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Enantioselective ring-opening of aziridines

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(54) **ENANTIOSELECTIVE RING-OPENING OF AZIRIDINES**

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(51) **Int. Cl.**
C07D 203/04 (2006.01)

(52) **U.S. Cl.** **548/954**

(58) **Field of Classification Search** 548/954
See application file for complete search history.

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(57) **ABSTRACT**

A process for the preparation of a nucleophilic addition product of an aziridine and a nucleophile, the process comprising treating the arizidine with the nucleophile in the presence of a biaryl phosphoric acid catalyst.

20 Claims, No Drawings

ENANTIOSELECTIVE RING-OPENING OF AZIRIDINES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application Ser. No. 60/947,019 filed Jun. 29, 2007, which is incorporated herein by reference in its entirety.

FIELD OF THE INVENTION

The present invention generally relates to a catalytic procedure for the stereoselective catalytic ring opening of aziridines.

BACKGROUND OF THE INVENTION

Aziridines are three-membered ring nitrogen-heterocycles that are attractive substrates in the synthesis of pharmaceuticals and other products. For example, it has been proposed that aziridines be used in the preparation of oseltamivir (Tamiflu®).

Aziridines are attractive substrates in synthetic methodologies, in part, because of their potential as chiral synthons. In one such method, the aziridine is derived from a chiral precursor. In another, achiral meso-arizidines are ring-opened by chiral catalyst activation or are kinetically resolved via catalytic ring-opening. For example, Jacobsen et al., *Org. Lett.* 1999, 1, 1611-1613 reported the use of chiral chromium based catalysts in the ring-opening of aziridines with TMS-N_3. Shibaski et al. later reported the use of catalysts derived from lanthanides provide good enantioselectivity for this desymmetrization strategy with both TMS-CN and TMS-N_3 as nucleophiles. Using this approach, Shibaski et al., *J. Am. Chem. Soc.* 2006, 128, 6312-6313 synthesized oseltamivir. While such approaches provide certain advantages, they also employ metal-based catalysts with the attendant disadvantages.

SUMMARY OF THE INVENTION

Among the various aspects of the present invention is the provision of a catalytic method for the stereoselective ring-opening of important synthetic starting materials (called synthons). Such new catalytic asymmetric methods for the synthesis of 1,2-diamines are highly desired in the pharmaceutical industry. For example, these ring-opened products are highly desired chiral diamines that are important starting materials in the synthesis of drugs like Tamiflu®. Also among the various embodiments is the stereoselective catalytic process for aziridine ring opening reactions; the provision of such a process which does not employ metal-based catalysts, the provision of a process which may be used with a wide range of nucleophiles, and the provision of such a process which is, nonetheless, highly selective.

Briefly, therefore, the present invention is directed to a process for the preparation of a nucleophilic addition product of an aziridine and a nucleophile, the process comprising treating the arizidine with the nucleophile in the presence of a biaryl phosphoric acid catalyst.

Other objects and features will be in part apparent and in part pointed out hereinafter.

ABBREVIATIONS AND DEFINITIONS

The following definitions and methods are provided to better define the present invention and to guide those of ordinary skill in the art in the practice of the present invention. Unless otherwise noted, terms are to be understood according to conventional usage by those of ordinary skill in the relevant art.

The term "acyl," as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxy group from the group —COOH of an organic carboxylic acid, e.g., RC(O)—, wherein R is R^1, R^1O—, R^1R^2N—, or R^1S—, R^1 is hydrocarbyl, heterosubstituted hydrocarbyl, or heterocyclo, and R^2 is hydrogen, hydrocarbyl or substituted hydrocarbyl.

The term "acyloxy," as used herein alone or as part of another group, denotes an acyl group as described above bonded through an oxygen linkage (—O—), e.g., RC(O)O— wherein R is as defined in connection with the term "acyl."

Unless otherwise indicated, the alkyl groups described herein are preferably lower alkyl containing from one to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include methyl, ethyl, propyl, isopropyl, butyl, hexyl, and the like.

Unless otherwise indicated, the alkenyl groups described herein are preferably lower alkenyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain or cyclic and include ethenyl, propenyl, isopropenyl, butenyl, isobutenyl, hexenyl, and the like.

Unless otherwise indicated, the alkynyl groups described herein are preferably lower alkynyl containing from two to eight carbon atoms in the principal chain and up to 20 carbon atoms. They may be straight or branched chain and include ethynyl, propynyl, butynyl, isobutynyl, hexynyl, and the like.

The terms "aryl" or "ar" as used herein alone or as part of another group denote optionally substituted homocyclic aromatic groups, preferably monocyclic or bicyclic groups containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl.

The terms "halide," "halogen" or "halo" as used herein alone or as part of another group refer to chlorine, bromine, fluorine, and iodine.

The term "heteroatom" shall mean atoms other than carbon and hydrogen.

The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group denote optionally substituted, fully saturated or unsaturated, monocyclic or bicyclic, aromatic or nonaromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heterocyclo group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroatom. Exemplary heterocyclo include heteroaromatics such as furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The term "heteroaromatic" as used herein alone or as part of another group denote optionally substituted aromatic groups having at least one heteroatom in at least one ring, and preferably 5 or 6 atoms in each ring. The heteroaromatic group preferably has 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring, and may be bonded to the remainder of the molecule through a carbon or heteroa-

tom. Exemplary heteroaromatics include furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, or isoquinolinyl and the like. Exemplary substituents include one or more of the following groups: hydrocarbyl, substituted hydrocarbyl, keto, hydroxy, protected hydroxy, acyl, acyloxy, alkoxy, alkenoxy, alkynoxy, aryloxy, halogen, amido, amino, nitro, cyano, thiol, ketals, acetals, esters and ethers.

The terms "hydrocarbon" and "hydrocarbyl" as used herein describe organic compounds or radicals consisting exclusively of the elements carbon and hydrogen. These moieties include alkyl, alkenyl, alkynyl, and aryl moieties. These moieties also include alkyl, alkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Unless otherwise indicated, these moieties preferably comprise 1 to 20 carbon atoms.

The "substituted hydrocarbyl" moieties described herein are hydrocarbyl moieties which are substituted with at least one atom other than carbon, including moieties in which a carbon chain atom is substituted with a heteroatom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen atom. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters, ethers, and thioethers.

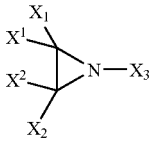
DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is directed to a stereoselective catalytic process for aziridine ring opening reactions. Advantageously, the process does not employ metal-based catalysts. It may also be used with a wide range of nucleophiles. In general, the process comprises treating an arizidine with a nucleophile in the presence of a biaryl phosphoric acid catalyst to produce a nucleophilic addition product.

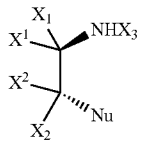
In one embodiment, the aziridines are meso- in nature and the chiral phosphoric acid catalyzes the addition of the nucleophile to provide the asymmetric ring opened product. In an alternative embodiment, the starting aziridines are racemic in nature, the chiral phosphoric acid catalyzes a kinetic resolution of the original racemic aziridine and also provide a chiral ring opened product simultaneously.

In one preferred embodiment, the aziridine corresponds to Formula A and the nucleophilic addition product corresponds to Formula B

Formula A



Formula B



wherein

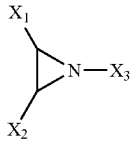
Nu is a nucleophile residue

X_1, X^1, X_2 and X^2 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heterocyclo, and, optionally, (i) X_1 and X_2 and the ring carbon atoms to which they are respectively bonded, in combination, form a fused ring system, (ii) X_1 and X^1 and the ring carbon atom to which they are bonded, in combination, form a spiro ring, or (ii) X_2 and X^2 and the ring carbon atom to which they are bonded, in combination, form a spiro ring, and

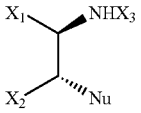
X_3 is hydrocarbyl, substituted hydrocarbyl, heterocyclo, silyl, acyl, or amine protecting group.

In one preferred embodiment, X^1 and X^2 are hydrogen and the aziridine corresponds to Formula I and the nucleophilic addition product corresponds to Formula II

Formula I



Formula II



wherein

Nu is a nucleophile residue

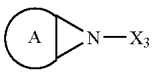
X_1 and X_2 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heterocyclo, or X_1 and X_2 and the ring carbon atoms to which they are respectively bonded, in combination, form a fused ring system.

X_3 is hydrocarbyl, substituted hydrocarbyl, heterocyclo, silyl, acyl, or amine protecting group.

In one embodiment, the aziridine corresponds to Formula I and X_1 and X_2 are independently hydrocarbyl or substituted. Thus, for example, X_1 or X_2, or both X_1 and X_2 may be lower alkyl such as methyl, ethyl, propyl, butyl, pentyl, or hexyl. By way of further example, X_1 or X_2, or both X_1 and X_2 may be substituted lower alkyl such as substituted methyl, ethyl, propyl, butyl, pentyl, or hexyl wherein the alkyl group is substituted with a heteroatom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen. These substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, protected hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters, ethers, and thioether. By way of further example, X_1 or X_2, or both X_1 and X_2 may be alkenyl, alkynyl or aryl. By way of further example, X_1 or X_2, or both X_1 and X_2 may be substituted alkenyl, substituted alkynyl or substituted aryl wherein the alkenyl, alkynyl, or aryl moiety is substituted with a heteroatom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen.

In another embodiment, the aziridine corresponds to Formula I and X_1 and X_2 and the ring carbon atoms to which they are respectively bonded, in combination, form a fused ring system as depicted in Formulae IA and IIA:

Formula IA



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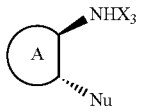
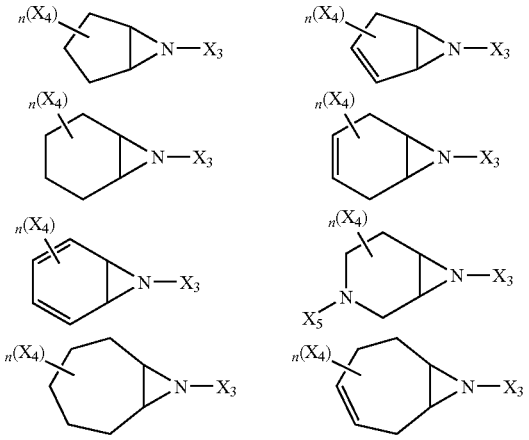
Formula IIA



wherein X_3 is as previously defined and A is a fused carbocyclic or heterocyclic ring system. This ring system may be monocyclic or polycyclic (see, e.g., Formulae IB and IIB). In one embodiment, for example, A is monocyclic, contains 4 to 7 ring atoms, and is carbocyclic or heterocyclic. When A is a monocyclic heterocycle, it may contain 4 to 7 ring atoms selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. In addition, A may be fully saturated, partially unsaturated or aromatic. For example, A may be a monocyclic, fused cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring, optionally substituted with a heteroatom as described elsewhere herein. By way of further example, A may be a fused, optionally substituted 5-membered heterocyclic ring or an optionally substituted 6-membered heterocylic ring. Exemplary 5-membered and 6-membered heterocycles include pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperidinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl. Exemplary 5-membered and 6-membered aromatic heterocyclic groups include imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. By way of further example, A may be an optionally substituted, fused cyclohexyl or phenyl ring with the substituent(s) being selected from lower alkyl, hydroxyl, alkoxyl, amino, halo, nitro and heterocyclo. In another embodiment, A may be an optionally substituted, fused pyridyl, pyrimidinyl, pyradizinyl, pyrizinyl, furyl, thienyl, isoxazolyl, or pyrrolyl; thus, for example, A may be an optionally substituted, fused pyridyl, furyl, thienyl, or pyrrolyl ring with the substituent(s) being selected from lower alkyl, hydroxyl, alkoxyl, amino, halo, and nitro. Exemplary aziridines corresponding to Formula IA include:



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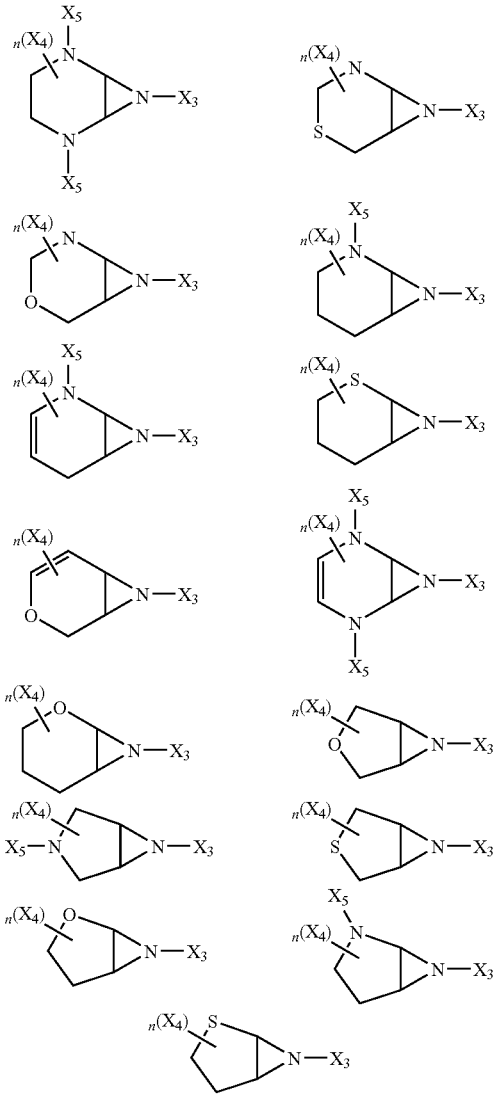
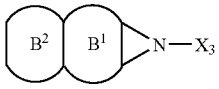


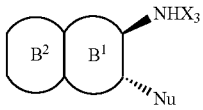
wherein n is an integer consistent with the rules of valence for each of the rings (e.g., generally from 1-5), X_3 is as previously defined, each X_4 is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen, heterocyclo, hydrocarbyloxy, hydroxy, keto, acyl, acyloxy, nitro, amino, amido, or thiol, and each X_5 is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclo, or acyl. In one embodiment, X_5 is hydrogen or acyl. Certain of these exemplified structures are meso- in nature and others are racemic and as described elsewhere herein, the chiral phosphoric acid catalyzes the addition of the nucleophile to provide an asymmetric (for meso-type structures) or chiral (for racemic type structures) nucleophilic addition product.

In another embodiment, A is a fused polycyclic ring system. Stated differently, in this embodiment the aziridine corresponds to Formula I, the nucleophilic addition product corresponds to Formula II, and X_1 and X_2 and the ring carbon atoms to which they are respectively bonded, in combination, form a polycyclic fused ring system. This is depicted, for example, Formulae IB and IIB:

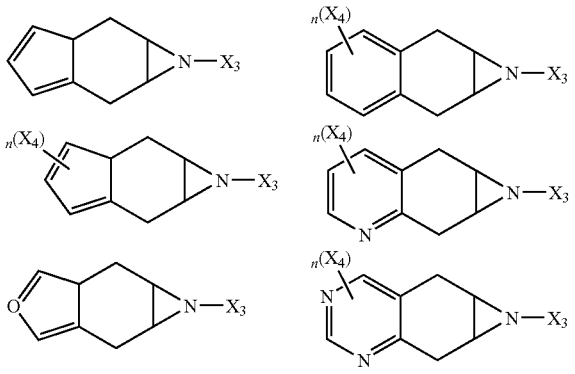
Formula IB



Formula IIB



wherein X_3 is as previously defined, and B^1 and B^2 are each monocyclic, independently containing 4 to 7 ring atoms, and independently being carbocyclic or heterocyclic. When B^1 or B^2 is a heterocycle, it may contain 4 to 7 ring atoms selected from the group consisting of carbon, oxygen, nitrogen, and sulfur. In addition, B^1 and B^2 may, independently be fully saturated, partially unsaturated or aromatic. For example, B^1 and B^2 may, independently, be a monocyclic, fused cyclobutyl, cyclopentyl, cyclohexyl, or cycloheptyl ring, optionally substituted with a heteroatom as described elsewhere herein. By way of further example, B^1 or B^2 may be a fused, optionally substituted 5-membered heterocyclic ring or an optionally substituted 6-membered heterocylic ring. Exemplary 5-membered and 6-membered heterocycles include pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, homopiperidinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl. Exemplary 5-membered and 6-membered aromatic heterocyclic groups include imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. By way of further example, B^1 and B^2 may be an optionally substituted, fused cyclohexyl or phenyl ring with the substituent(s) being selected from lower alkyl, hydroxyl, alkoxyl, amino, halo, nitro and heterocyclo. In another embodiment, B^1 and B^2 may independently be an optionally substituted, fused pyridyl, pyrimidinyl, pyradizinyl, pyrizinyl, furyl, thienyl, isoxazolyl, or pyrrolyl; thus, for example, B^1 and B^2 may independently be an optionally substituted, fused pyridyl, furyl, thienyl, or pyrrolyl ring with the substituent(s) being selected from lower alkyl, hydroxyl, alkoxyl, amino, halo, and nitro. Exemplary aziridines corresponding to Formula IB include:



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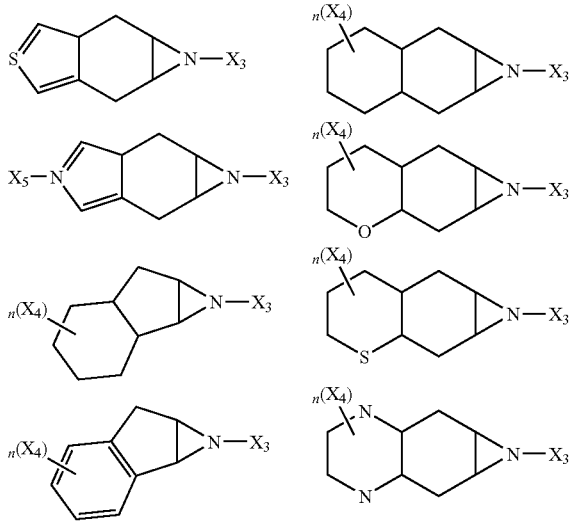


wherein n is an integer consistent with the rules of valence for each of the rings (e.g., generally from 1-5), X_3 is as previously defined, each X_4 is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen, heterocyclo, hydrocarbyloxy, hydroxy, keto, acyl, acyloxy, nitro, amino, amido, or thiol, and each X_5 is independently hydrogen, hydrocarbyl, substituted hydrocarbyl, heterocyclo, or acyl. In one embodiment, X_5 is hydrogen or acyl. Certain of these exemplified structures are meso- in nature and others are racemic and as described elsewhere herein, the chiral phosphoric acid catalyzes the addition of the nucleophile to provide an asymmetric (for meso-type structures) or chiral (for racemic type structures) nucleophilic addition product.

In general, X_3 may be any substituent that does not interfere with the chemical stability of the aziridine. In one embodiment, X_3 is hydrocarbyl; for example, X_3 may be alkyl, alkenyl, alkynyl, aryl, vinyl, allyl, or the like. In another embodiment, X_3 is substituted hydrocarbyl wherein the hydrocarbyl group is substituted with a heteroatom such as nitrogen, oxygen, silicon, phosphorous, boron, sulfur, or a halogen; exemplary substituents include halogen, heterocyclo, alkoxy, alkenoxy, alkynoxy, aryloxy, hydroxy, keto, acyl, acyloxy, nitro, amino, amido, nitro, cyano, thiol, ketals, acetals, esters, ethers, and thioether. In another embodiment, X_3 is silyl, such as trialkylsilyl, dialkylarylsilyl, or triarylsilyl. In another embodiment, X_3 is any substitutent conventionally used to hinder the reactivity of an amino group as described in Green, T., "Protective Groups in Organic Synthesis," Chapter 7, John Wiley and Sons, Inc., 1991, 315-385.

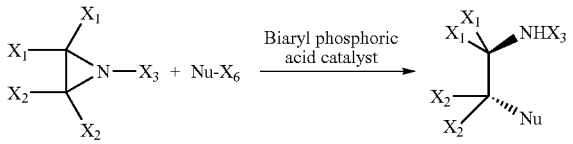
In one preferred embodiment, X_3 is acyl. For example, in this embodiment, X_3 may have the formula —C(O)A wherein A is hydrocarbyl, substituted hydrocarbyl, or heterocyclo. By way of further example, A may be optionally substituted alkyl, alkenyl, alkyl, or aryl. By way of further example, A may be phenyl or substituted phenyl. By way of further example, A may be substituted phenyl, with the phenyl substituents being selected from alkyl, substituted alkyl, aryl, substituted aryl, halo, nitro, amino, acyl, hydroxy, and alkoxy. By way of further example, A may be nitro, fluoro, or trifluoromethyl substituted phenyl. By way of further example, A may be heterocyclo.

In general, the nucleophile residue, Nu, is preferably a nucleophile residue selected from the group consisting of

carbon, oxygen, nitrogen, sulfur, or silyl based nucleophile residues. Carbon nucleophiles include alkyl and aryl carbanions, enamines, enolates, olefins and cyanide. Oxygen nucleophiles include alkyl and aryl alcohols, hydroxyl, and carboxylates. Sulfur nucleophiles include alkyl and arylsulfides, and thioacyl acids. Nitrogen nucleophiles include amines, amides and azides. Halogen nucleophiles include chloride, bromide, fluoride and iodide. Hydrogen nucleophiles include hydrogen from hydrogenation sources and hydrides. Other miscellaneous nucleophiles include cycloaddition nucleophiles, and heteroatom nucleophiles such as phosphorous nucleophiles, silanes, selenols, and cobalt nucleophiles. Organometallic reagents such as organocuprates, organozincs, organolithiums, Grignard reagents, enolates, acetylides, and the like may, under appropriate reaction conditions, be suitable nucleophiles. Hydride may also be a suitable nucleophile when reduction of the substrate is desired

In one preferred embodiment, the stereoselective ring opening of the aziridine proceeds as depicted in Reaction Scheme 1

Reaction Scheme I

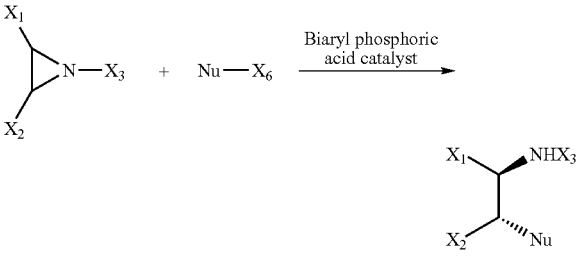


wherein Nu, X_1, X^1, X_2, X^2 and X_3 are as defined in connection with Formula I and IA and X_6 is a leaving group for the nucleophile. Exemplary nucleophile leaving groups (X_6) include silyl groups when the nucleophile is azide, cyanide or halide or a proton when the nucleophile is an alcohol. In one embodiment, the leaving group is a silyl leaving group such as trialkylsilyl (e.g., trimethylsilyl, triethylsilyl, etc.) or dialkylarylsilyl (e.g., dimethylphenylsilyl).

In one embodiment, X_1, X^1, X_2, and X^2 are selected such that the aziridine is meso- in nature. In this embodiment, the chiral phosphoric acid catalyzes the addition of the nucleophile to provide an asymmetric nucleophilic addition product. In an alternative embodiment, X_1, X^1, X_2, and X^2 are selected such that the aziridine is racemic in nature, the chiral phosphoric acid catalyzes a kinetic resolution of the original racemic aziridine and also provides a chiral nucleophilic addition product.

When X_1 and X_2 are hydrogen, the stereoselective ring opening of the aziridine proceeds as depicted in Reaction Scheme 2

Reaction Scheme 2



wherein Nu, X_1, X^1, X_2, X^2 and X_3 are as defined in connection with Formula I and IA and X_6 is a leaving group for the nucleophile. Exemplary nucleophile leaving groups (X_6) include silyl groups when the nucleophile is azide, cyanide or halide or a proton when the nucleophile is an alcohol. In one embodiment, the leaving group is a silyl leaving group such as trialkylsilyl (e.g., trimethylsilyl, triethylsilyl, etc.) or dialkylarylsilyl (e.g., dimethylphenylsilyl). In one embodiment, X_1 and X_2 are selected such that the aziridine is meso- in nature. In this embodiment, the chiral phosphoric acid catalyzes the addition of the nucleophile to provide the asymmetric ring opened product. In an alternative embodiment, X_1 and X_2 are selected such that the aziridine is racemic in nature, the chiral phosphoric acid catalyzes a kinetic resolution of the original racemic aziridine and also provide a chiral ring opened product simultaneously.

In one embodiment, the nucleophile is an amine. In this embodiment, for example, the nucleophile may be NHD_1D_2 wherein D_1 and D_2 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. Thus, for example, the nucleophile may be ammonia. By way of further example, the nucleophile may be a primary amine (NH_2D_1 wherein D_1 is optionally substituted alkyl, alkenyl, alkynyl, aryl or heterocyclo) or a secondary amine (NHD_1D_2 wherein D_1 and D_2 are independently optionally substituted alkyl, alkenyl, alkynyl, aryl or heterocyclo). In one embodiment, D_1 and D_2 are independently hydrogen, alkyl, aryl or heterocyclo; thus, for example, one of D_1 and D_2 may be heterocyclo and the other is hydrogen, alkyl or aryl. By way of further example, D_1 and D_2 are independently hydrogen, alkyl or aryl.

In another embodiment, the nucleophile is an amide. In this embodiment, for example, the nucleophile may be $D_1C(O)NHD_2$ wherein D_1 and D_3 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl or heterocyclo. In one embodiment, D_1 and D_2 are independently hydrogen, alkyl, aryl or heterocyclo; thus, for example, one of D_1 and D_2 may be heterocyclo and the other is hydrogen, alkyl or aryl. By way of further example, D_1 and D_2 are independently alkyl or aryl.

In one embodiment, the nucleophile is a silylazide and the nucleophile residue is azide (—N_3). Exemplary silyl azides include trialkylsilylazides, triarylsilylazides, and alkylarylsilylazides.

In another embodiment, the nucleophile is an alcohol and the residue is an alkoxy group, -OT_1, wherein T_1 is hydrocarbyl, substituted hydrocarbyl, or heterocyclo. Thus, for example, T_1 may be optionally substituted alkyl, alkenyl, alkynyl, aryl, or combinations thereof (e.g., alkaryl such as benzyl). In one embodiment, T_1 is alkyl. In another, T_1 is alkenyl. In yet another, T_1 is alkynyl. In yet another, T_1 is aryl. In yet another, T_1 is heterocyclo. In yet another, T_1 is heteroaromatic.

In another embodiment, the nucleophile is a mercaptan having the formula HSD_1 wherein D_1 is hydrocarbyl, substituted hydrocarbyl, or heterocyclo. For example, in one embodiment, D_1 is optionally substituted alkyl, alkenyl, alkynyl, aryl or heterocyclo). By way of further example, D_1 may be alkyl, alkenyl, alkynyl, aryl or heterocyclo).

In another embodiment, the nucleophile is a silylcyanide and the nucleophile residue is cyano (—CN). Exemplary silylcyanides include trialkylsilylcyanides, triarylsilylcyanides, and alkylarylsilylcyanides.

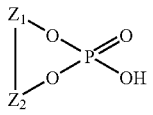
In another embodiment, the nucleophile is a halosilyl and the nucleophile residue is halo (chloro, bromo, fluoro, or iodo). Exemplary halosilyls include halotrialkylsilyls, halotriarylsilyls, and haloalkylarylsilyls.

In one embodiment of the present invention, chiral phosphoric acids catalyze the ring-opening of meso-aziridines with excellent enantioselectivity and in high yield using TMS-N_3 as the nucleophile. Such a reaction provides a pro-

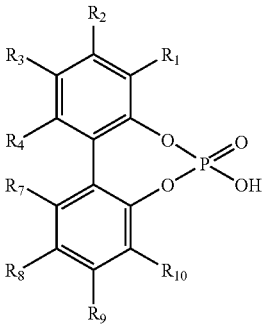
cedure whereby synthetically important, chiral 1,2-diamine analogues can be readily formed.

In general, the biaryl phosphoric acid catalyst corresponds to Formula III

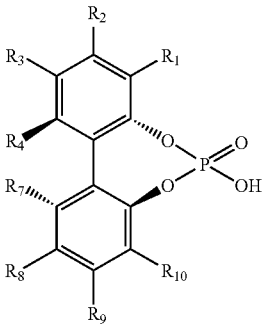
Formula III



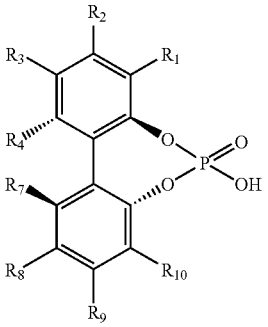
wherein Z_1 and Z_2 are independently aryl. Thus, for example, Z_1 and Z_2 may be optionally substituted phenyl, naphthyl or other fused aromatic rings. In one embodiment, the catalyst generally corresponds to biaryl phosphoric acid 1; in this embodiment, biaryl phosphoric acid 1 is preferably a biaryl phosphoric acid corresponding to biaryl phosphoric acid 1A or 1B:



Biaryl Phosphoric Acid 1



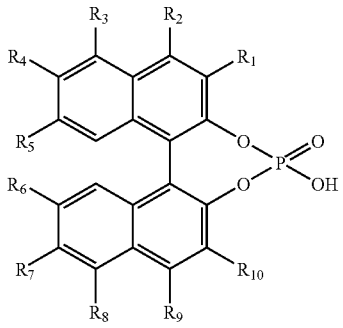
Biaryl Phosphoric Acid 1A



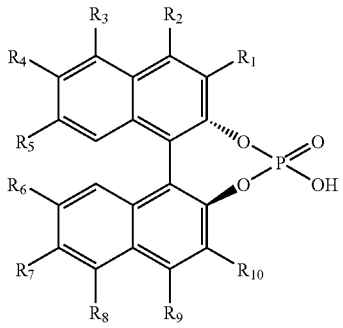
Biaryl Phosphoric Acid 1B

wherein (i) R_1, R_2, R_3, R_4, R_7, R_8, R_9 and R_{10} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, or thiourea, and (ii) one or more pairs of substituents, with an ortho relationship therebetween, selected from the group consisting of R_1, R_2, R_3, R_4, R_7, R_8, R_9 and R_{10} taken together optionally represent an optionally substituted carbocyclic or heterocyclic fused ring system.

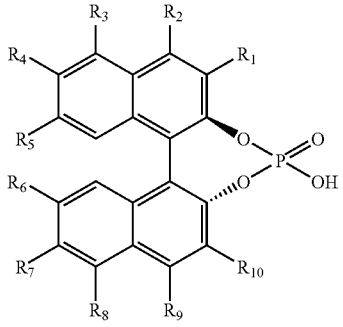
In one embodiment, the biaryl phosphoric acid catalyst comprises a fused ring system and corresponds to biaryl phosphoric acid 2; in this embodiment, biaryl phosphoric acid 2 is preferably a biaryl phosphoric acid corresponding to biaryl phosphoric acid 2A or 2B:



Biaryl Phosphoric Acid 2



Biaryl Phosphoric Acid 2A

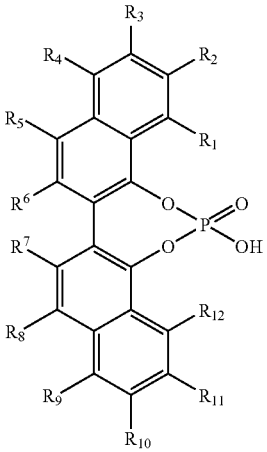


Biaryl Phosphoric Acid 2B

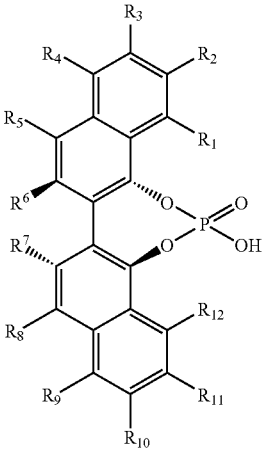
wherein (i) R_1, R_2, R_3, R_4, R_7, R_8, R_9 and R_{10} are as previously defined in connection with biaryl phosphoric acid I, and R_5 and R_6 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen, hydroxyl, alkoxyl, silyloxy,

amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, or thiourea, and (ii) one or more pairs of substituents, with an ortho relationship therebetween, selected from the group consisting of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10} taken together optionally represent an optionally substituted carbocyclic or heterocyclic fused ring system.

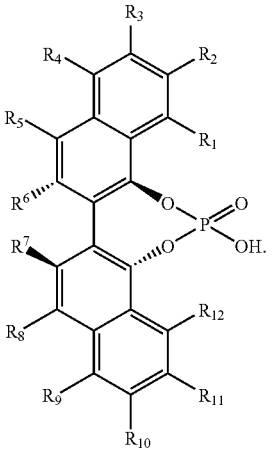
In one embodiment, the biaryl phosphoric acid catalyst comprises a fused ring system and corresponds to biaryl phosphoric acid 3; in this embodiment, biaryl phosphoric acid 3 is preferably a biaryl phosphoric acid corresponding to biaryl phosphoric acid 3A or 3B:



Biaryl Phosphoric Acid 3



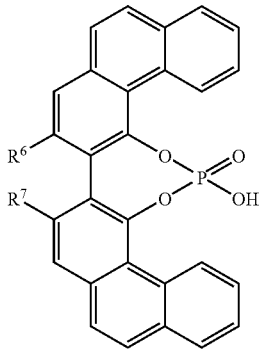
Biaryl Phosphoric Acid 3A



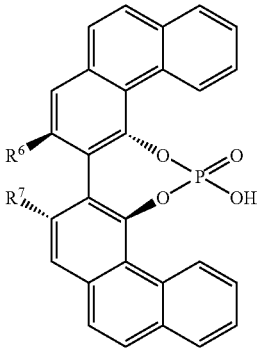
Biaryl Phosphoric Acid 3B

wherein (i) R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, halogen, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, or thiourea, and (ii) one or more pairs of substituents, with an ortho relationship therebetween, selected from the group consisting of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11} and R_{12} taken together optionally represent an optionally substituted carbocyclic or heterocyclic fused ring system.

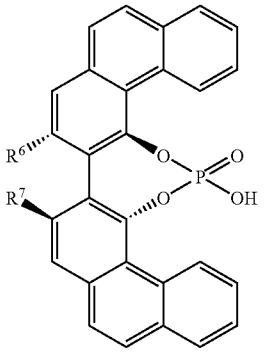
In one embodiment, the biaryl phosphoric acid catalyst comprises a fused ring system and corresponds to biaryl phosphoric acid 4; in this embodiment, biaryl phosphoric acid 4 is preferably a biaryl phosphoric acid corresponding to biaryl phosphoric acid 4A or 4B:



Biaryl Phosphoric Acid 4



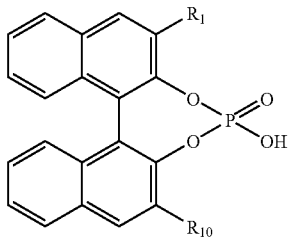
Biaryl Phosphoric Acid 4A



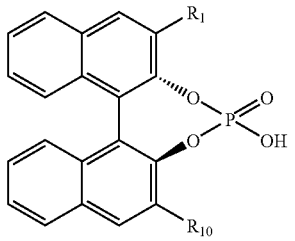
Biaryl Phosphoric Acid 4B

wherein R_6 and R_7 are independently hydrocarbyl, substituted hydrocarbyl, halogen, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, or thiourea. In a preferred embodiment, R_6 and R_7 are preferably hydrocarbyl, more preferably alkyl or phenyl.

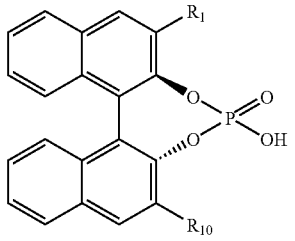
In one embodiment, the biaryl phosphoric acid catalyst comprises a fused ring system and corresponds to biaryl phosphoric acid 5; in this embodiment, biaryl phosphoric acid 5 is preferably a biaryl phosphoric acid corresponding to biaryl phosphoric acid 5A or 5B:



Biaryl Phosphoric Acid 5



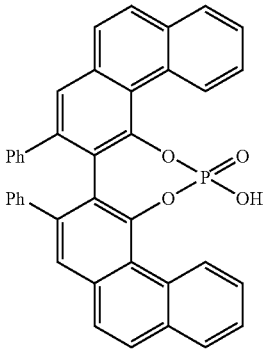
Biaryl Phosphoric Acid 5A



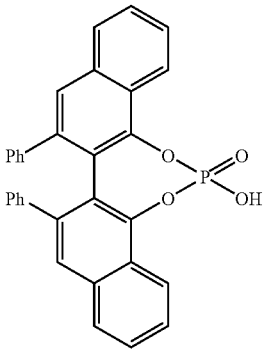
Biaryl Phosphoric Acid 5B

wherein R_1 and R_{10} are independently hydrocarbyl, substituted hydrocarbyl, halogen, hydroxyl, alkoxyl, silyloxy, amino, nitro, sulfhydryl, alkylthio, imine, amide, phosphoryl, phosphonate, phosphine, carbonyl, carboxyl, carboxamide, anhydride, silyl, thioalkyl, alkylsulfonyl, arylsulfonyl, selenoalkyl, ketone, aldehyde, ester, heteroalkyl, nitrile, guanidine, amidine, acetal, ketal, amine oxide, aryl, heteroaryl, azide, aziridine, carbamate, epoxide, hydroxamic acid, imide, oxime, sulfonamide, thioamide, thiocarbamate, urea, or thiourea. In a preferred embodiment, R_1 and R_{10} are preferably hydrocarbyl, more preferably alkyl or phenyl.

In one preferred embodiment, the biaryl phosphoric acid catalyst is VAPOL phosphoric acid (VAPOL PA-1) or VANOL phosphoric acid (VANOL PA-2):



VAPOL PA-1



VAPOL PA-2

wherein Ph is phenyl.

Having described the invention in detail, it will be apparent that modifications and variations are possible without departing the scope of the invention defined in the appended claims. Furthermore, it should be appreciated that all examples in the present disclosure are provided as non-limiting examples.

EXAMPLES

The following non-limiting examples are provided to further illustrate the present invention. It should be appreciated by those of skill in the art that the techniques disclosed in the examples that follow represent approaches the inventors have found function well in the practice of the invention, and thus can be considered to constitute examples of modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments that are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

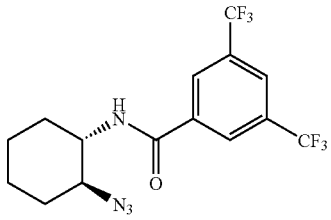
Example 1

General Procedure for the Preparation of Racemic Products Using TMS-N_3

The aziridine (0.25 mmol), phenylphosphinic acid, Tf_2NH, or a mixture of (R) and (S) VAPOL-phosphoric acid (10 to 100 mol %), were weighed into a test tube. The air was removed under vacuum and replaced with argon. TMS-N_3 (0.67-4 equiv.) was added via syringe to the test-tube followed by $(CH_2Cl)_2$ or CH_2Cl_2 (0.5 mL). The reaction was stirred at room temperature to 60° C. until product formation was significant which was monitored by TLC. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography.

General Procedure for the Enantioselective Ring Opening TMS-N_3

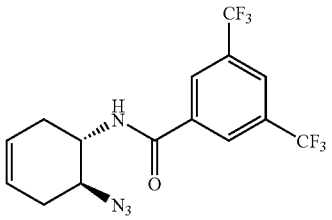
To a flame-dried test tube was added aziridine (0.25-0.38 mmol) and acid catalyst (10 mol %). The air was removed and replaced with argon. TMS-N_3 (0.25-1 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.25-1.0 mL). The reaction was stirred at room temperature to 60° C. and monitored by TLC. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography.



1-Azido-2-[N-(3,5-Bis-trifluoromethylbenzoyl)amino]-cyclohexane To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane (0.128 g, 3.38 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (33 μL, 0.25 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 21 h. The reaction was

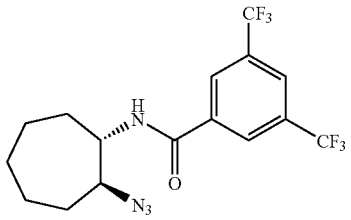
diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered white solid (0.093 g, 97%). Mp=138.9-139.4° C. HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90/10, 1.0 mL/min), $t_{r\text{-}minor}$ 6.15 min, $t_{r\text{-}major}$ 8.65 min. 1H NMR (500 MHz, $CDCl_3$): δ1.28-1.41 (m, 3H), 1.47-1.55 (m, 1H), 1.76 (m, 1H), 1.87 (m, 1H), 2.16 (m, 2H), 3.27 (m, 1H), 3.95 (m, 1H), 6.34 (d, J=7.7 Hz, 1H), 7.98 (s, 1H), 8.19 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$):

δ 24.1, 24.2, 30.6, 31.9, 53.7, 63.5, 119.7, 121.8, 123.9, 125.0, 125.4, 127.3, 132.1 (q, J=34 Hz), 136.6, 164.6. HRMS (ESI) Calcd for $C_{15}H_{14}F_6N_4O$ ([M+H]$^+$) 381.1145, Found 381.1140. $[a]^{29}_D$+63.8 (c=1.04, $CHCl_3$).



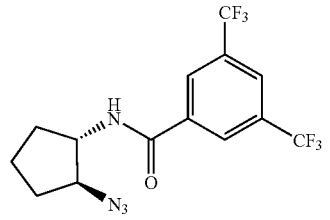
4-Azido-5-[N-(3,5-Bis-trifluoromethylbenzoyl)amino]-cyclohexene To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[4.1.0]hept-3-ene (0.127 g, 0.38 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (33 μL, 0.25 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 21 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered white solid (0.080 g, 84%). Mp=126.3-128.4° C. HPLC analysis: Chiralcel AS-H (hexane/iPrOH=95/5, 1.0 mL/min), $t_{r\text{-}minor}$ 11.33 min $t_{r\text{-}major}$ 18.73 min. 1H NMR (500 MHz, $CDCl_3$): δ2.16-2.25 (m, 2H), 2.49-2.59 (m, 2H), 3.72 (m, 1H), 4.20 (m, 1H), 5.62 (m, 2H), 7.24 (d, J=8.0 Hz, 1H), 7.90 (s, 1H), 8.16 (s, 2H). ^{13}C NMR (125 MHz,

$CDCl_3$ δ 29.9, 30.8, 49.8, 59.2, 119.5, 121.7, 123.8, 124.6, 124.9, 126.0, 127.4, 127.4, 13 2.0 (q, J=34 Hz), 136.3, 165.2. HRMS (ESI) Calcd for $C_{15}H_{12}F_6N_4O$ ([M+H]$^+$) 379.0988, Found 379.0997. $[a]^{29}_D$+70.3 (c=1.10, $CHCl_3$).



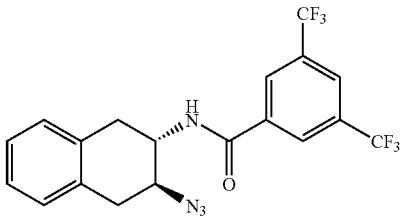
trans-1-Azido-2-[N-(3,5-Bis-trifluoromethylbenzoyl) amino]-cycloheptane To a flame-dried test tube was added 8-(3,5-Bis-trifluoromethylbenzoyl)-8-azbicyclo[5.1.0]octane (0.088 g, 0.25 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (66 μL, 0.50 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 91 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered white solid (0.063 g, 64%). Mp=139.3-140.9° C. HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90/10, 1.0 mL/min), $t_{r\text{-}minor}$ 5.35 min, $t_{r\text{-}major}$ 8.27 min. 1H NMR (500 MHz, $CDCl_3$): δ 1.51-1.57 (m, 3H), 1.60-1.81 (m, 5H), 1.89-1.99 (m, 2H), 3.53 (m, 1H), 4.02 (m, 1H), 7.17 (d, J=7.8, 1H), 7.91 (s, 1H), 8.17 (s, 2H). ^{13}C NMR (125 MHz,

$CDCl_3$): δ 22.9, 23.8, 27.3, 30.5, 31.8, 56.5, 66.5, 119.5, 121.7, 128.9, 124.8, 126.0, 127. 4, 131.9 (q, J=34 Hz), 136.5, 164.6. HRMS (ESI) Calcd for $C_{16}H_{16}F_6N_4O$ ([M+H]$^+$) 395.1301, Found 395.1302. $[a]^{29}_D$+36.9 (c=1.04, $CHCl_3$).



trans-1-Azido-2-[N-(3,5-Bis-trifluoromethyl benzoyl) amino]-cyclopentane To a flame-dried test tube was added 6-(3,5-Bis-trifluoromethylbenzoyl)-6-azabicyclo[3.1.0]hexane (0.12 g, 0.38 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (33 μL, 0.25 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 48 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered colorless oil (0.063 g, 84%). Mp=99.5-100.5° C. HPLC analysis: Chiralcel AS-H (hexane/iPrOH=95/5, 1.0 mL/min), $t_{r\text{-}minor}$ 12.16 min, $t_{r\text{-}major}$ 14.04 min. 1H NMR (500 MHz, $CDCl_3$): δ1.62-1.82 (m, 4H), 2.02-2.08 (m, 1H), 2.14-2.22 (m, 1H), 3.90 (q, J=6.7 Hz, 1H), 4.25 (m, 1H), 7.41 (d, J=7.7 Hz, 1H), 7.86 (s, 1H), 8.12 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$):

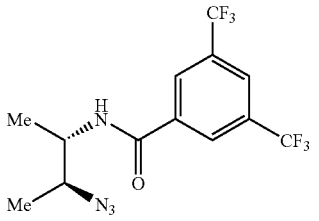
δ 16.9, 18.7, 49.5, 61.7, 119.6, 121.8, 123.9, 125.1, 127.2, 132.2 (q, J=34 Hz), 136.4, 164.3. HRMS (ESI) Calcd for $C_{14}H_{12}F_6N_4O$ ([M+H]$^+$) 367.0988, Found 367.0988. $[a]^{29}_D$+40.2 (c=1.01, $CHCl_3$).



trans-2-Azido-3-[N-(3,5-Bis-trifluoromethylbenzoyl) amino]-tetralin To a flame-dried test tube was added N-(3,5-Bis-trifluoromethylbenzoyl)-2,3-iminotetralin (0.096 g, 0.25 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (66 μL, 0.50 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (1.0 mL). The reaction was stirred at ambient temperature for 48 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/CH_2Cl_2. Recovered white solid (0.096 g, 90%). Mp=146.8-147.6° C.

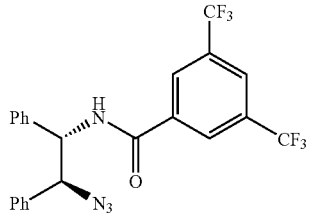
HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90/10, 1.0 mL/min), $t_{r\text{-}minor}$ 8.05 min, $t_{r\text{-}major}$ 15.71 min. 1H NMR (500 MHz, $CDCl_3$): δ 2.89 (m, 1H), 3.0 (m, 1H), 3.23 (dd, 11.4, 5.3 Hz, 1H), 3.39 (dd, 11.3, 5.4 Hz, 1H), 3.98 (m, 1H), 4.41 (m, 1H), 6.62 (d, J=7.6 Hz, 1H), 7.05-7.18 (m, 4H), 7.97 (s, 1H), 8.18 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$):

δ 33.1, 33.9, 50.3, 59.4, 119.5, 121.7, 123.9, 125.2, 126.0, 126.9, 127.3, 128.9, 128.9, 13 2.3 (q, J=34 Hz), 136.2, 164.9. HRMS (ESI) Calcd for $C_{19}H_{14}F_6N_4O$ ($[M+H]^+$) 429.1145, Found 429.1146. $[a]^{29}_D$+53.3 (c=1.07, $CHCl_3$).



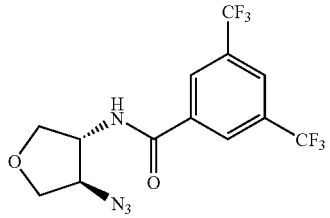
anti-2-Azido-3-[N-(3,5-Bis-trifluoromethylbenzoyl) amino]-butane To a flame-dried test tube was added cis-1-(3,5-Bis-trifluoromethylbenzoyl)-2,3-dimethylaziridine (0.118 g, 0.38 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (33 μL, 0.25 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 21 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered colorless oil (0.077 g, 88%). Mp=50.7-51.4° C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH=95/5, 1.0 mL/min), $t_{r\text{-}minor}$ 5.76 min, $t_{r\text{-}major}$ 6.96 min. 1H NMR (500 MHz, $CDCl_3$): δ 1.31 (m, 6H), 3.74 (m, 1H), 4.29 (m, 1H), 6.34 (brs, 1H), 7.98 (s, 1H), 8.17 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$):

δ 16.9, 18.7, 49.5, 61.7, 119.6, 121.8, 123.9, 125.1, 127.2, 132.2 (q, J=34 Hz), 136.4, 164.3. HRMS (ESI) Calcd for $C_{13}H_{12}F_6N_4O$ ($[M+H]^+$) 355.0988, Found 355.0985. $[a]^{29}_D$+28.3 (c=1.15, $CHCl_3$).



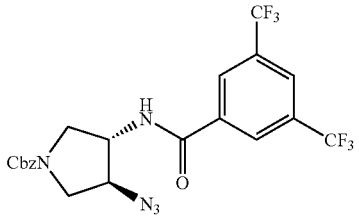
anti-1-Azido-2-[N-(3,5-Bis-trifluoromethylbenzoyl) amino]-1,2-diphenylethane To a flame-dried test tube was added cis-1-(3,5-Bis-trifluoromethylbenzoyl)-2,3-diphenylaziridine (0.16 g, 0.38 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (33 μL, 0.25 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (1.0 mL). The reaction was stirred at ambient temperature for 48 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered white solid (0.113 g, 95%). Mp=140.3-11.0° C. HPLC analysis: Chiralcel AS-H (hexane/iPrOH=98/2, 1.0 mL/min), $t_{r\text{-}major}$ 13.49 min, $t_{r\text{-}minor}$ 20.61 min. 1H NMR (500 MHz, $CDCl_3$): δ 4.97 (d, J=6.1 Hz, 1H), 5.48 (t, J=6.6 Hz, 1H), 7.21-7.31 (m, 10H), 7.44 (brs, 1H), 7.90 (s, 1H), 8.09 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$):

δ 58.8, 71.6, 119.5, 121.6123.8, 125.1, 125.9, 126.9, 127.1, 127.3, 127.3, 128.1, 128.6, 128.8, 132.0 (q, J=34 Hz), 136.2, 164.5. HRMS (ESI) Calcd for $C_{23}H_{16}F_6N_4O$ ($[M+Na]^+$) 501.1121, Found 501.1128. $[a]^{29}_D$+33.0 (c=1.05, $CHCl_3$).



trans-3-Azido-4-[N-(3,5-Bis-trifluoromethylbenzoyl) amino]-tetrahydrofuran To a flame-dried test tube was added 3-Oxa-6-(3,5-Bis-trifluoromethylbenzoyl)-6-azbicyclo [3.1.0]hexane (0.081 g, 0.25 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (132 μL, 1.0 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.25 mL). The reaction was stirred at ambient temperature for 48 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with CH_2Cl_2/ether. Recovered white solid (0.045 g, 49%). Mp=103.3-104.6° C. HPLC analysis: Chiralcel AS-H (hexane/iPrOH=98/2, 0.75 mL/min), $t_{r\text{-}minor}$ 30.39 min, $t_{r\text{-}major}$ 32.55 min. 1H NMR (500 MHz, $CDCl_3$): δ 3.68 (dd, J=6.8 Hz, 1H), 3.89 (m, 1H), 4.03-4.07 (m, 1H), 4.11-4.18 (m, 1H), 4.19 (m, 1H), 4.56 (m, 1H) 7.01 (br s, 1H), 7.98 (s, 1H), 8.21 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$):

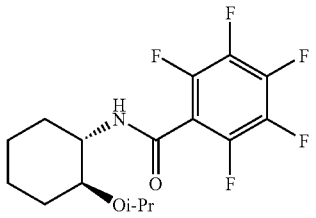
δ 57.4, 66.2, 70.9, 71.5, 119.1, 121.7, 123.8, 125.4, 126.0, 127.4, 132.2 (q, J=34 Hz), 135.4, 164.7. HRMS (ESI) Calcd for $C_{13}H_{10}F_6N_4O_2$ ($[M+H]^+$) 369.0781, Found 369.0781. $[a]^{29}_D$+42.7 (c=1.04, $CHCl_3$).



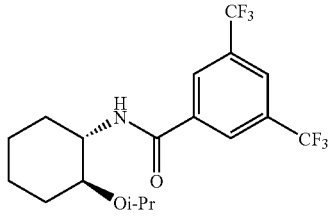
trans-1-Carbobenzyloxy-3-azido-4-[N-(3,5-Bis-trifluoromethylbenzoyl)amino]pyrrolidine To a flame-dried test tube was added 3-Carbobenzyloxy-6-(3,5-Bis-trifluoromethylbenzoyl)-3,6-diazbicyclo[3.1.0]hexane (0.110 g, 0.25 mmol) and (S)-VAPOL phosphoric acid (15 mg, 10 mol %). The air was removed and replaced with argon. TMS-N_3 (132 μL, 1.0 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 96 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with CH_2Cl_2/ether. Recovered white solid (0.122 g, 96%). Mp=47.0-48.4° C. HPLC analysis: Chiralcel OD-H (hexane/iPrOH=95/5, 1.0 mL/min), $t_{r\text{-}major}$ 10.79 min, $t_{r\text{-}minor}$ 28.65 min. 1H NMR (500 MHz, $CDCl_3$): δ 3.52-4.01 (m, 4H), 4.25-4.39 (m, 1H), 4.63-4.71 (m, 1H), 4.89-4.99 (m, 1H), 513-5.24 (m, 1H), 7.22-7.24 (m, 3H), 7.83 (d, J=5.5 Hz, 1H), 8.09 (m, 2H), 8.51 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$):

δ 41.6, 48.9, 49.2, 54.6, 54.9, 63.1, 64.0, 67.3, 67.8, 119.6, 121.8, 123.9, 125.3, 126.2, 127.6, 128.2, 128.4, 128.5, 132.1

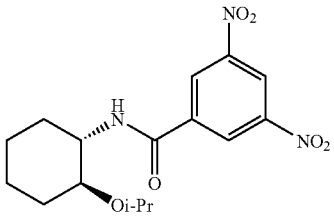
(q, J=35 Hz), 135.1, 154.9, 164.6. HRMS (ESI) Calcd for $C_{21}H_{17}F_6N_5O_3$ ([M+H]$^+$) 502.1310, Found 502.1312. $[a]^{29}_{D}$+5.73 (c=1.03, $CHCl_3$).



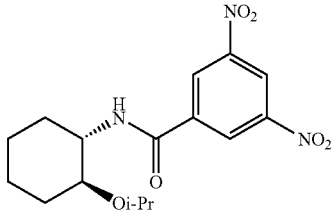
2,3,4,5,6-Pentafluoro-N-(2-isopropoxy-cyclohexyl)-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-pentafluorophenyl-methanone (0.044 g, 0.15 mmol) and phenylphosphinic acid (4.3 mg, 20 mol %). The air was removed and replaced with argon. Isopropanol (60 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with hexanes/EtOAc. Recovered white solid (0.050 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (m, 6H), 1.27 (m, 4H), 1.72 (m, 2H), 2.01 (m, 1H), 2.23 (m, 1H), 3.22 (m, 1H), 3.65 (m, 2H), 5.99 (br s, 1H).



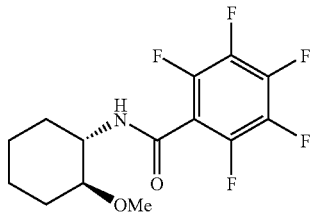
N-(2-Isopropoxy-cyclohexyl)-3,5-bis-trifluoromethyl-benzamide To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane (0.051 g, 0.15 mmol) and phenylphosphinic acid (4.3 mg, 20 mol %). The air was removed and replaced with argon. Isopropanol (60 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.55 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.024 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (m, 6H), 1.37 (m, 4H), 1.64 (m, 1H), 1.68 (m, 1H), 2.13 (m, 1H), 2.29 (m, 1H), 3.23 (m, 1H), 3.62 (m, 2H), 6.19 (brs, 1H), 7.99 (s, 1H), 8.18 (s, 2H).



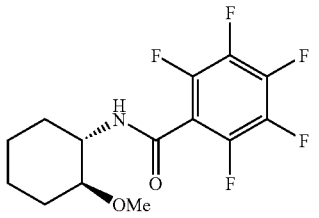
N-(2-Isopropoxy-cyclohexyl)-3,5-dinitro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-(3,5-dinitro-phenyl)-methanone (0.043 g, 0.15 mmol) and phenylphosphinic acid (4.3 mg, 20 mol %). The air was removed and replaced with argon. isopropanol (60 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.02 g, 39%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.10 (d, 6H), 1.29 (m, 4H), 1.65 (m, 2H), 2.03 (m, 1H), 2.32 (m, 1H), 2.23 (m, 1H), 3.67 (m, 2H), 6.31 (br s, 1H), 8.81 (s, 2H), 9.09 (s, 1H).



N-(2-Isopropoxy-cyclohexyl)-3,5-dinitro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-(3,5-dinitro-phenyl)-methanone (0.043 g, 0.15 mmol) and BINOL phosphoric acid (5.0 mg, 10 mol %). The air was removed and replaced with argon. isopropanol (60 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.012 g, 23%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.10 (d, 6H), 1.29 (m, 4H), 1.65 (m, 2H), 2.03 (m, 1H), 2.32 (m, 1H), 2.23 (m, 1H), 3.67 (m, 2H), 6.31 (br s, 1H), 8.81 (s, 2H), 9.09 (s, 1H). HPLC analysis: Chiralcel AD-H (hexane/iPrOH=90:10, 1.0 mL/min), $t_{r\text{-}major}$ 12.51 min, $t_{r\text{-}minor}$ 13.17 min (8% ee).

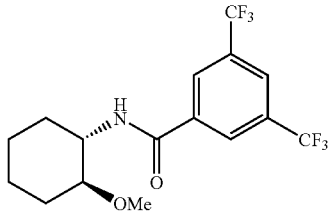


2,3,4,5,6-Pentafluoro-N-(2-methoxy-cyclohexyl)-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-pentafluorophenyl-methanone (0.044 g, 0.15 mmol) and phenylphosphinic acid (11 mg, 50 mol %). The air was removed and replaced with argon. Methyl alcohol (36 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.041 g, 89%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (m, 4H), 1.71 (m, 2H), 2.18 (m, 2H), 3.17 (m, 1H), 3.31 (s, 3H), 3.82 (m, 1H), 6.06 (brs, 1H).

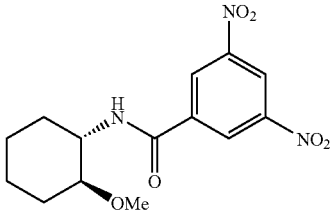


2,3,4,5,6-Pentafluoro-N-(2-methoxy-cyclohexyl)-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-pentafluorophenyl-methanone (0.029 g, 0.10 mmol) and (R) BINOL phosphoric acid (4.0 mg, 10 mol %). The air was removed and replaced with argon. Methyl alcohol (24 μL, 0.6 mmol) was added via syringe to the test-tube followed by dichloromethane (0.25 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.026 g, 84%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (m, 4H), 1.71 (m, 2H), 2.18 (m, 2H), 3.17 (m, 1H), 3.31 (s, 3H), 3.82 (m, 1H), 6.06 (brs, 1H).

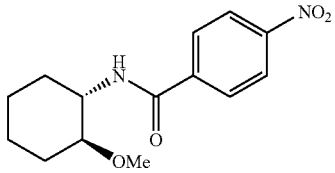
HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90:10, 1.0 mL/min), $t_{r\text{-}major}$ 7.85 min, $t_{r\text{-}minor}$ 16.88 min (2% ee).



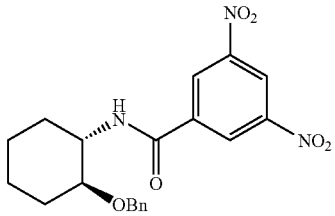
N-(2-Methoxy-cyclohexyl)-3,5-bis-trifluoromethyl-benzamide To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane (0.051 g, 0.15 mmol) and phenylphosphinic acid (11 mg, 50 mol %). The air was removed and replaced with argon. Methyl alcohol (12 mL, 0.3 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.027 g, 49%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.22 (m, 4H), 1.64 (m, 2H), 2.11 (m, 2H), 3.17 (m, 1H), 3.29 (s, 3H), 3.79 (m, 1H), 6.37 (s, 1H), 7.91 (s, 1H), 8.09 (s, 2H).



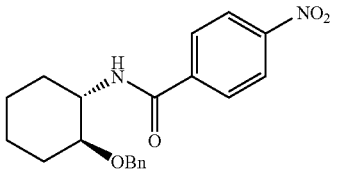
N-(2-Methoxy-cyclohexyl)-3,5-dinitro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-(3,5-dinitro-phenyl)-methanone (0.0.44 g, 0.15 mmol) and phenylphosphinic acid (11 mg, 50 mol %). The air was removed and replaced with argon. Methyl alcohol (36 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.25 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.031 g, 66%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.28 (m, 4H), 1.78 (m, 2H), 2.21 (m, 2H), 3.14 (m, 1H), 3.28 (s, 3H), 3.81 (m, 1H), 6.63 (d, 1H), 8.89 (s, 2H), 9.05 (s, 1H).



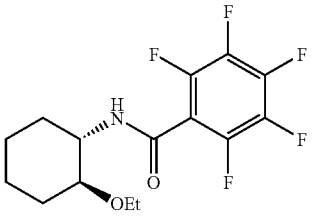
N-(2-Methoxy-cyclohexyl)-4-nitro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-(4-nitro-phenyl)-methanone (0.036 g, 0.15 mmol) and phenylphosphinic acid (11.0 mg, 50 mol %). The air was removed and replaced with argon. Methyl alcohol (36 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.029 g, 71%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.23 (m, 4H), 1.71 (m, 2H), 2.09 (m, 1H), 2.24 (m, 1H), 3.11 (m, 1H), 3.29 (m, 3H), 3.82 (m, 1H), 6.24 (br s, 1H), 7.84 (d, 2H), 8.19 (d, 2H).



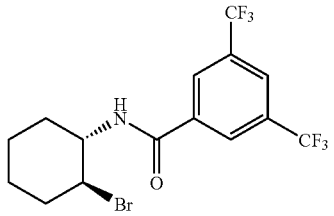
N-(2-Benzyloxy-cyclohexyl)-3,5-dinitro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-(3,5-dinitro-phenyl)-methanone (0.044 g, 0.15 mmol) and (S)-3,3'-Bis(triphenylsilyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate (13.0 mg, 10 mol %). The air was removed and replaced with argon. Benzyl alcohol (30 μL, 0.9 mmol) was added via syringe to the test-tube followed by dichloromethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.032 g, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24-1.86 (m, 6H), 2.29 (m, 2H), 3.31 (m, 1H), 3.89 (m, 1H), 4.39 (m, 1H), 4.71 (m, 1H), 6.06 (br s, 1H), 7.24 (m, 5H), 8.75 (s, 2H), 9.12 (s, 1H).



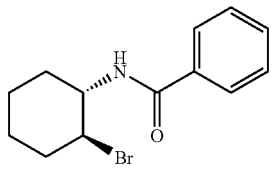
N-(2-Benzyloxy-cyclohexyl)-4-nitro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-(4-nitro-phenyl)-methanone (0.024 g, 0.1 mmol) and phenylphosphinic acid (4.0 mg, 40 mol %). The air was removed and replaced with argon. Benzyl alcohol (68 μL, 0.6 mmol) was added via syringe to the test-tube followed by dichloromethane (0.25 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.030 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09-1.84 (m, 6H), 2.21-2.35 (m, 2H), 3.29 (m, 1H), 3.88 (m, 1H), 4.38 (d, J=12.4 Hz, 1H), 4.68 (d, J=12.4 Hz, 1H), 5.96 (s, 1H), 7.24 (m, 5H), 7.72 (d, J=8.8 Hz, 2H), 8.21 (d, J=8.8 Hz, 2H).



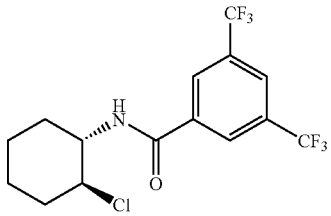
N-(2-Ethoxy-cyclohexyl)-2,3,4,5,6-pentafluoro-benzamide To a flame-dried test tube was added (7-Aza-bicyclo[4.1.0]hept-7-yl)-pentafluorophenyl-methanone (0.044 g, 0.15 mmol) and (S)-VAPOL phosphoric acid (9 mg, 10 mol %). The air was removed and replaced with argon. Trimethylsilyl ethoxide (47 μL, 0.3 mmol) was added via syringe to the test-tube followed by dichloromethane (0.25 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.011 g, 21%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.96-1.78 (m, 6H), 1.99-2.89 (m, 2H), 3.22 (m, 2H), 3.53 (m, 2H), 3.79 (m, 2H), 5.83 (s, 1H).



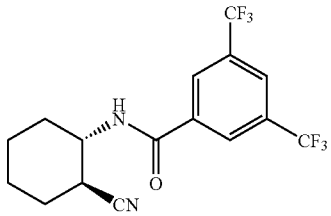
N-(2-Bromo-cyclohexyl)-3,5-bis-trifluoromethyl-benzamide To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane (0.051 g, 0.15 mmol) and (R)-VAPOL phosphoric acid (9 mg, 10 mol %). The air was removed and replaced with argon. Bromotrimethylsilane 30 μL, 0.23 mmol) was added via syringe to the test-tube followed by dichloromethane (1.0 mL). The reaction was stirred at −78° C. for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.070 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (m, 3H), 1.72 (m, 2H), 1.97 (m, 1H), 2.21 (m, 1H), 2.40 (m, 1H), 3.99 (m, 1H), 4.21 (m, 1H), 6.81 (br s, 1H), 7.92 (s, 1H), 8.19 (s, 2H). HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90:10, 1.0 mL/min), $t_{r\text{-}major}$ 7.77 min, $t_{r\text{-}minor}$ 5.75 min (5% ee).



N-(2-Bromo-cyclohexyl)-benzamide To a flame-dried test tube was added 7-aza-bicyclo[4.1.0]hept-7-yl)-phenyl-methanone (0.020 g, 0.1 mmol) and (R)—PA-1 (6 mg, 10 mol %). The air was removed and replaced with argon. Bromotrimethylsilane (14 μL, 0.11 mmol) was added via syringe to the test-tube followed by dichloromethane (1 mL). The reaction was stirred at −78° C. for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.025 g, 91% yield). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.13-1.98 (m, 6H), 2.32 (m, 2H), 4.01 (m, 2H), 6.09 (s, 1H), 7.38 (m, 3H), 8.71 (m, 2H).



N-(2-Chloro-cyclohexyl)-3,5-bis-trifluoromethyl-benzamide To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane (0.067 g, 0.2 mmol) and (R)-VAPOL phosphoric acid (12 mg, 10 mol %). The air was removed and replaced with argon. Chlorotrimethylsilane (16 μL, 0.125 mmol) was added via syringe to the test-tube followed by dichloromethane (0.25 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.043 g, 93%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.41 (m, 3H), 1.69 (m, 3H), 2.17 (m, 2H), 3.75 (m, 1H), 3.99 (m, 1H), 6.73 (br s, 1H), 7.85 (s, 1H), 8.15 (s, 2H). HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90:10, 1.0 mL/min), $t_{r\text{-}major}$ 7.73 min, $t_{r\text{-}minor}$ 5.91 min (9% ee).



N-(2-Cyano-cyclohexyl)-3,5-bis-trifluoromethyl-benzamide To a flame-dried test tube was added 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane (0.051 g, 0.38 mmol) and (R)-VAPOL phosphoric acid (9 mg, 10 mol %). The air was removed and replaced with argon. Trimethylsilyl cyanide (80 μL, 0.60 mmol) was added via syringe to the test-tube followed by 1,2-dichloroethane (0.5 mL). The reaction was stirred at ambient temperature for 24 h. The reaction was diluted with CH_2Cl_2, concentrated on silica gel, and purified by flash column chromatography with 6:1 hexanes/EtOAc. Recovered white solid (0.0334 g, 61%). ^{1}H NMR

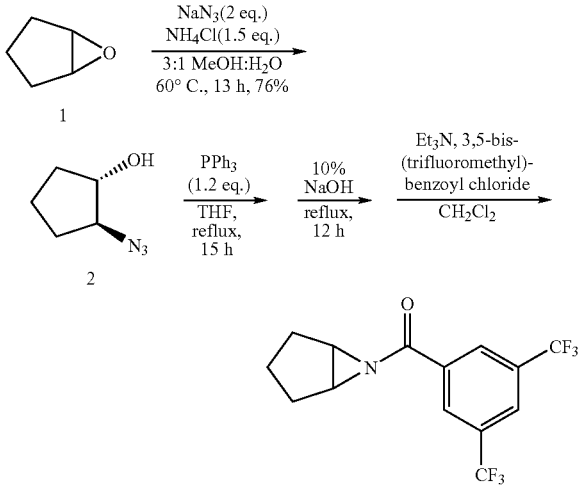
(250 MHz, $CDCl_3$): δ 1.23-2.21 (m, 6H), 2.69 (m, 2H), 4.11 (m, 2H), 6.38 (s, 1H), 7.91 (s, 1H), 8.24 (s, 1H). HPLC analysis: Chiralcel AS-H (hexane/iPrOH=90:10, 1.0 mL/min), $t_{r\text{-}major}$ 6.09 min, $t_{r\text{-}minor}$ 7.44 min (8% ee).

Procedure for the Preparation of Aziridine Substrates

Aziridines 7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid benzyl ester, 7-aza-bicyclo[4.1.0]heptane-7-carboxylic acid tert-butyl ester, and (7-Aza-bicyclo[4.1.0]hept-7-yl)-(4-nitro-phenyl)-methanone were prepared by literature procedure.[2]

Aziridines (7-Aza-bicyclo[4.1.0]hept-7-yl)-(3,5-dinitro-phenyl)-methanone, 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[3.1.0]heptane, 7-(3,5-Bis-trifluoromethylbenzoyl)-7-azabicyclo[4.1.0]hept-3-ene, 8-(3,5-Bis-trifluoromethylbenzoyl)-8-azbicyclo[5.1.0]octane, N-(3,5-Bis-trifluoromethylbenzoyl)-2,3-iminotetralin, and cis-1-(3,5-Bis-trifluoromethylbenzoyl)-2,3-dimethylaziridine, were prepared by the literature procedure.[3]

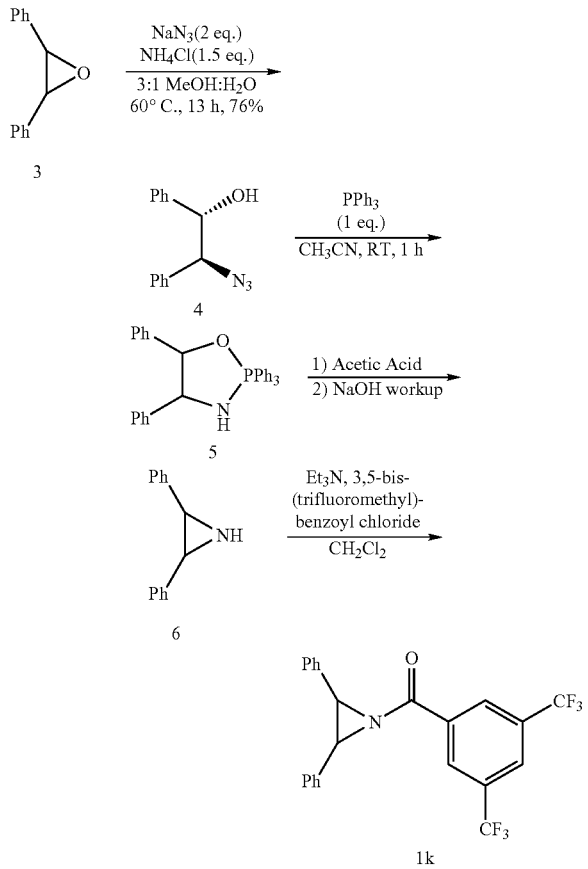
6-(3,5-Bis-trifluoromethylbenzoyl)-6-azabicyclo[3.1.0]hexane was prepared by the following modified procedure of the reported method.[3,4]



To a solution of 3:1 MeOH:H_2O (300 mL) was added cyclopentene oxide (1)(13 mL, 149.0 mmol), followed by the addition of NaN_3 (19.4 g, 298.0 mmol) and NH_4Cl (12.4 g, 223.5 mmol). The mixture was heated at 60° C. for 13 h. Most of the MeOH was evaporated in vacuo and then extracted three times with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated to afford 2 as a tan oil (17.7 g, 94%).

Azido alcohol 2 (5.0 g, 39.3 mmol) was added to a flame-dried flask. The air was removed and replaced with argon. Anhydrous THF (40.0 mL) was added followed by PPh_3 (12.3 g, 47.0 mmol) and heated under reflux for 15 h. Most of the THF was removed in vacuo at ambient temperature. Added 10% NaOH (50 mL) and refluxed for 12 h then extracted three times each with ether then CH_2Cl_2, washed with brine, dried over $MgSO_4$ and concentrated at ambient temperature leaving about 100 mL CH_2Cl_2. Benzoylation was completed in CH_2Cl_2 following the reported literature procedure.[3] Calculations for the benzoylation were based on using 18.1 mmol 3,5-bis-(trifluoromethyl)-benzoyl chloride.

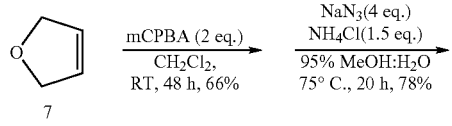
cis-1-(3,5-Bis-trifluoromethylbenzoyl)-2,3-diphenylaziridine was prepared by the following modified procedure of the reported method.[3,5]



To a solution of 3:1 MeOH:H_2O (40 mL) was added cis-stilbene oxide (3)(5.2 g, 27.0 mmol), followed by the addition of NaN_3 (3.5 g, 54 mmol) and NH_4Cl (2.2 g, 40.5 mmol). The mixture was heated at 60° C. for 13 h. Most of the MeOH was evaporated in vacuo and then extracted three times with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and concentrated to afford a tan oil (6 g, 76%).

Azido alcohol 4 (4.0 g, 13.6 mmol) was added to a flame dried flask. The air was removed and replaced with argon. Anhydrous CH_3CN (16.0 mL) was added followed by PPh_3 (3.6 g, 13.6 mmol) and allowed to stir for 1 h at ambient temperature and then placed in a −20° C. freezer overnight. A white precipitate formed which was recovered by filtration. The crystals were put in CH_2Cl_2 (6.0 mL) and concentrated acetic acid (12 μL) was added and stirred for 30 min. The solution was diluted with ether (100 mL) and extracted twice with 2M HCl. Added 2M NaOH to the HCl layer until basic and extracted twice with CH_2Cl_2, dried over Na_2SO_4, and concentrated. The benzoylation was completed in CH_2Cl_2 following the reported literature procedure.[3] Calculations for the benzoylation were based on using 18.1 mmol 3,5-bis-(trifluoromethyl)-benzoyl chloride.

3-Oxa-6-(3,5-Bis-trifluoromethylbenzoyl)-6-azbicyclo[3.1.0]hexane was prepared by the following modified procedure of the reported method.[3,6,7,8]



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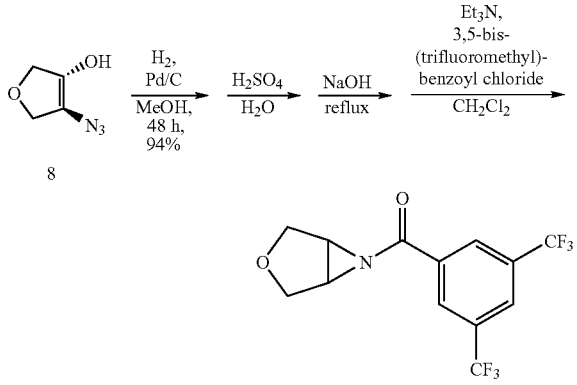


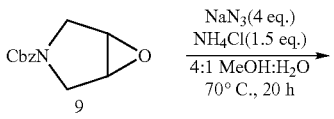
2,4-Dihydrofuran (7)(5.3 mL, 71.3 mmol) was added to a 500 mL round bottom flask containing CH_2Cl_2 (250 mL). mCPBA was added and the solution stirred at ambient temperature for two days. The solution was washed twice with aqueous $Na_2S_2O_3$, then sat. Na_2CO_3 and dried over Na_2SO_4. The organic layer was then concentrated to afford the epoxide as a colorless oil (3.7 g, 66%).

NaN_3 (11.2 g, 172 mmol) and NH_4Cl (3.6 g, 64.5 mmol) were added to 80 mL 95% MeOH in H_2O and stirred until most dissolved. The above epoxide (3.7 g, 43 mmol) was added and the solution was heated at 75° C. for 20 h. It was then cooled to room temperature and filtered to remove excess NaN_3. The filtrate was diluted with water and extracted four times with EtOAc, dried over Na_2SO_4, and concentrated to afford azido alcohol 8 as a tan oil (4.3 g, 78%)

To a flame dried 100 mL round bottom flask under argon was added 10% Pd/C (304 mg) followed by MeOH (15 mL) while stirring. Added azido alcohol 8 via syringe and stirred under an atmosphere of hydrogen for 48 h. Reaction was monitored by TLC until completion and filtered over a pad of celite and concentrated to afford the amino alcohol a tan solid (1.5 g, 94%)

The amino alcohol (1.5 g, 14.5 mmol) was added to a 100 mL round bottom flask. Approximately 4 mL H_2O was added and the mixture cooled to 0° C. Concentrated H_2SO_4 (0.78 mL) in H_2O (1.8 mL) was added dropwise and the mixture stirred at 0° C. for 1 h. The H_2O was removed by distillation and continued heating at 10° C. for 1 h. Added 20% NaOH and heated at 100° C. overnight. The solution was cooled to room temperature and extracted four times with CH_2Cl_2 and dried over Na_2SO_4. Most of the solvent was removed carefully in vacuo (the resulting aziridine is volatile). The benzoylation was completed in CH_2Cl_2 following the reported literature procedure.[3] Calculations for the benzoylation were based on using 18.1 mmol 3,5-bis-(trifluoromethyl)-benzoyl chloride.

3-Carbobenzyloxy-6-(3,5-Bis-trifluoromethylbenzoyl)-3,6-diazbicyclo[3.1.0]hexane was prepared by the following modified procedure of the reported method.[3,9]



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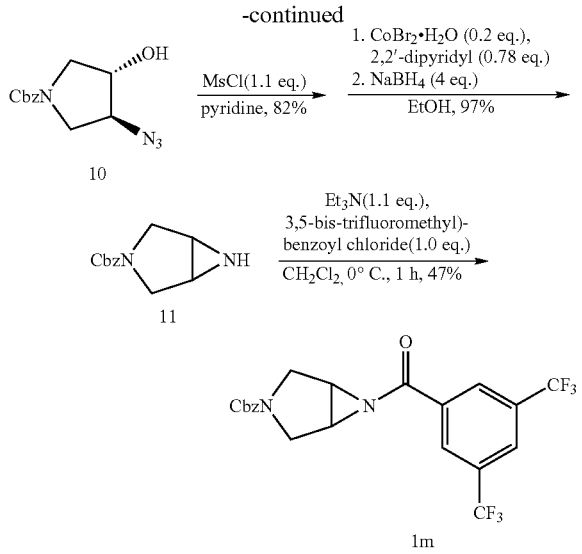

To a solution of 4:1 MeOH:H_2O was added epoxide 9 (4.8 g, 22.0 mmol) followed by the addition of NaN_3 (2.86 g, 44.0 mmol) and NH_4Cl (1.8 g, 33.0 mmol) while stirring. The mixture was heated at 70° C. for 20 h and then diluted with H_2O, extracted three times with CH_2Cl_2 and dried over Na_2SO_4. The organic layer was concentrated to afford a red oil, which was carried on to the next step. The air was removed from the flask and replaced with argon. Pyridine (13.0 mL) was added and cooled to 0° C. Methanesulfonyl chloride (1.9 mL, 24.2 mmol) was added slowly dropwise via syringe. The solution was allowed to warm to ambient temperature and stirred for 20 h. The reaction mixture was poured over ice cold H_2O and extracted with CH_2Cl_2 twice and then washed with two 50 mL portions of 1M HCl followed by brine. The organic phase was concentrated to afford a red oil (6.1 g, 82%), which was diluted with EtOH (60 mL) and added to a 500 mL flask containing a 0° C. solution of $CoBr_2.H_2O$ (0.92 g, 4 mmol) and 2,2'-dipyridyl (2.2 g, 14 mmol) in 300 mL absolute EtOH. Sodium borohydride (3.1 g, 82.0 mmol) was added very slowly in small portions over 1 h while keeping at 0° C. The mixture was allowed to slowly warm to ambient temperature and stirred for an additional 2 h. The mixture was then slowly poured over H_2O (1000 mL) and extracted three times with CH_2Cl_2, dried over Na_2SO_4 and concentrated to afford a brown oil which was purified by flash column chromatography with CH_2Cl_2 and MeOH. Recovered 3.77 g, 97% of aziridine 11.

Aziridine 11 (2.0 g, 9.2 mmol) was added to an oven dried flask. The air was removed and replaced with argon. CH_2Cl_2 (20 mL) was added followed by Et_3N (1.4 mL, 10.1 mmol) and cooled to 0° C. A bubbler was attached to the flask and 3,5-Bis-(trifluoromethyl)benzoylchloride (1.64 mL, 9.2 mmol) in CH_2Cl_2 (6.0 mL) was added slowly dropwise. The Solution was stirred at 0° C. for 1 h. H_2O (20 mL) was added and let warm to ambient temperature and extracted three times with CH_2Cl_2, washed with brine, dried over Na_2SO_4, concentrated and purified by flash column chromatography with 6:1 hexanes:acetone to afford a 1 m as a colorless oil (1.8 g, 47%).

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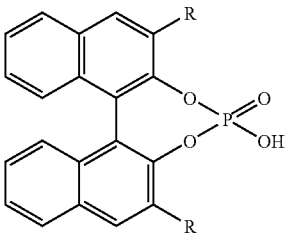
Example 2

Preliminary Studies—Brønsted Acid-Catalyzed Ring-Opening of Aziridines: The catalytic asymmetric ring-opening of aziridines is an important, actively pursued area of research. Chiral Phosphoric Acid Catalysts can be seen in Table 1. The method of the current invention involves catalyzation of the ring-opening of meso-aziridines by the chiral Brønsted acids with azide to provide a 1,2-diamine precursors in high enantiomeric excess (see Table 2). These desymmetrization reactions occur at room temperature and with very high yield. Chiral 1,2-diamines have an important value synthetically and this methodology is the first example of a chiral Brønsted acid catalyzing such ring-opening type reaction with high selectivity. PA5 has been shown to be an excellent catalyst in the limited study so far. Development of a method for the kinetic resolution of aziridines using PA5 is also foreseen.

A general procedure for the catalytic asymmetric ring opening of meso aziridines: The aziridine (1.5 equiv) and chiral Brønsted acid (10 mol %) were weighed into a flame-dried, screw-cap test tube with septa and stir bar. The test tube was evacuated and back-filled with argon and repeated three times. To the mixture was added azidotrimethylsilane (1 equiv) drop-wise followed by immediate addition of 0.5 mL of dry 1,2-dichloroethane via syringe. The mixture was stirred vigorously for the desired reaction time as monitored by TLC for product formation. Dichloromethane (4-5 mL) and a scoop of silica gel were added and the solvent removed by rotary evaporation to give a crude mixture adhered to silica that was purified by column chromatography to provide the desired product.

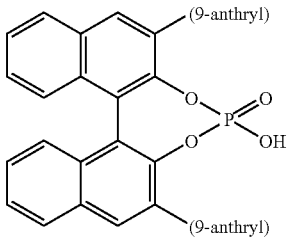
TABLE 1



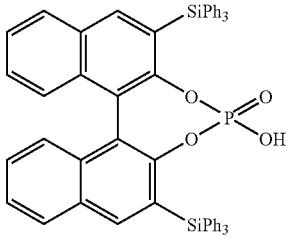
PA1a
R = H
PA1b
R = 4-(β-Naph)-C_6H_4
PA1c

TABLE 1-continued

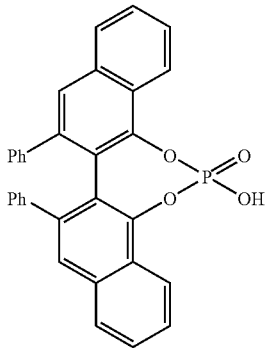
R = 4-(α-Naph)-C_6H_4
PA1d
R = β-Naph



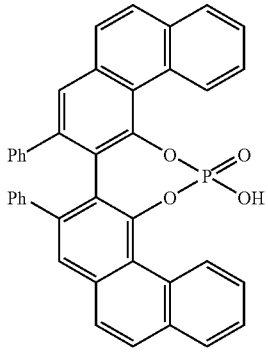
PA2



PA3

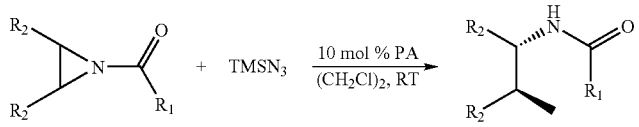


PA4

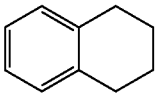
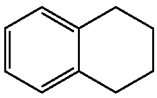
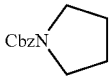


PA5

TABLE 2



meso-10 11

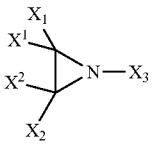
entry	R_1	R_2	time, h	PA	yield, %[a]	ee	entry	R_1	R_2	time, h	PA	yield, %[a]	ee
1	Ot-Bu	—$(CH_2)_4$—	30	PA5	48	0	1	3,5-$CF_3C_6H_3$	—$(CH_2)_4$—	21	PA5	94	96
2	OBn	—$(CH_2)_4$—	22	PA5	49	0	2	3,5-$CF_3C_6H_3$	—$(CH_2)_4$—	21	PA4	90	94
3	3,5-$NO_2C_6H_3$	—$(CH_2)_4$—	6	PA5	90	77	3	3,5-$CF_3C_6H_3$	—CH_2CH═$CHCH_2$—	21	PA5	84	92
4	3,5-$NO_2C_6H_3$	—$(CH_2)_4$—	46	PA3	90	0	4	3,5-$CF_3C_6H_3$	Me	21	PA5	88	86
5	C_6F_5	—$(CH_2)_4$—	21	PA5	58	12	5	3,5-$CF_3C_6H_3$	$CH_3(CH_2)_2$—	23	PA5	33	58
6	3,5-$CF_3C_6H_3$		21	PA5	78	71	6	3,5-$CF_3C_6H_3$	—$(CH_2)_5$—	23	PA5	31	93
7	3,5-$CF_3C_6H_3$		96	PA5	90	70	7	3,5-$CF_3C_6H_3$	—$(CH_2)_5$—	91	PA5	64	91
8	3,5-$CF_3C_6H_3$	—CH_2OCH_2—	48	PA5	49	87	8	3,5-$CF_3C_6H_3$	—$(CH_2)_5$—	72	PA5	95	69 @ 60° C.
9	3,5-$CF_3C_6H_3$	—C_6H_5—	48	PA5	95	83	9	3,5-$CF_3C_6H_3$	—$(CH_2)_3$—	55	PA5	68	84
10	3,5-$CF_3C_6H_3$		96	PA5	96	67							

[a]Isolated yields.

What is claimed is:

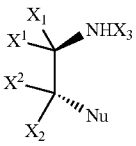
1. A process for the preparation of a nucleophilic addition product of an aziridine and a nucleophile, the process comprising treating the arizidine with the nucleophile in the presence of a biaryl phosphoric acid catalyst.

2. The process of claim **1** wherein the aziridine has the formula



and

the nucleophilic addition product has the formula



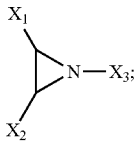
wherein

Nu is a nucleophile residue,

X_1, X^1, X_2 and X^2 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heterocyclo, and, optionally, (i) X_1 and X_2 and the ring carbon atoms to which they are respectively bonded, in combination, form a fused ring system, (ii) X_1 and X^1 and the ring carbon atom to which they are bonded, in combination, form a spiro ring, or (ii) X_2 and X^2 and the ring carbon atom to which they are bonded, in combination, form a spiro ring, and

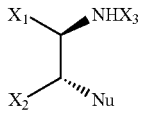
X_3 is hydrocarbyl, substituted hydrocarbyl, heterocyclo, silyl, acyl or amine protecting group.

3. The process of claim **1** wherein the aziridine has the formula



and

the nucleophilic addition product has the formula



wherein

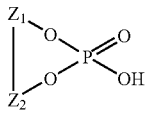
Nu is a nucleophile residue,

X_1, and X_2 are independently hydrogen, hydrocarbyl, substituted hydrocarbyl, or heterocyclo, and, optionally, (i)

X_1 and X_2 and the ring carbon atoms to which they are respectively bonded, in combination, form a fused ring system, and

X_3 is hydrocarbyl, substituted hydrocarbyl, heterocyclo, silyl, acyl or amine protecting group.

4. The process of claim **2** wherein the biaryl phosphoric acid catalyst has the formula



wherein Z_1 and Z_2 are aryl.

5. The process of claim **1** wherein the nucleophile is a silylazide and Nu is azide.

6. The process of claim **1** wherein the nucleophile is a trialkylsilylazide and Nu is —N_3.

7. The process of claim **1** wherein the nucleophile is an alcohol and Nu is —OT_1 wherein T_1 is hydrocarbyl, substituted hydrocarbyl or heterocyclo.

8. The process of claim **1** wherein the nucleophile is a cyanide and Nu is cyano.

9. The process of claim **1** wherein the nucleophile is a halonucleophile and Nu is chloro, bromo, fluoro or iodo.

10. The process of claim **2** wherein the nucleophile is a silylazide and Nu is azide.

11. The process of claim **2** wherein the nucleophile is a trialkylsilylazide and Nu is —N_3.

12. The process of claim **2** wherein the nucleophile is an alcohol and Nu is —OT_1 wherein T_1 is hydrocarbyl, substituted hydrocarbyl or heterocyclo.

13. The process of claim **2** wherein the nucleophile is a cyanide and Nu is cyano.

14. The process of claim **2** wherein the nucleophile is a halonucleophile and Nu is chloro, bromo, fluoro or iodo.

15. The process of claim **2** wherein X_3 is hydrocarbyl or acyl.

16. The process of claim **2** wherein X_3 is —C(O)A wherein A is hydrocarbyl, substituted hydrocarbyl, or heterocyclo.

17. The process of claim **3** wherein X_3 is —C(O)A wherein A is hydrocarbyl, substituted hydrocarbyl, or heterocyclo.

18. The process of claim **1** wherein the nucleophile is an amine, amide, azide, mercaptan, alcohol, alkoxide, thiolate, carbanion, cyanide, thiocyanate, acetate, formate or chloroformate, bisulfite, organocuprate, organozinc, organolithium, Grignard reagent, enolate, acetylide, or hydride.

19. The process of claim **1** wherein the aziridine is meso- in nature and the phosphoric acid catalyzes the addition of the nucleophile to provide an asymmetric nucleophilic addition product.

20. The process of claim **1** wherein the aziridine is racemic in nature and the phosphoric acid catalyzes a kinetic resolution of the racemic aziridine to provide a chiral nucleophilic addition product.

* * * * *