2, 39.9, 35.0, 33.1, 28.6, 27.3, 21.5; C\(_{16}\)H\(_{22}\)NO\(_2\) (M+H): 260.2. Found: 260.2. Enantiometric excess was determined by HPLC with Chiralcel AD-H column (97.5:2.5 hexane:2-propanol), 0.4 mL/min; major enantiomer \(t_e = 13.7\) min, minor enantiomer \(t_e = 12.8\) min.

Having thus described in detail various embodiments of the present invention, it is to be understood that the invention defined by the above paragraphs is not to be limited to particular details set forth in the above description as many apparent variations thereof are possible without departing from the spirit and scope of the present invention.
WHAT IS CLAIMED IS:

1. A method of performing a catalytic asymmetric O-nitroso Aldol / Michael reaction comprising:
   reacting a cyclic α,β-unsaturated ketone substrate with a nitroso substrate in the presence of a proline-based catalyst to provide a heterocyclic product.

2. The method of claim 1, where the cyclic α,β-unsaturated ketone substrate has a structure (I):

   ![Structure Image]

   where:
   each R¹ represents a substituent independently selected from the group consisting of hydrogen, halogen, -OR¹, -OC(O)R¹, -CN, -C(O)R¹, -CO₂R¹, -C(O)NR²R², -NO₂,
   -NR²R², -NR²C(O)R³, -NR²CO₂R¹, -NR²S(O)₂R³, -SR¹, -S(O)R¹, -S(O)₂R¹,
   -S(O)₂NR²R², C₁₋₈ alkyl, C₂₋₈ dialkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclol;
   each X¹ independently represents -CR²R³, -NR², -O-, or -S-;
   R² and R³ represent substituents independently selected from the group consisting of hydrogen, halogen, -OR¹, -OC(O)R¹, -CN, -C(O)R¹, -CO₂R¹,
   -C(O)NR²R², -NO₂, -NR²R², -NR²C(O)R³, -NR²CO₂R¹, -NR²S(O)₂R³, -SR¹,
   -S(O)R¹, -S(O)₂R¹, -S(O)₂NR²R², C₁₋₈ alkyl, C₂₋₈ dialkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclol;
   each R² and R³, together with the atom to which they are attached, may form a 5-, 6- or 7-membered heterocyclic ring; and
   X² represents -C- or -S-;
   each R¹ and R² is independently selected from the group consisting of hydrogen, C₁₋₈ alkyl, C₂₋₈ dialkyl, C₂₋₈ dialkynyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclol;

3. The method of claim 1, where the cyclic α,β-unsaturated ketone substrate has a structure (II):
where:

each $R^4$ represents a substituent independently selected from the group consisting of hydrogen, halogen, -OR$^{iii}$, -OC(O)R$^{iii}$, -CN, -C(O)R$^{iii}$, -CO$_2$R$^{iii}$, -C(O)NR$^{iv}$, -NO$_2$, -NR$^{iii}$R$^{iv}$, -NR$^{iii}$C(O)R$^{iv}$, -NR$^{iii}$CO$_2$R$^{iv}$, -NR$^{iii}$S(O)$_2$R$^{iv}$, -SR$^{iii}$, -S(O)R$^{iii}$, -S(O)$_2$R$^{iii}$, -S(O)$_2$NR$^{iv}$, C$_{1-8}$ alkyl, C$_{2-8}$ alkenyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each $X^3$ independently represents -CR$^5$R$^6$, -NR$^5$, -O-, or -S-;

$R^5$ and $R^6$ represent substituents independently selected from the group consisting of hydrogen, halogen, -OR$^{iii}$, -OC(O)R$^{iii}$, -CN, -C(O)R$^{iii}$, -CO$_2$R$^{iii}$, -C(O)NR$^{iv}$, -NO$_2$, -NR$^{iii}$R$^{iv}$, -NR$^{iii}$C(O)R$^{iv}$, -NR$^{iii}$CO$_2$R$^{iv}$, -NR$^{iii}$S(O)$_2$R$^{iv}$, -SR$^{iii}$, -S(O)R$^{iii}$, -S(O)$_2$R$^{iii}$, -S(O)$_2$NR$^{iv}$, C$_{1-8}$ alkyl, C$_{2-8}$ alkenyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each $R^3$ and $R^4$, together with the atom to which they are attached, may form a 5-, 6-, or 7-membered heterocyclic ring; and

$X^4$ represents C or S;

each $R^{iii}$ and $R^{iv}$ is independently selected from the group consisting of hydrogen, C$_{1-8}$ alkyl, C$_{2-8}$ alkenyl, C$_{2-8}$ alkynyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

4. The method of claim 1, where the cyclic $\alpha,\beta$-unsaturated ketone substrate has a structure (IIa):

where,
each \( R^b \) represents a substituent independently selected from the group consisting of hydrogen, halogen, -OR, -OC(O)R, -CN, -C(O)R, -CO₂R, -C(O)NR₂R, -NO₂, -NR₂R, -NR₂C(O)R, -NR₂CO₂R, -NR₂S(O)₂R, -SR, -S(O)R, -S(O)₂R, -S(O)₂NR₂R, C₁₈ alkyl, C₂-8 alkenyl, C₂-8 alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocycl; 

n is 0, 1, 2 or 3; and 

each \( R^c \) and \( R^d \) is independently selected from the group consisting of hydrogen, C₁-₈ alkyl, C₂-8 alkenyl, C₂-8 alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocycl.

5. The method of claim 1, where the cyclic \( \alpha,\beta \)-unsaturated ketone substrate has a structure (III):

```
X⁵ X⁵
  \   \   \\
  R⁷    R⁷
  \     \ \\
   \   \ \\
   \   \ \\
   X⁵
```

where:

each \( R^7 \) represents a substituent independently selected from the group consisting of hydrogen, halogen, -OR, -OC(O)R, -CN, -C(O)R, -CO₂R, -C(O)NR₂R, -NO₂, -NR₂R, -NR₂C(O)R, -NR₂CO₂R, -NR₂S(O)₂R, -SR, -S(O)R, -S(O)₂R, -S(O)₂NR₂R, C₁₈ alkyl, C₂-8 alkenyl, C₂-8 alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocycl;

each \( X^5 \) independently represents -CR₈R₉, -NR₈, -O-, or -S-;

\( R^8 \) and \( R^9 \) represent substituents independently selected from the group consisting of hydrogen, halogen, -OR, -OC(O)R, -CN, -C(O)R, -CO₂R, -C(O)NR₂R, -NO₂, -NR₂R, -NR₂C(O)R, -NR₂CO₂R, -NR₂S(O)₂R, -SR, -S(O)R, -S(O)₂R, -S(O)₂NR₂R, C₁₈ alkyl, C₂-8 alkenyl, C₂-8 alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocycl;

each \( R^8 \) and \( R^9 \), together with the atom to which they are attached, may form a 5-, 6- or 7-membered heterocyclic ring; and

\( X^6 \) represents C or S;
each \( R^v \) and \( R^{vi} \) is independently selected from the group consisting of hydrogen, C\(_{1-8}\) alkyl, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, C\(_{3-8}\) cycloalkyl, C\(_{6-10}\) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

6. The method of claim 1, where the cyclic \( \alpha,\beta \)-unsaturated ketone substrate has a structure (IV):

\[
\begin{array}{c}
\text{IV} \\
\includegraphics[width=0.3\textwidth]{image.png}
\end{array}
\]

where:

\( R^{10} \) represents a substituent independently selected from the group consisting of hydrogen, halogen, -OR\(^{vi}\), -OC(O)R\(^{vi}\), -CN, -C(O)R\(^{vi}\), -CO\(_2\)R\(^{vi}\), -C(O)NR\(^{vi}\)R\(^vii\), -NO\(_2\), -NR\(^{vi}\)R\(^vii\), -NR\(^{vi}\)C(O)R\(^vii\), -NR\(^vii\)CO\(_2\)R\(^vii\), -NR\(^{vii}\)S(O)\(_2\)R\(^vii\), -NR\(^vii\)R\(^vii\), -S(O)R\(^vii\), -S(O)\(_2\)R\(^vii\), -S(O)\(_2\)NR\(^vii\)R\(^vii\), C\(_{1-8}\) alky1, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, C\(_{3-8}\) cycloalkyl, C\(_{6-10}\) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each \( X^7 \) independently represents -CR\(^{11}\)R\(^{12}\), -NR\(^{11}\), -O-, or -N-;

\( R^{11} \) and \( R^{12} \) represent substituents independently selected from the group consisting of hydrogen, halogen, -OR\(^{vi}\), -OC(O)R\(^{vi}\), -CN, -C(O)R\(^{vi}\), -CO\(_2\)R\(^{vi}\), -C(O)NR\(^{vi}\)R\(^vii\), -NO\(_2\), -NR\(^{vii}\)R\(^vii\), -NR\(^{vii}\)C(O)R\(^vii\), -NR\(^vii\)CO\(_2\)R\(^vii\), -NR\(^{vii}\)S(O)\(_2\)R\(^vii\), -SR\(^vii\), -S(O)R\(^vii\), -S(O)\(_2\)R\(^vii\), -S(O)\(_2\)NR\(^vii\)R\(^vii\), C\(_{1-8}\) alky1, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, C\(_{3-8}\) cycloalkyl, C\(_{6-10}\) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each \( R^{11} \) and \( R^{12} \), together with the atom to which they are attached, may form a 5-, 6- or 7-membered heterocyclic ring; and

\( X^8 \) represents -C- or -S-;

each \( R^{vi} \) and \( R^{viii} \) is independently selected from the group consisting of hydrogen, C\(_{1-8}\) alky1, C\(_{2-8}\) alkenyl, C\(_{2-8}\) alkynyl, C\(_{3-8}\) cycloalkyl, C\(_{6-10}\) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

7. The method of claim 1, where the cyclic \( \alpha,\beta \)-unsaturated ketone substrate is selected from the group consisting of:
8. The method of claim 1, where the nitroso substrate has a structure (V):

![Structure V]

where:

\( R^{13} \) represents 1 to 5 substituents each independently selected from the group consisting of hydrogen, halogen, -OR\(^x\), -OC(O)R\(^x\), -CN, -C(O)R\(^x\), -CO\(_2\)R\(^x\), -C(O)NR\(^x\)R\(^x\), -NO\(_2\), -NR\(^x\)R\(^x\), -NR\(^x\)C(O)R\(^3\), -NR\(^x\)CO\(_2\)R\(^x\), -NR\(^x\)S(O)\(_2\)R\(^x\), -SR\(^x\), -S(O)R\(^x\), -S(O)\(_2\)R\(^x\), -S(O)\(_2\)NR\(^x\)R\(^x\), C\(_1\)-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C\(_3\)-8 cycloalkyl, C\(_6\)-10 aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each \( R^x \) and \( R^x \) is independently selected from the group consisting of C\(_1\)-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C\(_3\)-8 cycloalkyl, C\(_6\)-10 aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

9. The method of claim 8, where the nitroso substrate is selected from the group consisting of:

![Substrates]

10. The method of claim 1, where the proline-based catalyst has a structure (VI):

![Catalyst Structure VI]
where:

1. **R**\(^{14}\) is selected from the group consisting of:

   - \begin{align*}
       \text{and } \quad \text{and }
   \end{align*}

2. **R**\(^{15}\) is a substituent selected from the group consisting of hydrogen, C\(_{1-8}\) alkyl, C2-8 alkenyl, C2-8 alkynyl, C\(_{3-8}\) cycloalkyl, C\(_{6-10}\) aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

11. The method of claim 10, where the proline-based catalyst is selected from the group consisting of:

12. The method of claim 2, where the heterocyclic product has the formula (VII):

13. The method of claim 3, where the heterocyclic product has the formula (VIII):
14. The method of claim 4, where the heterocyclic product has the formula (VIIIa):

15. The method of claim 5, where the heterocyclic product has the formula (IX):

16. The method of claim 6, where the heterocyclic product has the formula (X):

17. The method of claim 1, where the cyclic α,β-unsaturated ketone substrate has a structure (II):
where:

each $R^{18}$ represents a substituent independently selected from the group consisting of hydrogen, halogen, -OR$^x$, -OC(O)R$^x$, -CN, -C(O)R$^x$, -CO$_2$R$^x$, -C(O)NR$^{xii}$R$^{xii}$, -NO$_2$, -NR$^{xii}$R$^{xii}$, -NR$^{xii}$C(O)R$^3$, -NR$^{xii}$CO$_2$R$^{xii}$, -NR$^{xii}$S(O)R$^{xii}$, -SR$^{xii}$, -S(O)R$^{xii}$, -S(O)$_2$R$^{xii}$, -S(O)$_2$NR$^{xii}$R$^{xii}$, C$_{1-8}$ alkyl, C2-8 alkenyl, C2-8 alkynyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each $X^{15}$ independently represents -CR$^{19}$R$^{20}$, -NR$^{19}$-, -O-, or -S-;

$R^{19}$ and $R^{20}$ represent substituents independently selected from the group consisting of hydrogen, halogen, -OR$^x$, -OC(O)R$^x$, -CN, -C(O)R$^x$, -CO$_2$R$^x$, -C(O)NR$^{xii}$R$^{xii}$, -NO$_2$, -NR$^{xii}$C(O)R$^3$, -NR$^{xii}$CO$_2$R$^{xii}$, -NR$^{xii}$S(O)R$^{xii}$, -SR$^{xii}$, -S(O)R$^{xii}$, -S(O)$_2$R$^{xii}$, -S(O)$_2$NR$^{xii}$R$^{xii}$, C$_{1-8}$ alkyl, C2-8 alkenyl, C2-8 alkynyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

each $R^{19}$ and $R^{20}$, together with the atom to which they are attached, may form a 5-, 6- or 7-membered heterocyclic ring; and

$X^{16}$ represents C or S;

each $R^{xii}$ and $R^{xili}$ is independently selected from the group consisting of hydrogen, C$_{1-8}$ alkyl, C2-8 alkenyl, C2-8 alkynyl, C$_{3-8}$ cycloalkyl, C$_{6-10}$ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl.

18. A process of making an $\alpha$-aminoxyketone or an $\alpha$-aminooxylaldehyde comprising reacting an aldehyde of formula (I) or ketone of formula (II):

![Diagram](image)

(I)  

with a nitroso compound of formula (IIIa) or (IIIb):

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in the presence of a solvent and a catalyst of formula (IV):

wherein:

R, R¹ and R² independently represent either hydrogen; a substituted or unsubstituted alkyl group; a substituted or unsubstituted alkoxy group; a substituted or unsubstituted alkoxy carbonyl group; a substituted or unsubstituted aryl group; or R¹ and R² together form a cycloalkyl ring;

R³ is each independently selected from the group consisting of:
consisting of hydrogen, halogen, -OR⁴, -OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴, -C(O)NR⁴R⁵, -NO₂, -NR⁴R⁵, -NRC(O)R⁴, -NR⁴CO₂R⁵, -NR⁴S(O)₂R⁵, -SR⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NR⁴R⁵, C₁-₈ alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; wherein each R⁴ and R⁵ may be independently selected from the group consisting of C₁-₈ alkyl, C₂-₈ alkenyl, C₂-₈ alkynyl, C₃-₈ cycloalkyl, C₆-₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;

n is an integer from 0-5;

R⁴ is substituted or unsubstituted alkyl;

X¹, X² and X³ independently represent oxygen; sulfur; substituted or unsubstituted nitrogen; or substituted or unsubstituted carbon; and

Z represents a substituted or unsubstituted 4 to 10-membered ring which optionally contain up to three additional heteroatoms.

19. The process of claim 18 wherein:
R, R¹ and R² independently represent either hydrogen; a substituted or unsubstituted
C₁-C₈ alkyl group; a substituted or unsubstituted C₁-C₈ alkoxy group; a substituted or unsubstituted C₁-C₈ alkoxy carbonyl group; a substituted or unsubstituted aryl group, wherein the groups when substituted are substituted by the group consisting of of hydrogen, halogen, -OR⁴, -OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴, -C(O)NR₄R⁵, -NO₂, -NR₄R⁵, -NRC(O)R⁴, -NR₄CO₂R⁵, -NR₄S(O)₂R⁵, -SR⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NR₄R⁵, C₁₈ alkyl, C₃₈ cycloalkyl, C₆₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; or
R¹ and R² together form a C₃-C₈ cycloalkyl ring;
R³ is each independently selected from the group consisting of:
consisting of hydrogen, halogen, -OR⁴, -OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴, -C(O)NR₄R⁵, -NO₂, -NR₄R⁵, -NRC(O)R⁴, -NR₄CO₂R⁵, -NR₄S(O)₂R⁵, -SR⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NR₄R⁵, C₁₈ alkyl, C₂₈ alkenyl, C₂₈ alkynyl, C₃₈ cycloalkyl, C₆₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; wherein
each R⁴ and R⁵ may be independently selected from the group consisting of
C₁₈ alkyl, C₂₈ alkenyl, C₂₈ alkynyl, C₃₈ cycloalkyl, C₆₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;
R⁴ is a substituted or unsubstituted C₁-C₈ alkyl, wherein when substituted are
substituted by the group consisting of halogen, -OR⁴, -OC(O)R⁴, -CN, -C(O)R⁴, -CO₂R⁴, -C(O)NR₄R⁵, -NO₂, -NR₄R⁵, -NRC(O)R⁴, -NR₄CO₂R⁵, -NR₄S(O)₂R⁵, -SR⁴, -S(O)R⁴, -S(O)₂R⁴, -S(O)₂NR₄R⁵, C₁₈ alkyl, C₂₈ alkenyl, C₃₈ cycloalkyl, C₆₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl; wherein
each R⁴ and R⁵ may be independently selected from the group consisting of
C₁₈ alkyl, C₂₈ alkenyl, C₂₈ alkynyl, C₃₈ cycloalkyl, C₆₁₀ aryl, 5- to 10-membered heteroaryl, and 3- to 10-membered heterocyclyl;
n is an integer from 0-3;
X¹, X² and X³ independently represent oxygen; sulfur; substituted or unsubstituted nitrogen; or substituted or unsubstituted carbon wherein the groups when substituted are substituted by the group consisting of hydrogen, halogen and C₁₈ alkyl; and
Z represents a substituted or unsubstituted C₄-C₁₀ membered ring, wherein the ring contains one additional heteroatom selected from the group consisting of oxygen
and nitrogen and the groups when substituted are substituted by the group consisting of hydrogen, halogen, C₁₋₈ alkyl and C₁₋₈ alkoxy,

20. The process of claim 18 or 19 wherein the enantioselectivity is greater than 99% enantiomeric excess (ee).