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(54) Titre : SYNTHÈSE D'ARYL PYRROLIDONES
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(57) **Abrégé/Abstract:**

The invention provides methods of asymmetrically synthesizing aryl pyrrolidones with high yield and high enantiomeric excess.



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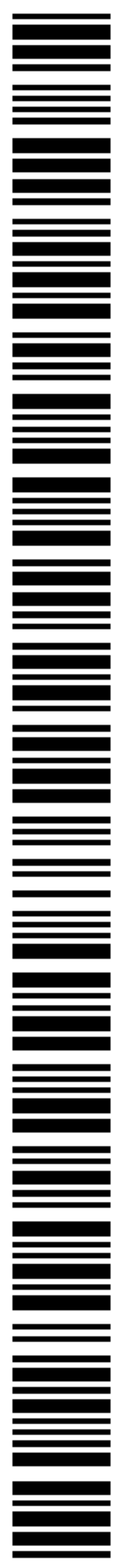
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(57) Abstract: The invention provides methods of asymmetrically synthesizing aryl pyrrolidones with high yield and high enantiomeric excess.



WO 2006/081562 A3

PATENT APPLICATION

SYNTHESIS OF ARYL PYRROLIDONES

CROSS-REFERENCES TO RELATED APPLICATIONS

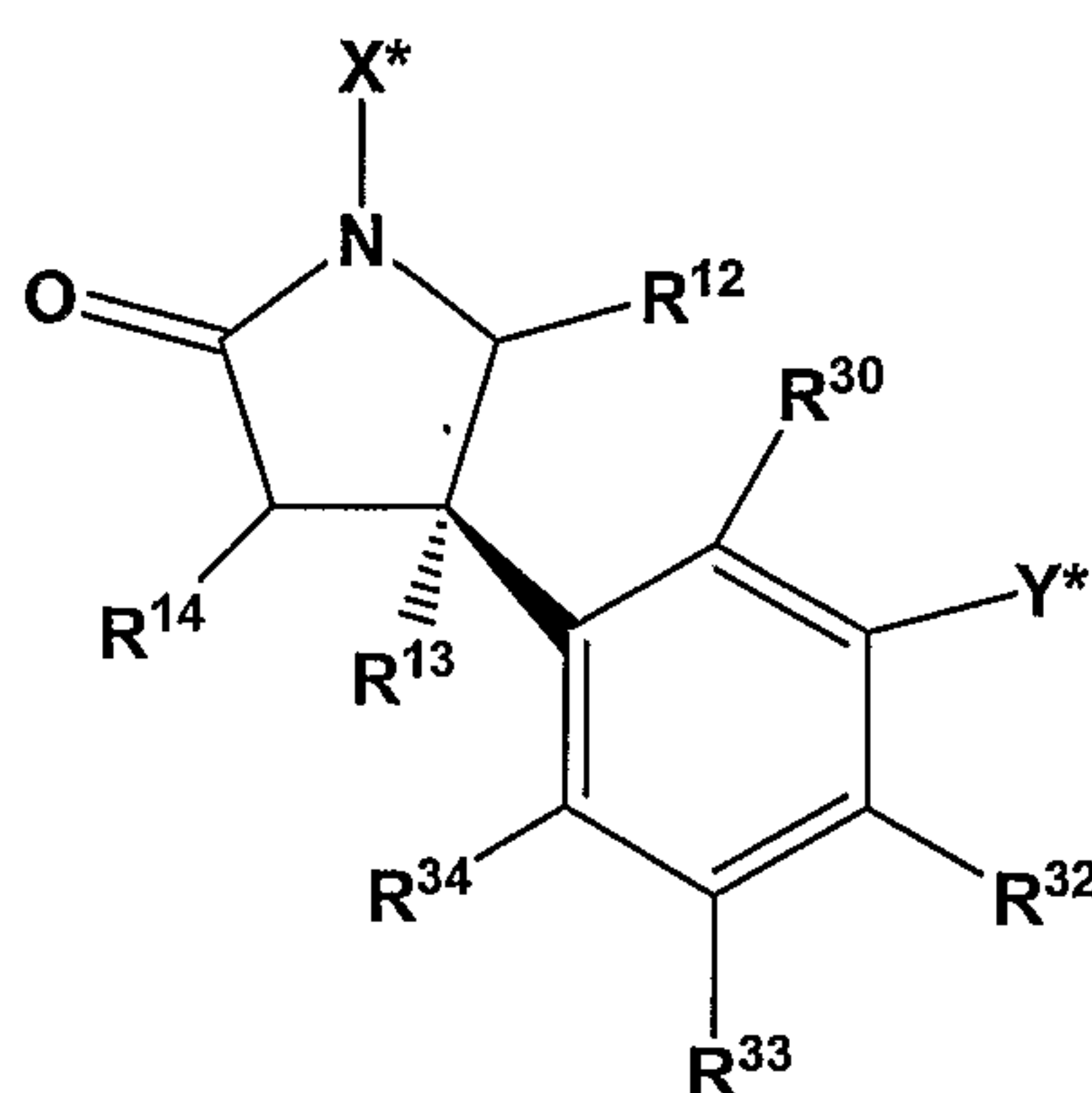
[0001] The present application claims priority to U.S. Provisional Patent Application No. 60/648,039, filed on January 28, 2005, which is incorporated herein by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[0002] The present invention relates generally to processes for the asymmetric synthesis of aryl pyrrolidones, such as aryl pyrrolidones useful as intermediates in the production of HIV inhibitors.

BACKGROUND OF THE INVENTION

[0003] Aryl pyrrolidones of the type shown below are currently being studied as antiviral agents, *e.g.*, HIV inhibitors, in clinical settings. Clinical trials and New Drug Application (NDA) submissions require practical, large-scale synthesis of the active drug.



Consequently, it is desirable to find new synthetic procedures for making aryl pyrrolidones. Since these pyrrolidones contain at least one chiral center, an asymmetric synthesis scheme that creates the above compound in high yield and high enantiomeric excess (“ee”) is preferred.

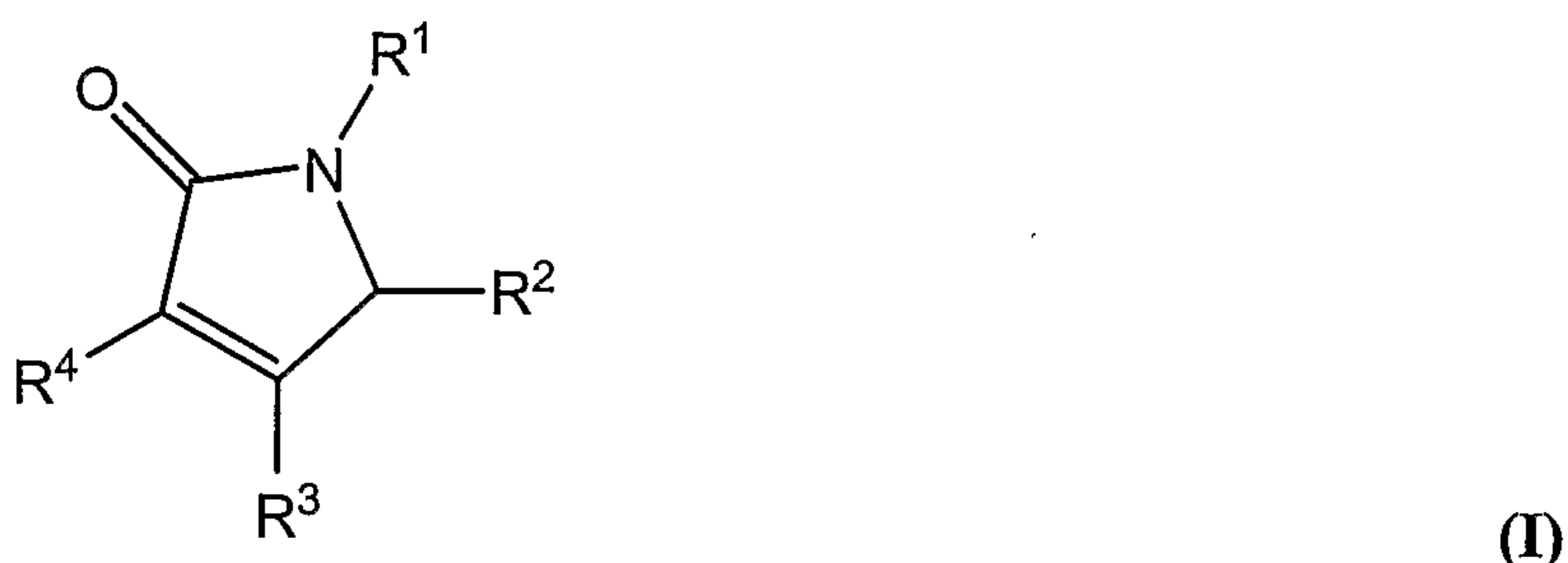
[0004] Asymmetric synthesis of aryl piperidinones has previously been reported, Senda *et al.*, *J. Org. Chem.*, **66**: 6852-6856 (2001) (“Senda”). To date, however, the asymmetric

synthesis of aryl pyrrolidones has not been reported. An asymmetric synthesis, yielding a high ee of a desired enantiomer would represent a significant advance in the art.

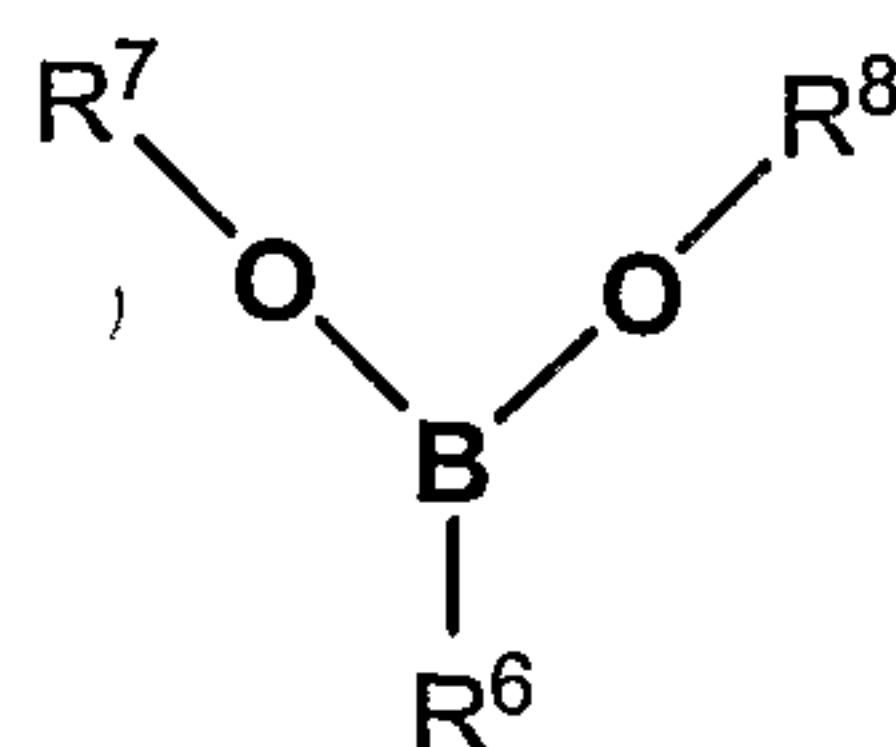
SUMMARY OF THE INVENTION

[0005] In a first aspect, the invention provides a method of asymmetric synthesis. The product of this synthesis can be an amide-containing heterocycle or a pharmaceutically acceptable salt thereof. The method comprises contacting an organometallic rhodium (I) complex, a chiral ligand, an α,β unsaturated amide-containing heterocycle, and a boronic ester under conditions sufficient to form a mixture comprising an amide-containing heterocycle and its enantiomer, thereby asymmetrically synthesizing the amide-containing heterocycle or pharmaceutically acceptable salt thereof. This mixture has an ee of about 60% or greater. In a second aspect, the invention provides a mixture comprising an amide-containing heterocycle and its enantiomer.

[0006] In an exemplary embodiment, the α,β unsaturated amide-containing heterocycle has a structure according to Formula I:



in which R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^2 , R^3 , and R^4 are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{5a} , NO_2 , CN , halogen, $C(O)R^{5b}$, $NR^{5a}R^{5b}$, $C(O)NR^{5a}R^{5b}$ and $C(O)OR^{5b}$. R^{5a} is H or substituted or unsubstituted alkyl. R^{5b} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. An exemplary boronic ester has a formula according to Formula II:



(II)

in which R^6 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. R^7 and R^8 are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{10} , NO_2 , CN, and halogen. R^7 and R^8 , taken together with the oxygen atoms to which they are joined, can also optionally form a substituted or unsubstituted 5- to 8-membered ring. R^{10} is H or substituted or unsubstituted alkyl.

[0007] The present invention presents several advances in the art. One advance is the first asymmetric synthesis of an aryl 5-membered lactam. The only previously known asymmetric synthesis in this field was of aryl 6-membered lactams, as reported in Senda. It must be noted that the reaction conditions for aryl 6-membered lactams are not always similar to aryl 5-membered lactams. For example, in Senda, when a N-benzyl 6-membered lactam substrate was reacted with an aryl moiety, yields of up to 75% were recorded. Surprisingly, for aryl 5-membered lactams, a N-benzyl 5-membered lactam substrate only produces a yield of 35%. When the benzyl group was substituted for a phenyl group, the reaction yield jumped from 35% to about 80%.

DETAILED DESCRIPTION OF THE INVENTION AND EMBODIMENTS

I. Definitions

[0008] The symbol $\sim$, whether utilized as a bond or displayed perpendicular to a bond indicates the point at which the displayed moiety is attached to the remainder of the molecule, solid support, etc.

[0009] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In

general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0010] Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and
5 individual isomers are encompassed within the scope of the present invention.

[0011] The compounds of the invention may be prepared as a single isomer (*e.g.*, enantiomer, *cis-trans*, positional, diastereomer) or as a mixture of isomers. In a preferred embodiment, the compounds are prepared as substantially a single isomer. Methods of preparing substantially isomerically pure compounds are known in the art. For example, enantiomerically enriched mixtures and pure enantiomeric compounds can be prepared by using synthetic intermediates that are enantiomerically pure in combination with reactions that either leave the stereochemistry at a chiral center unchanged or result in its complete inversion. Alternatively, the final product or intermediates along the synthetic route can be resolved into a single stereoisomer. Techniques for inverting or leaving unchanged a particular stereocenter, and those for resolving mixtures of stereoisomers are well known in the art and it is well within the ability of one of skill in the art to choose and appropriate method for a particular situation. *See, generally, Furniss et al. (eds.), VOGEL'S ENCYCLOPEDIA OF PRACTICAL ORGANIC CHEMISTRY 5TH ED., Longman Scientific and Technical Ltd., Essex, 1991, pp. 809-816; and Heller, Acc. Chem. Res. 23: 128 (1990).*

[0012] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (³H), iodine-125 (¹²⁵I) or carbon-14 (¹⁴C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

[0013] Where substituent groups are specified by their conventional chemical formulae, written from left to right, they equally encompass the chemically identical substituents, which would result from writing the structure from right to left, *e.g.*, -CH₂O- is intended to also recite -OCH₂-.

[0014] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent

radicals, having the number of carbon atoms designated (*i.e.* C₁-C₁₀ means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-
 5 hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butylnyl, and the higher homologs and isomers. The term “alkyl,” unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below, such as “heteroalkyl.” Alkyl groups that are limited to hydrocarbon groups are termed “homoalkyl”.

[0015] The term “alkylene” by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified, but not limited, by $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$, and further includes those groups described below as “heteroalkylene.” Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A “lower alkyl” or “lower alkylene” is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0016] The terms “alkoxy,” “alkylamino” and “alkylthio” (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0017] The term “heteroalkyl,” by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and at least one heteroatom selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which the alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-\text{CH}_2\text{CH}_2\text{OCH}_3$, $-\text{CH}_2\text{CH}_2\text{NHCH}_3$, $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_3$, $-\text{CH}_2\text{SCH}_2\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{S}(\text{O})\text{CH}_3$, $-\text{CH}_2\text{CH}_2\text{S}(\text{O})_2\text{CH}_3$, $-\text{CH}=\text{CHOCH}_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{CH}_2\text{CH}=\text{NOCH}_3$, and $-\text{CH}=\text{CHN}(\text{CH}_3)\text{CH}_3$. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{NH-OCH}_3$ and $-\text{CH}_2\text{O-Si}(\text{CH}_3)_3$. Similarly, the term “heteroalkylene” by itself or as part of another substituent

means a divalent radical derived from heteroalkyl, as exemplified, but not limited by, $-\text{CH}_2-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-$ and $-\text{CH}_2-\text{S}-\text{CH}_2-\text{CH}_2-\text{NH}-\text{CH}_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene
 5 linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-\text{C}(\text{O})_2\text{R}'-$ represents both $-\text{C}(\text{O})_2\text{R}'-$ and $-\text{R}'\text{C}(\text{O})_2-$.

[0018] The terms “cycloalkyl” and “heterocycloalkyl”, by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of “alkyl” and “heteroalkyl”, respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include, but are not limited to, cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include, but are not limited to, 1-(1,2,5,6-tetrahydropyridyl), 1-piperidiny, 2-piperidiny, 3-piperidiny, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like.

[0019] The terms “halo” or “halogen,” by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as “haloalkyl,” are meant to include monohaloalkyl and polyhaloalkyl. For example, the term “halo($\text{C}_1\text{-C}_4$)alkyl” is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0020] The term “aryl” means, unless otherwise stated, a polyunsaturated, aromatic, substituent that can be a single ring or multiple rings (preferably from 1 to 3 rings), which are fused together or linked covalently. The term “heteroaryl” refers to aryl groups (or rings) that contain from one to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, benzyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl,

2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxaliny, 5-quinoxaliny, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0021] For brevity, the term “aryl” when used in combination with other terms (*e.g.*,
 5 aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term “arylalkyl” is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0022] Each of the above terms (*e.g.*, “alkyl,” “heteroalkyl,” “aryl” and “heteroaryl”) are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0023] Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) are generically referred to as “alkyl group substituents,” and they can be one or more of a variety of groups selected from, but not limited to: -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR''', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂ in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R'', R''' and R'''' each preferably independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl, *e.g.*, aryl substituted with 1-3 halogens, substituted or unsubstituted alkyl, alkoxy or thioalkoxy groups, or arylalkyl groups. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present. When R' and R'' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R'' is meant to include, but not be limited to, 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term “alkyl” is meant to include groups

including carbon atoms bound to groups other than hydrogen groups, such as haloalkyl (*e.g.*, -CF₃ and -CH₂CF₃) and acyl (*e.g.*, -C(O)CH₃, -C(O)CF₃, -C(O)CH₂OCH₃, and the like).

[0024] Similar to the substituents described for the alkyl radical, substituents for the aryl and heteroaryl groups are generically referred to as “aryl group substituents.” The substituents are selected from, for example: halogen, -OR', =O, =NR', =N-OR', -NR'R'', -SR', -halogen, -SiR'R''R''', -OC(O)R', -C(O)R', -CO₂R', -CONR'R'', -OC(O)NR'R'', -NR''C(O)R', -NR'-C(O)NR''R''', -NR''C(O)₂R', -NR-C(NR'R''R''')=NR''', -NR-C(NR'R'')=NR'', -S(O)R', -S(O)₂R', -S(O)₂NR'R'', -NRSO₂R', -CN and -NO₂, -R', -N₃, -CH(Ph)₂, fluoro(C₁-C₄)alkoxy, and fluoro(C₁-C₄)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R'', R''' and R'''' are preferably independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. When a compound of the invention includes more than one R group, for example, each of the R groups is independently selected as are each R', R'', R''' and R'''' groups when more than one of these groups is present.

[0025] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-(CRR')_q-U-, wherein T and U are independently -NR-, -O-, -CRR'- or a single bond, and q is an integer of from 0 to 3. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-(CH₂)_r-B-, wherein A and B are independently -CRR'-, -O-, -NR-, -S-, -S(O)-, -S(O)₂-, -S(O)₂NR'- or a single bond, and r is an integer of from 1 to 4. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula - (CRR')_s-X-(CR''R''')_d-, where s and d are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -S(O)₂-, or -S(O)₂NR'-. The substituents R, R', R'' and R''' are preferably independently selected from hydrogen or substituted or unsubstituted (C₁-C₆)alkyl.

[0026] As used herein, the term “heteroatom” is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0027] “Protecting group,” as used herein refers to a portion of a substrate that is substantially stable under a particular reaction condition, but which is cleaved from the substrate under a different reaction condition. A protecting group can also be selected such

that it participates in the direct oxidation of the aromatic ring component of the compounds of the invention. For examples of useful protecting groups, *see*, for example, Greene *et al.*, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, John Wiley & Sons, New York, 1991.

[0028] “Enantiomeric excess”, or “ee” as used herein is an expression for the extra amount
5 of one enantiomer over another in a mixture of enantiomers. “ee” is usually stated as a percentage. Algebraically,

$$\text{e.e.} = \frac{|R - S|}{R + S} \times 100\%$$

For more information on “ee”, *see*, for example, Wade, L.G., ORGANIC CHEMISTRY, 5th Ed., Prentice Hall, New Jersey, 2003, pp. 167-207.

[0029] By “disorder associated with HIV infection” or “disease associated with HIV infection” herein is meant a disease state which is marked by HIV infection. Such disorders associated with HIV infection include, but are not limited to, AIDS; Kaposi’s sarcoma; opportunistic infections such as those caused by *Pneumocystis carinii* and *Mycobacterium tuberculosis*; oral lesions, including thrush, hairy leukoplakia, and aphthous ulcers; generalized lymphadenopathy; shingles; thrombocytopenia; aseptic meningitis; neurologic disease such as toxoplasmosis, cryptococcosis, CMV infection, primary CNS lymphoma, and HIV-associated dementia; peripheral neuropathies, seizures; and myopathy.

[0030] As used herein, “HIV reverse transcriptase inhibitor” is intended to refer to both nucleoside and non-nucleoside inhibitors of HIV reverse transcriptase (RT). Examples of nucleoside RT inhibitors include, but are not limited to, AZT, ddC, ddI, d4T, and 3TC. Examples of non-nucleoside RT inhibitors include, but are not limited to, delavirdine (Pharmacia and Upjohn U90152S), efavirenz (DuPont), nevirapine (Boehringer Ingelheim), Ro 18,893 (Roche), trovirdine (Lilly), MKC-442 (Triangle), HBY 097 (Hoechst), ACT (Korean Research Institute), UC-781 (Rega Institute), UC-782 (Rega Institute), RD4-2025 (Tosoh Co. Ltd.), and MEN 10979 (Menarini Farmaceutici).

[0031] As used herein, “HIV protease inhibitor” is intended to refer to compounds which inhibit HIV protease. Examples include, but are not limited, saquinavir (Roche, Ro31-8959), ritonavir (Abbott, ABT-538), indinavir (Merck, MK-639), amprenavir (Vertex/Glaxo Wellcome), nelfinavir (Agouron, AG-1343), palinavir (Boehringer Ingelheim), BMS-232623 (Bristol-Myers Squibb), GS3333 (Gilead Sciences), KNI-413 (Japan Energy), KNI-272

(Japan Energy), LG-71350 (LG Chemical), CGP-61755 (Ciba-Geigy), PD 173606 (Parke Davis), PD 177298 (Parke Davis), PD 178390 (Parke Davis), PD 178392 (Parke Davis), U-140690 (Pharmacia and Upjohn), and ABT-378. Additional examples include the cyclic protease inhibitors disclosed in WO93/07128, WO 94/19329, WO 94/22840, and PCT Application Number US96/03426.

[0032] By “therapeutically effective dose” herein is meant a dose that produces effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.,* Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); and Pickar, *Dosage Calculations* (1999)).

[0033] “Reactive functional group,” as used herein refers to groups including, but not limited to, olefins, acetylenes, alcohols, phenols, ethers, oxides, halides, aldehydes, ketones, carboxylic acids, esters, amides, cyanates, isocyanates, thiocyanates, isothiocyanates, amines, hydrazines, hydrazones, hydrazides, diazo, diazonium, nitro, nitriles, mercaptans, sulfides, disulfides, sulfoxides, sulfones, sulfonic acids, sulfinic acids, acetals, ketals, anhydrides, sulfates, sulfenic acids isonitriles, amidines, imides, imidates, nitrones, hydroxylamines, oximes, hydroxamic acids thiohydroxamic acids, allenes, ortho esters, sulfites, enamines, ynamines, ureas, pseudoureas, semicarbazides, carbodiimides, carbamates, imines, azides, azo compounds, azoxy compounds, and nitroso compounds. Reactive functional groups also include those used to prepare bioconjugates, *e.g.,* N-hydroxysuccinimide esters, maleimides and the like. Methods to prepare each of these functional groups are well known in the art and their application to or modification for a particular purpose is within the ability of one of skill in the art (*see, for example,* Sandler and Karo, eds. *ORGANIC FUNCTIONAL GROUP PREPARATIONS*, Academic Press, San Diego, 1989).

[0034] “Non-covalent protein binding groups” are moieties that interact with an intact or denatured polypeptide in an associative manner. The interaction may be either reversible or irreversible in a biological milieu. The incorporation of a “non-covalent protein binding group” into a chelating agent or complex of the invention provides the agent or complex with the ability to interact with a polypeptide in a non-covalent manner. Exemplary non-covalent interactions include hydrophobic-hydrophobic and electrostatic interactions. Exemplary ‘non-covalent protein binding groups’ include anionic groups, *e.g.,* phosphate,

thiophosphate, phosphonate, carboxylate, boronate, sulfate, sulfone, thiosulfate, and thiosulfonate.

[0035] As used herein, "linking member" refers to a covalent chemical bond that includes at least one heteroatom. Exemplary linking members include $-C(O)NH-$, $-C(O)O-$, $-NH-$,
5 $-S-$, $-O-$, and the like.

[0036] The term "targeting group" is intended to mean a moiety that is: (1) able to actively direct the entity to which it is attached (*e.g.*, contrast agent) to a target region, *e.g.*, a tumor; or (2) is preferentially passively absorbed by or entrained within a target tissue, for example a tumor. The targeting group can be a small molecule, which is intended to include both non-peptides and peptides. The targeting group can also be a macromolecule, which includes, but is not limited to, saccharides, lectins, receptors, ligand for receptors, proteins such as BSA, antibodies, poly(ethers), dendrimers, poly(amino acids) and so forth.

[0037] The term "cleavable group" is intended to mean a moiety that allows for release of the chelate from the rest of the conjugate by cleaving a bond linking the chelate (or chelate linker arm construct) to the remainder of the conjugate. Such cleavage is either chemical in nature, or enzymatically mediated. Exemplary enzymatically cleavable groups include natural amino acids or peptide sequences that end with a natural amino acid.

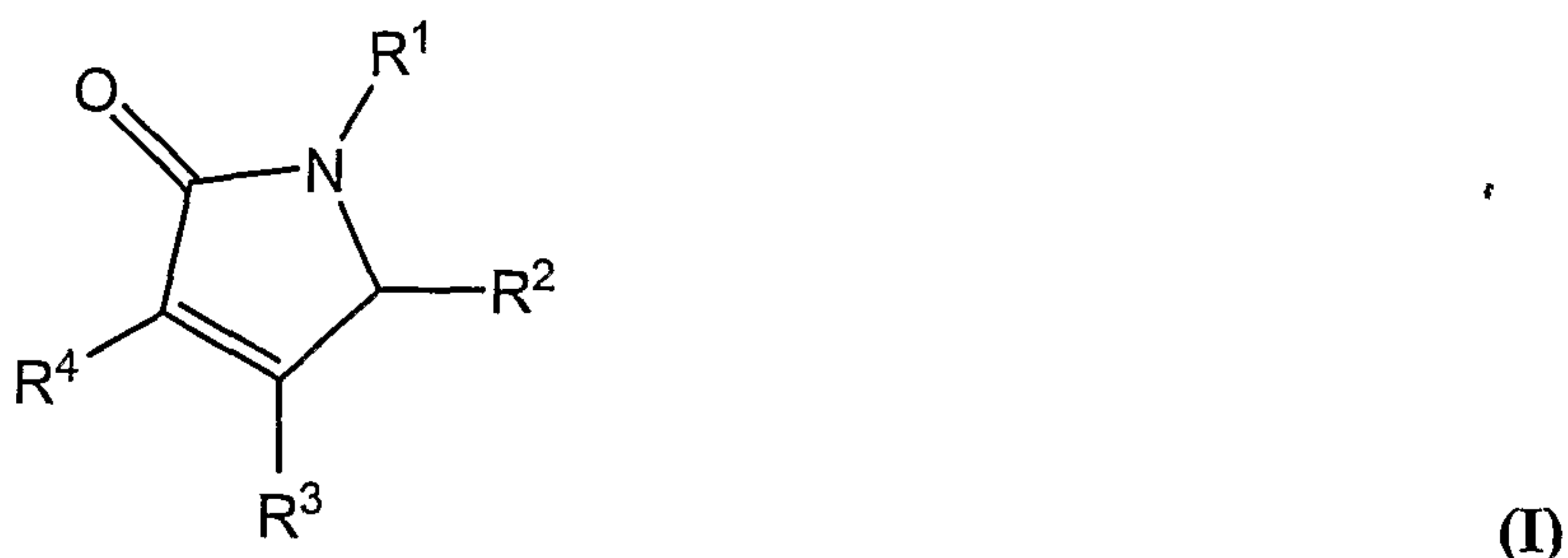
[0038] In addition to enzymatically cleavable sites, it is within the scope of the present invention to include one or more sites that are cleaved by the action of an agent other than an enzyme. Exemplary non-enzymatic cleavage agents include, but are not limited to, acids, bases, light (*e.g.*, nitrobenzyl derivatives, phenacyl groups, benzoin esters), and heat. Many cleavable groups are known in the art. *See*, for example, Jung *et al.*, *Biochem. Biophys. Acta*, **761**: 152-162 (1983); Joshi *et al.*, *J. Biol. Chem.*, **265**: 14518-14525 (1990); Zarling *et al.*, *J. Immunol.*, **124**: 913-920 (1980); Bouizar *et al.*, *Eur. J. Biochem.*, **155**: 141-147 (1986); Park *et al.*, *J. Biol. Chem.*, **261**: 205-210 (1986); Browning *et al.*, *J. Immunol.*, **143**: 1859-1867 (1989). Moreover a broad range of cleavable, bifunctional (both homo- and hetero-bifunctional) spacer arms are commercially available from suppliers such as Pierce.

II. The Methods

[0039] In a first aspect, the invention provides a method of synthesis. The product of this synthesis can be an amide-containing heterocycle or a pharmaceutically acceptable salt thereof. The method comprises: a) contacting an organometallic rhodium (I)

complex, a chiral ligand, an α,β unsaturated amide-containing heterocycle, and a boronic ester under conditions sufficient to form a product comprising an amide-containing heterocycle, thereby synthesizing the amide-containing heterocycle or pharmaceutically acceptable salt thereof.

- 5 [0040] In an exemplary embodiment, the α,β unsaturated amide-containing heterocycle has a structure according to Formula I:

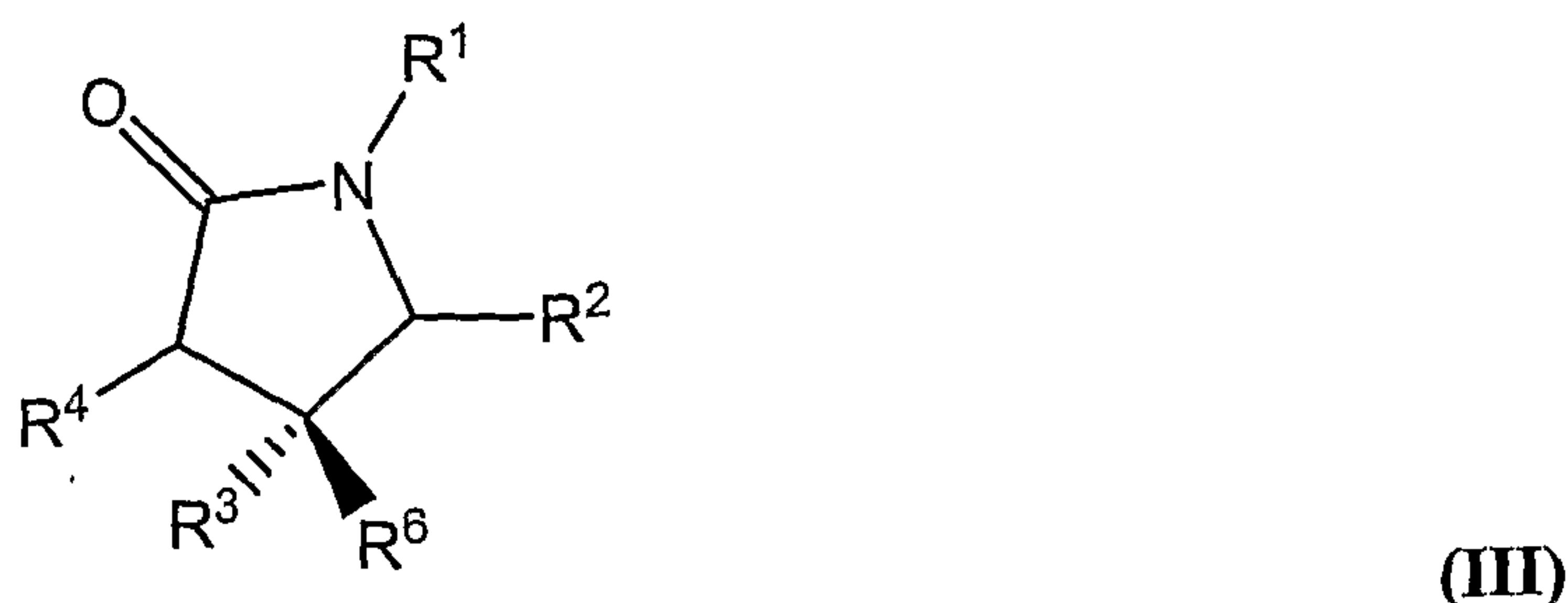


in which R^1 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^2 , R^3 , and R^4 are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{5a} , NO_2 , CN, halogen, $C(O)R^{5b}$, $NR^{5a}R^{5b}$, $C(O)NR^{5a}R^{5b}$ and $C(O)OR^{5b}$. R^{5a} is H or substituted or unsubstituted alkyl. R^{5b} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. An exemplary boronic ester has a formula according to Formula II:

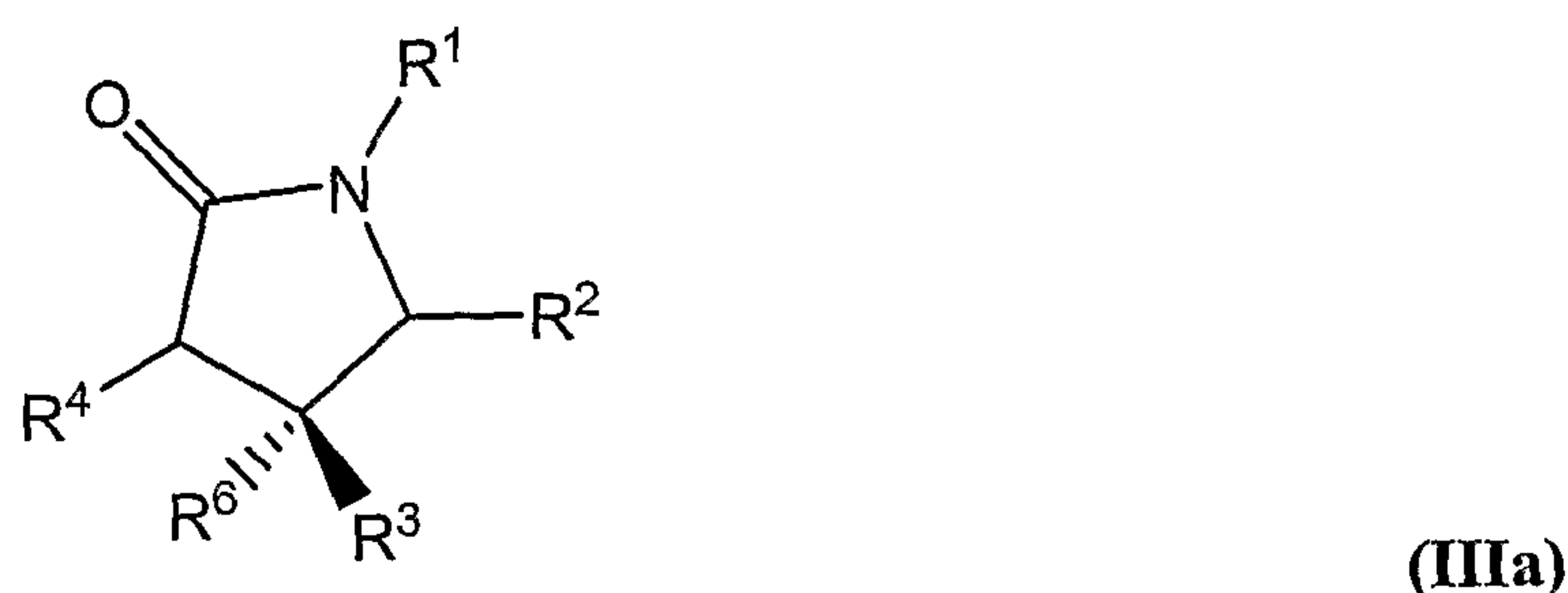


in which R^6 is substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl. R^7 and R^8 are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{10} , NO_2 , CN, and halogen. R^7 and R^8 , taken together with the oxygen atoms to

which they are joined, can also optionally form a substituted or unsubstituted 5- to 8-membered ring. R^{10} is H or substituted or unsubstituted alkyl. The amide-containing heterocycle can have a formula according to Formula III:



In an exemplary embodiment, the synthesis is asymmetric. In an exemplary embodiment, the product is an enantiomerically pure and has a formula according to Formula III. In another exemplary embodiment, the synthesis produces an enantiomer of the amide-containing heterocycle according to Formula III. In another exemplary embodiment, the product further comprises an amide-containing heterocycle that has a formula according to Formula IIIa:



[0041] In an exemplary embodiment, the product has an ee of about 10% or greater. In another exemplary embodiment, the product has an ee of about 30% or greater. In another exemplary embodiment, the product has an ee of about 50% or greater. In another exemplary embodiment, the product has an ee of about 60% or greater. In another exemplary embodiment, the product has an ee of about 70% or greater. In another exemplary embodiment, the product has an ee of about 80% or greater. In another exemplary embodiment, the product has an ee of about 90% or greater. In another exemplary embodiment, the product has an ee of about 95% or greater. In another exemplary embodiment, the product has an ee of about 97% or greater. In another exemplary embodiment, the product has an ee of about 98% or greater. In another exemplary embodiment, the product has an ee of about 99.0% or greater. In another exemplary embodiment, the product has an ee of about 99.2% or greater. In another exemplary embodiment, the product has an ee of about 99.4% or greater. In another exemplary

embodiment, the product has an ee of about 99.6% or greater. In another exemplary embodiment, the product has an ee of about 99.8% or greater.

[0042] In an exemplary embodiment, the method has a yield of about 20% or greater. In an exemplary embodiment, the method has a yield of about 30% or greater. In an exemplary embodiment, the method has a yield of about 40% or greater. In an exemplary embodiment, the method has a yield of about 50% or greater. In an exemplary embodiment, the method has a yield of about 60% or greater. In an exemplary embodiment, the method has a yield of about 70% or greater. In an exemplary embodiment, the method has a yield of about 80% or greater. In an exemplary embodiment, the method has a yield of about 90% or greater. In an exemplary embodiment, the method has a yield of about 95% or greater.

[0043] In an exemplary embodiment, the method is conducted at a temperature of between 40 and 150°C. In another exemplary embodiment, the method is conducted at a temperature of between 50 and 130°C. In an exemplary embodiment, the method is conducted at a temperature of between 60 and 110°C. In an exemplary embodiment, the method is conducted for a length of time between 2 hours and 8 hours. In another exemplary embodiment, the method is conducted for a length of time between 3 hours and 7 hours. In another exemplary embodiment, the organometallic rhodium (I) complex includes a chiral ligand selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. In another exemplary embodiment, the chiral ligand comprises an aryl substituted phosphine. In another exemplary embodiment, the chiral ligand is (R)-BINAP or (S)-BINAP.

[0044] In another exemplary embodiment, R⁶ is a member selected from substituted or unsubstituted phenyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted benzoimidazolyl, substituted or unsubstituted quinazolinyl and substituted or unsubstituted quinoxalinyl.

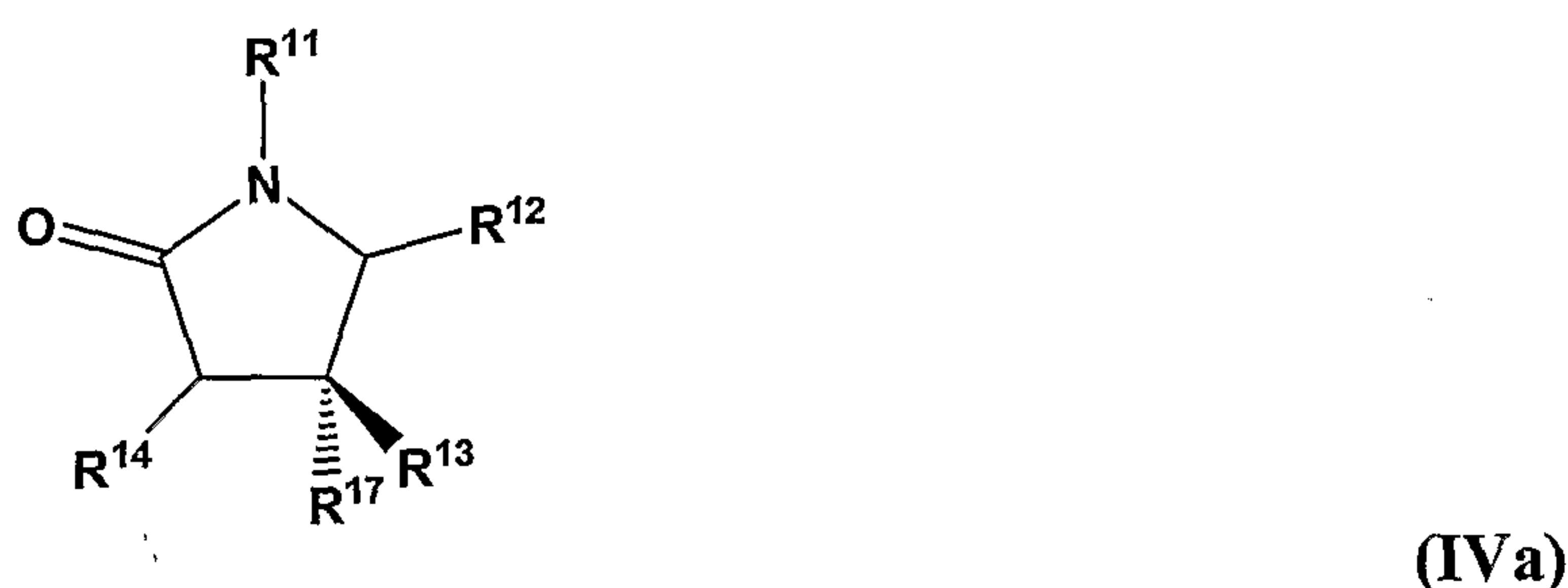
[0045] In an exemplary embodiment, R¹ is a member selected from substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In an exemplary embodiment, R¹ is substituted or unsubstituted phenyl. In an exemplary embodiment, the product can have an ee of about 80% or greater.

[0046] In an exemplary embodiment, the method can further comprise: b) purifying the mixture of step a), thus producing a product with an ee that is greater than the ee after step a). In an exemplary embodiment, the purifying can comprise subjecting the mixture to a recovery method comprising column chromatography and recrystallization.

[0047] In a second aspect, the invention provides a mixture of an amide-containing heterocycle and its enantiomer. This mixture can comprise a compound according to Formula IV:



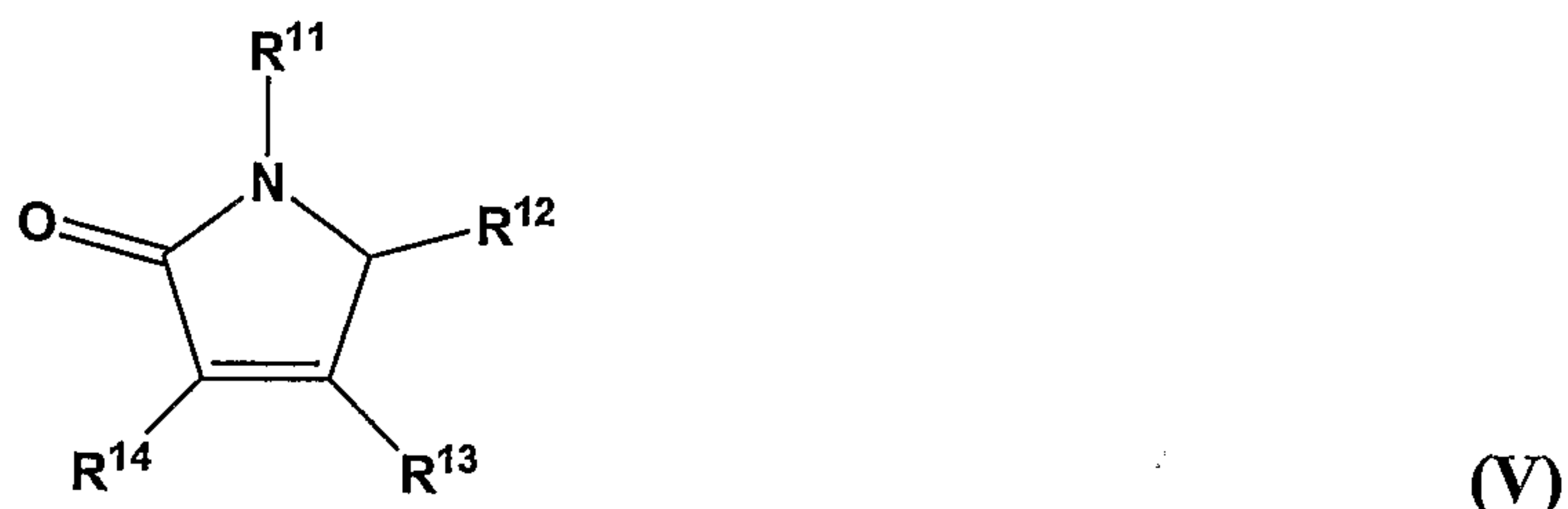
and a compound according to Formula IVa:



in which R^{11} is substituted or unsubstituted alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{12} , R^{13} , and R^{14} are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{15} , NO_2 , CN , halogen, $C(O)R^{15}$, $NR^{15}R^{16}$, $C(O)NR^{15}R^{16}$ and $C(O)OR^{15}$. R^{15} is a member selected from H and substituted or unsubstituted alkyl. R^{16} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{17} is a member selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. In an exemplary embodiment, the mixture has an ee of about 60% or greater.

[0048] In an exemplary embodiment, the mixture can be produced according to a process. This process involves contacting an organometallic rhodium (I) complex, a chiral ligand, an

α,β unsaturated N-substituted heterocycle according to Formula V under conditions sufficient to form a mixture. The α,β unsaturated N-substituted heterocycle has a formula according to Formula V:

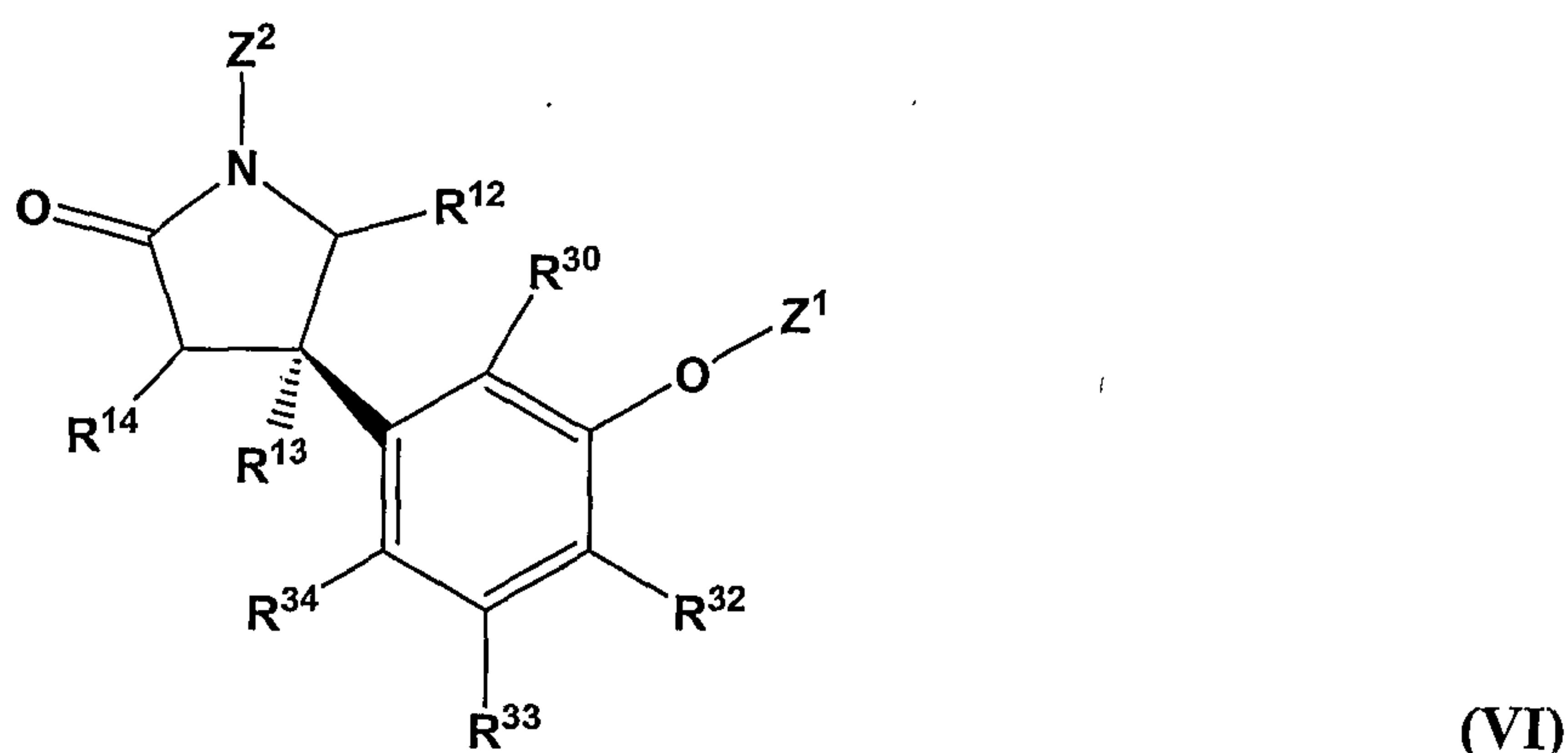


in which R^{11} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{12} , R^{13} , and R^{14} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{15} , NO_2 , CN , halogen, $C(O)R^{15}$, $NR^{15}R^{16}$, $C(O)NR^{15}R^{16}$ and $C(O)OR^{15}$. R^{15} is a member selected from H and substituted or unsubstituted alkyl. R^{16} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. The boronic ester can have a formula according to Formula II:

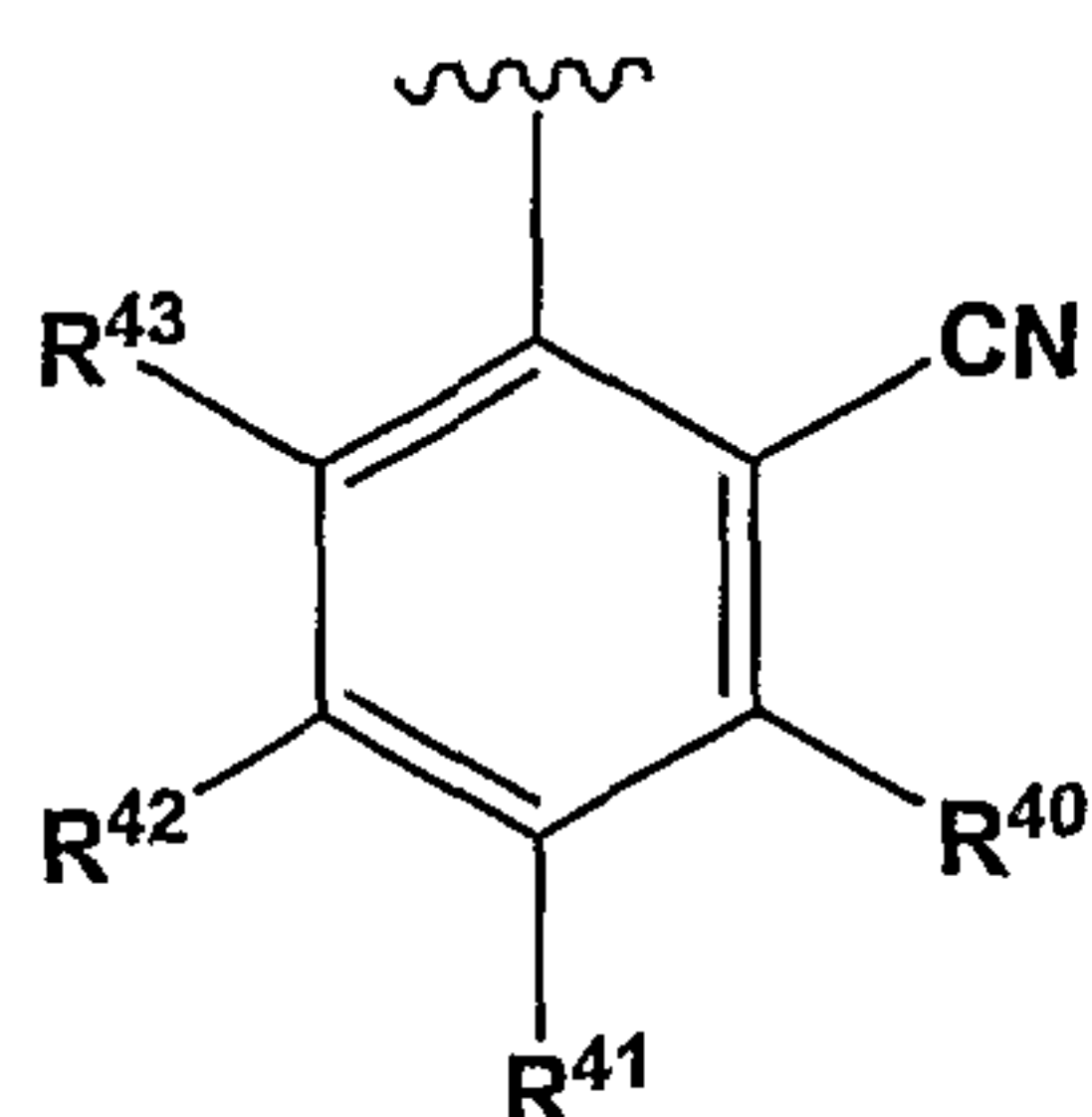


in which R^6 is substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^7 and R^8 are each independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{10} , NO_2 , CN , and halogen. R^7 and R^8 , taken together with the oxygen atoms to which they are joined, can also optionally form a substituted or unsubstituted 5- to 8-membered ring. R^{10} is H and substituted or unsubstituted alkyl. In another exemplary embodiment, R^{11} is a member selected from substituted or unsubstituted phenyl and substituted or unsubstituted benzyl. In another exemplary embodiment, R^{11} is substituted or unsubstituted phenyl.

[0049] In a third aspect, the invention provides a method of producing a compound and its enantiomer. The compound can have a structure according to Formula VI:



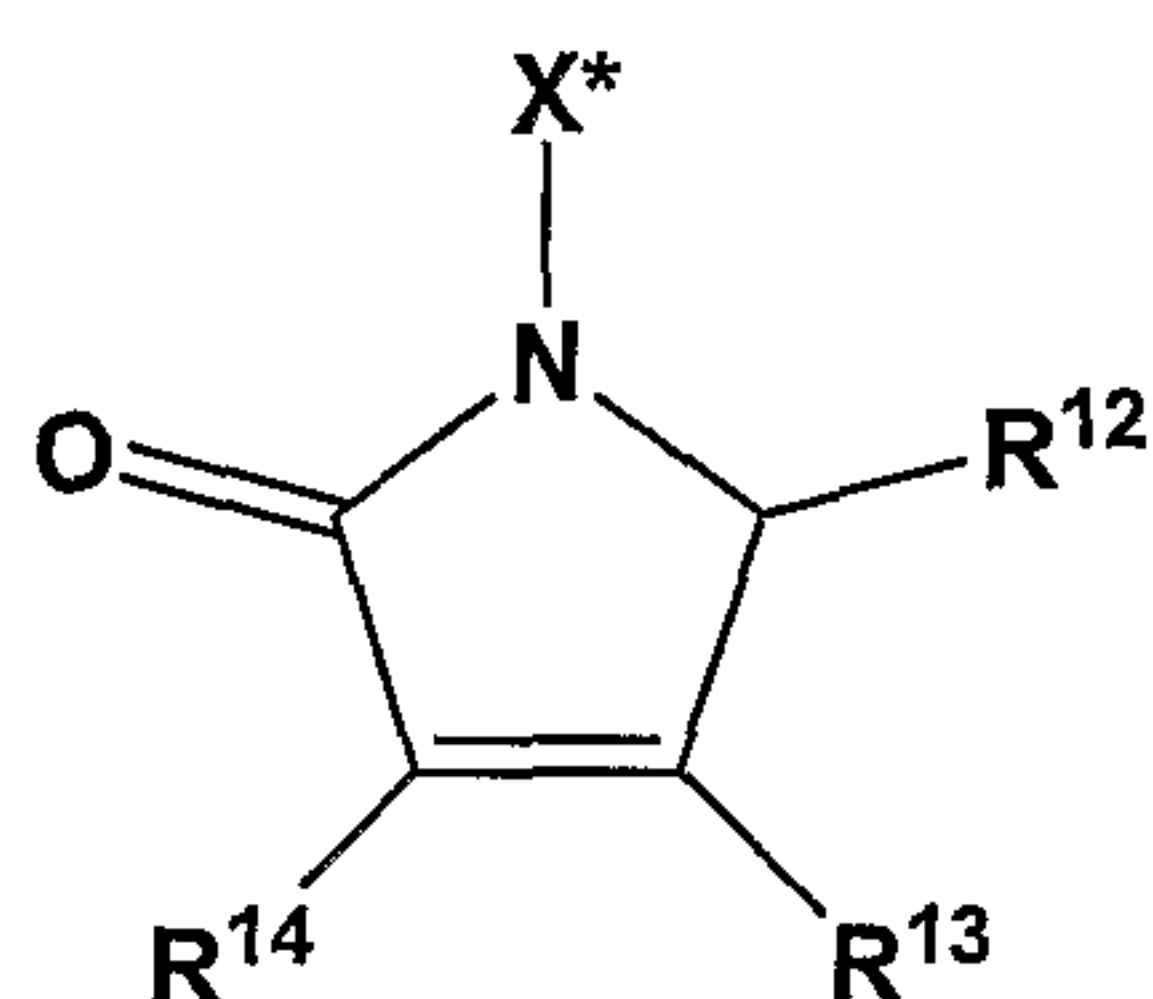
in which R^{12} , R^{13} , and R^{14} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{15} , NO_2 , CN, halogen, $C(O)R^{15}$, $NR^{15}R^{16}$, $C(O)NR^{15}R^{16}$ and $C(O)OR^{15}$. R^{15} is a member selected from H and substituted or unsubstituted alkyl. R^{16} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{30} , R^{32} , R^{33} , and R^{34} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{19} , NO_2 , CN, halogen, $C(O)R^{19}$, $NR^{19}R^{20}$, $C(O)NR^{19}R^{20}$ and $C(O)OR^{19}$. R^{33} and R^{34} or R^{33} and R^{32} or R^{32} and Z^1 together with the atoms to which they are attached form at least a 5-membered ring selected from substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. R^{19} is a member selected from H, substituted or unsubstituted aryl and substituted or unsubstituted alkyl. R^{20} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. Z^1 is a moiety according to Formula VII:



(VII)

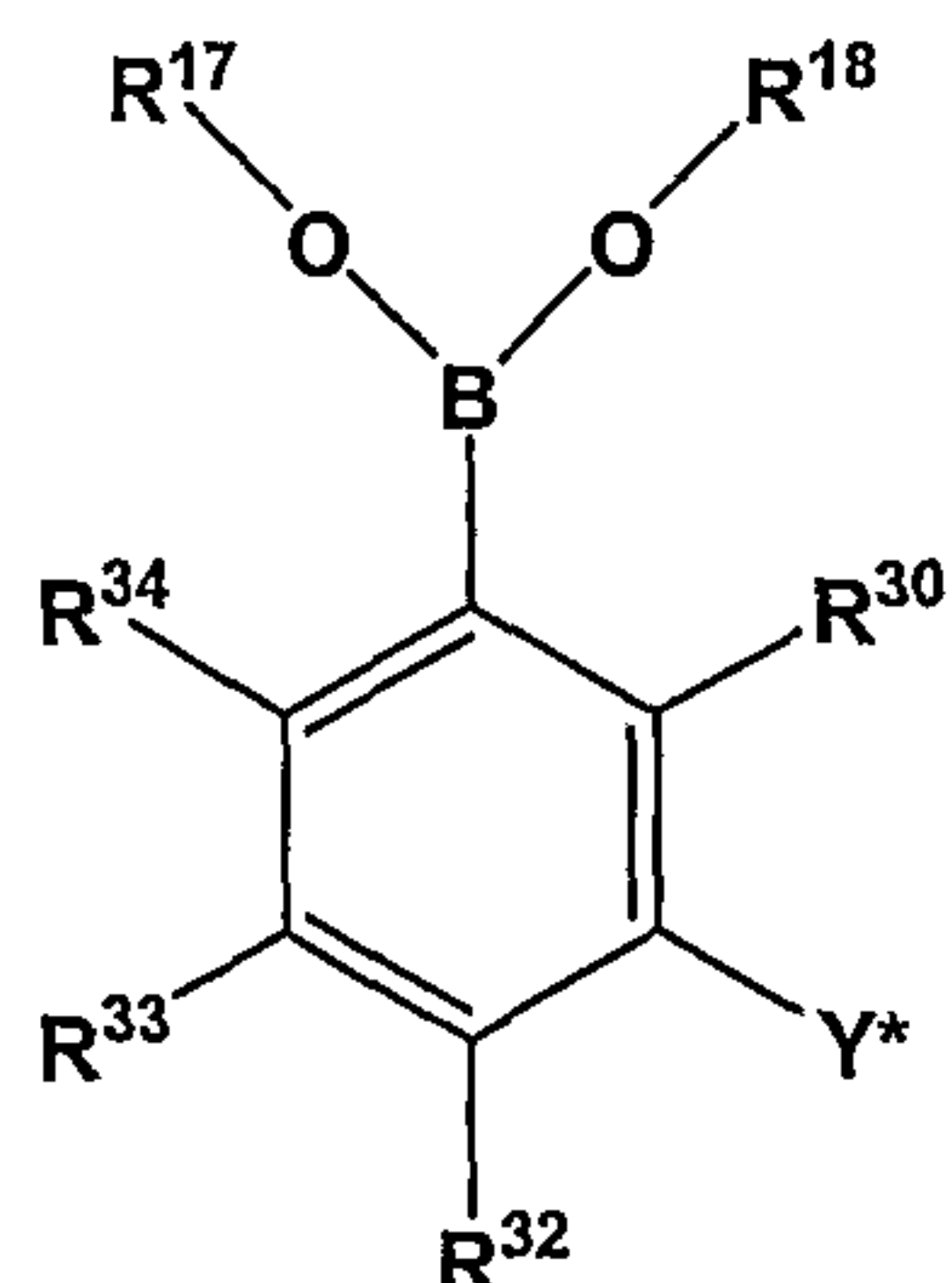
in which R^{40} , R^{41} , and R^{42} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted-aryl, substituted or unsubstituted heteroaryl, OR^{44} , NO_2 , CN, and halogen. R^{44} is a member selected from H and substituted or unsubstituted alkyl. R^{43} is halogen. Z^2 is a member selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl.

[0050] The method comprises: a) contacting an organometallic rhodium (I) complex, a chiral ligand, an α,β unsaturated amide-containing heterocycle, and a boronic ester under conditions sufficient to form a mixture comprising an amide-containing heterocycle according to Formula IX and its enantiomer, wherein the mixture has an ee of about 60% or greater. The α,β unsaturated N-substituted heterocycle according to Formula VIII:



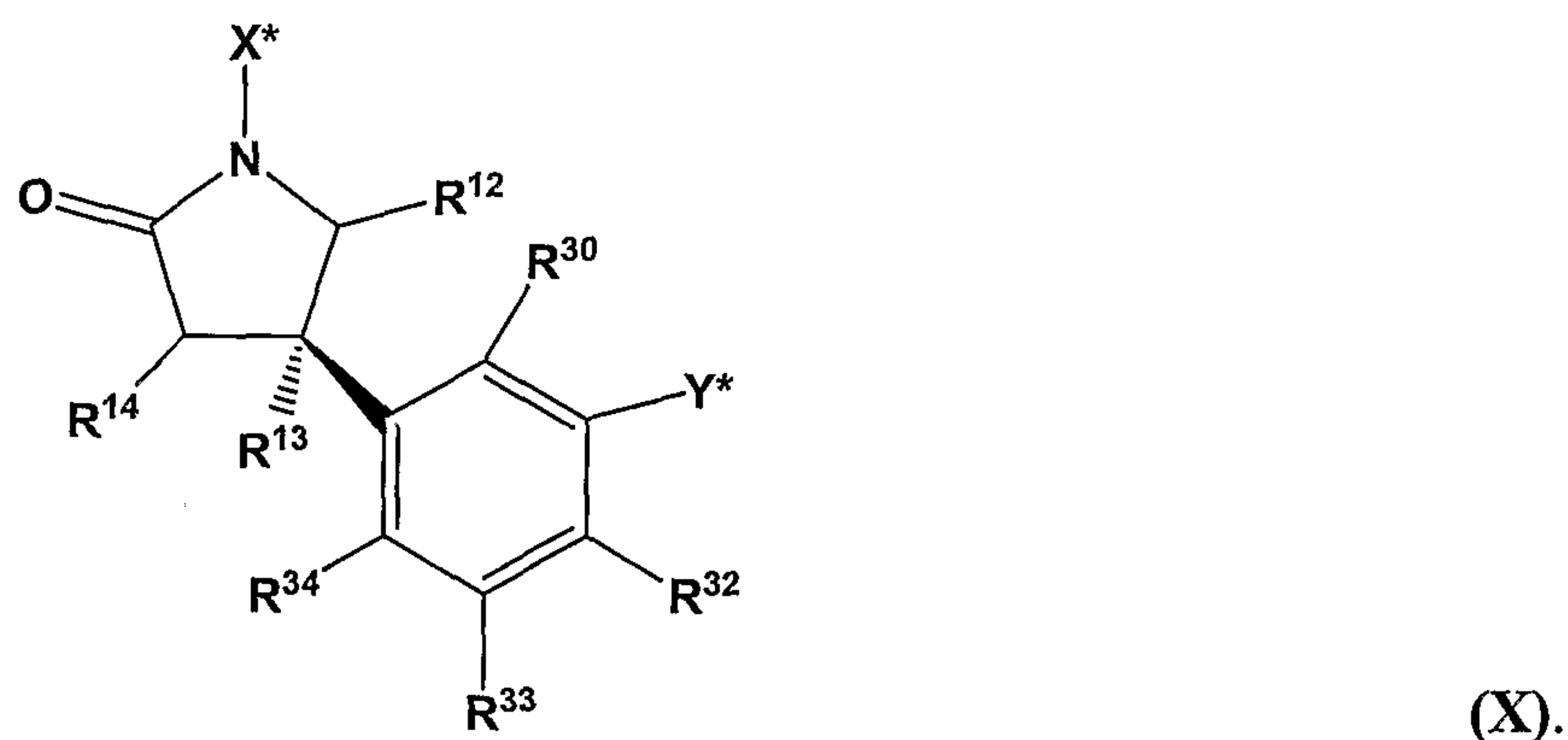
(VIII)

in which X^* is a protecting group. R^{12} , R^{13} , and R^{14} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{25} , NO_2 , CN, and halogen. The boronic ester can have a formula according to Formula IX:

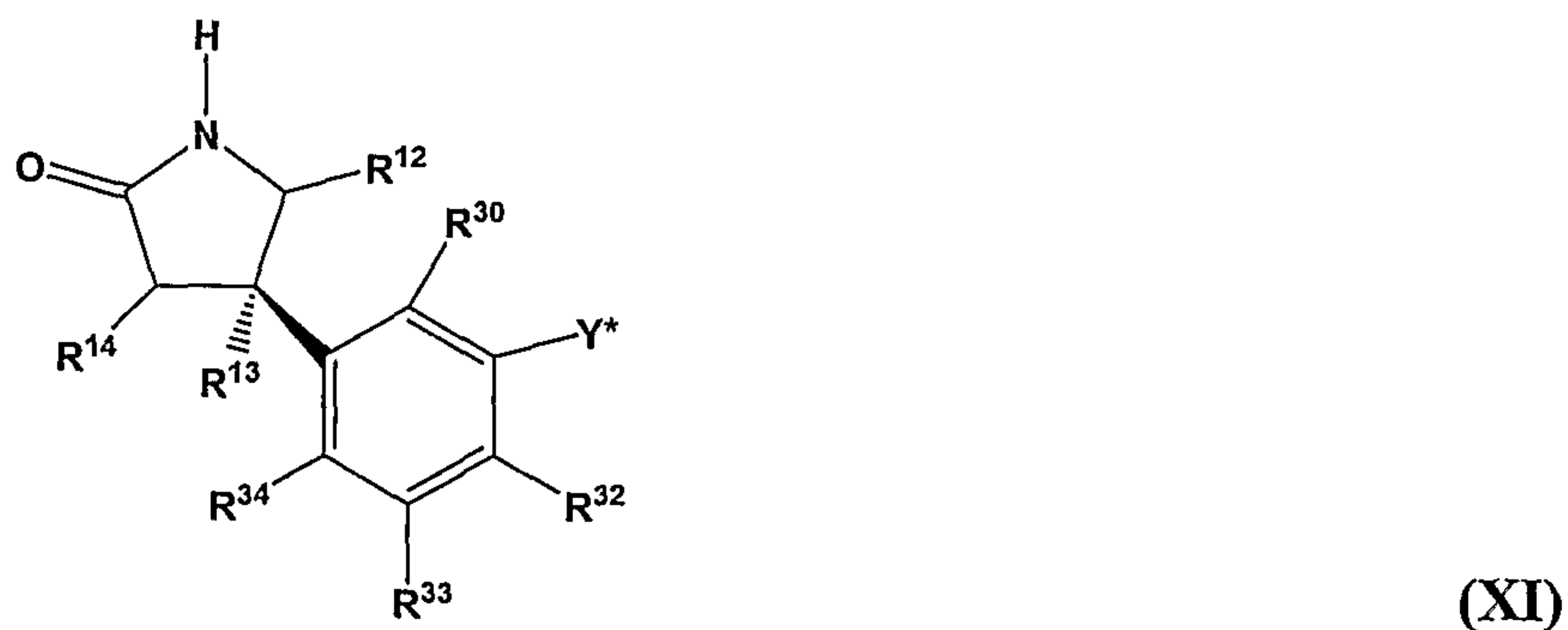


(IX)

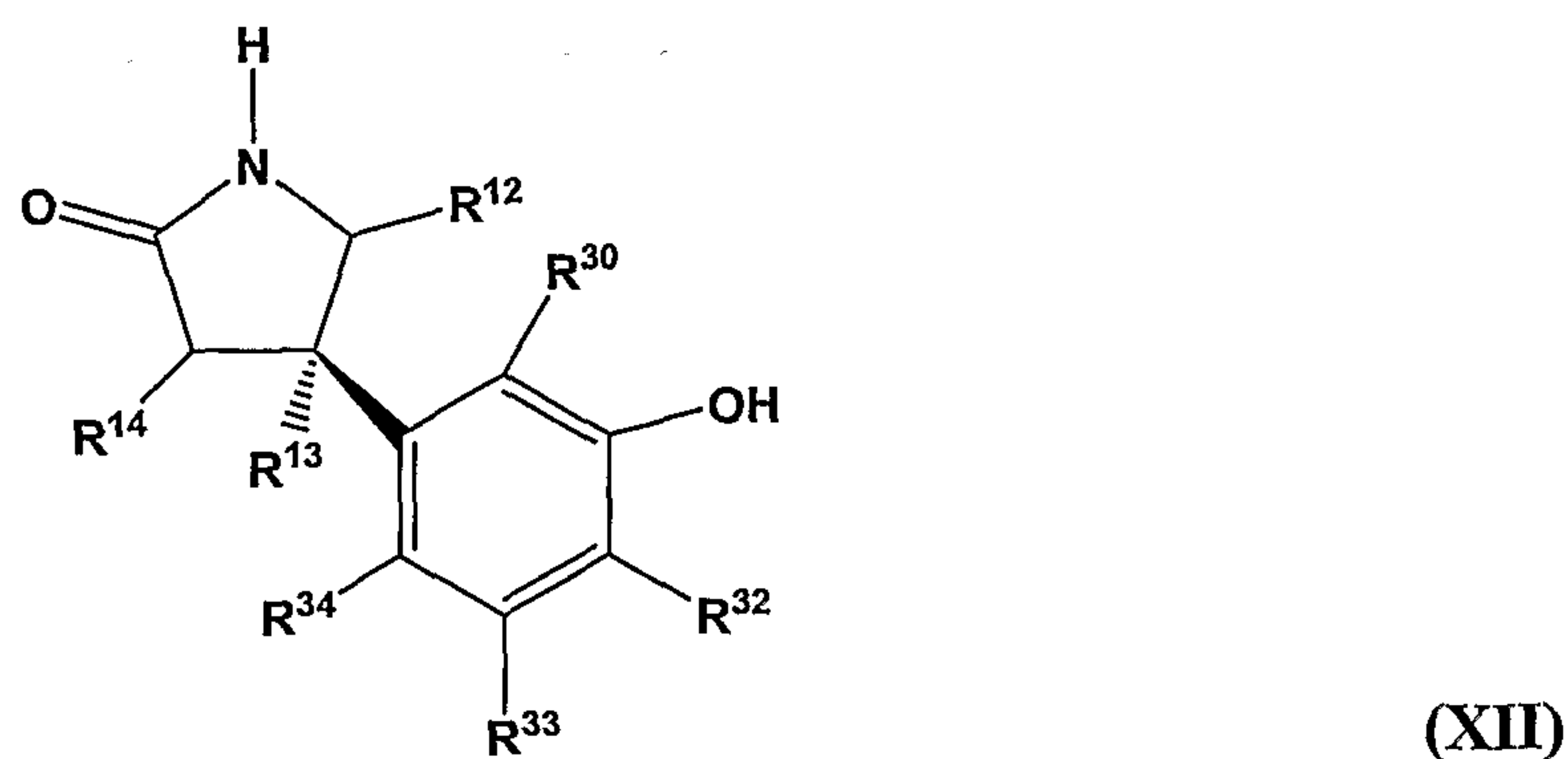
R^{30} , R^{32} , R^{33} , and R^{34} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{19} , NO_2 , CN, and halogen. Y^* is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{19} , NO_2 , CN, and halogen. R^{17} and R^{18} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R^{17} and R^{18} , taken together with the oxygen atoms to which they are joined, optionally form a substituted or unsubstituted 4- to 8-membered ring. R^{19} is a member selected from H, substituted or unsubstituted aryl and substituted or unsubstituted alkyl. The amide-containing heterocycle has a formula according to Formula X:



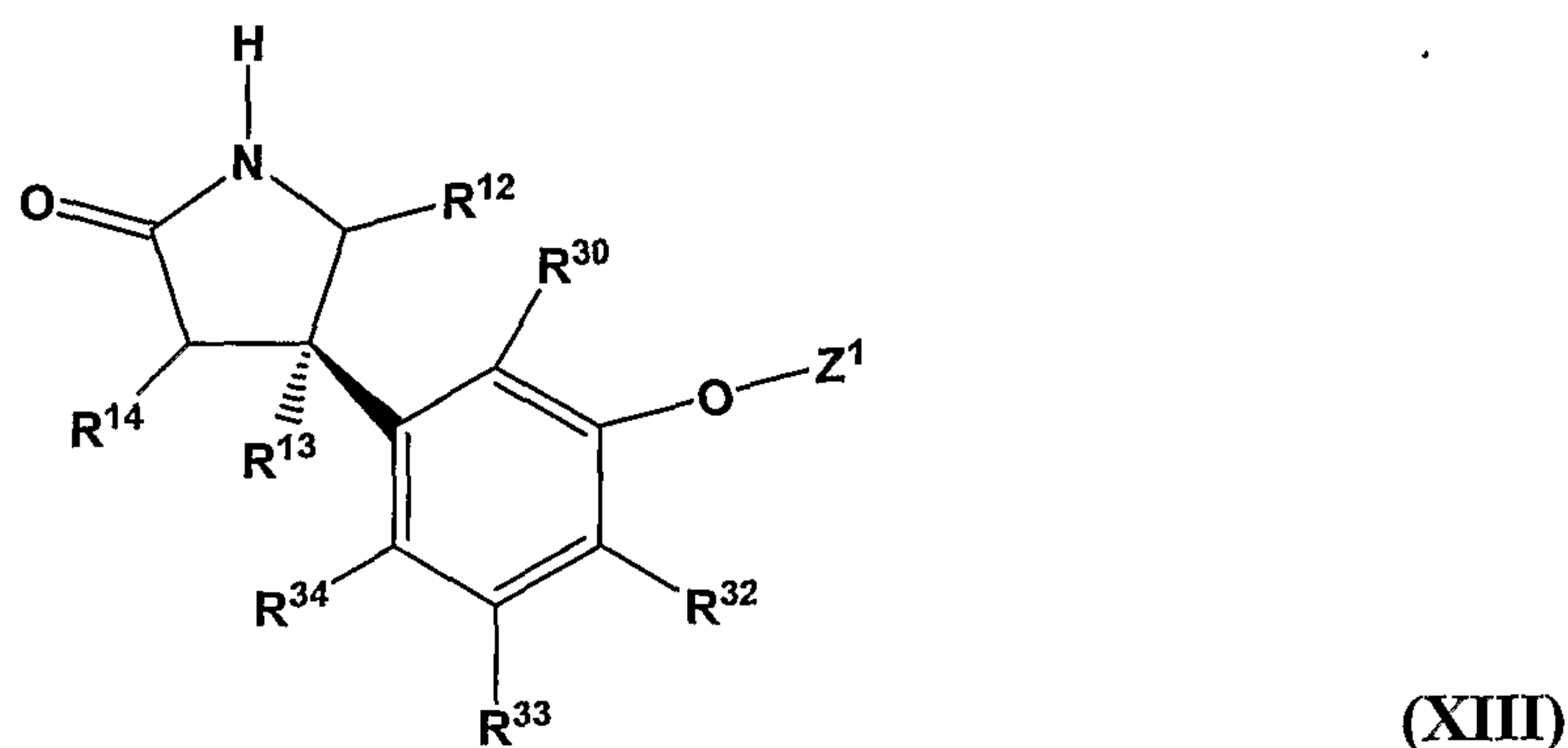
The method further comprises: b) subjecting the product of step a) to a deprotection reaction removing X^* , producing a compound according to Formula XI:



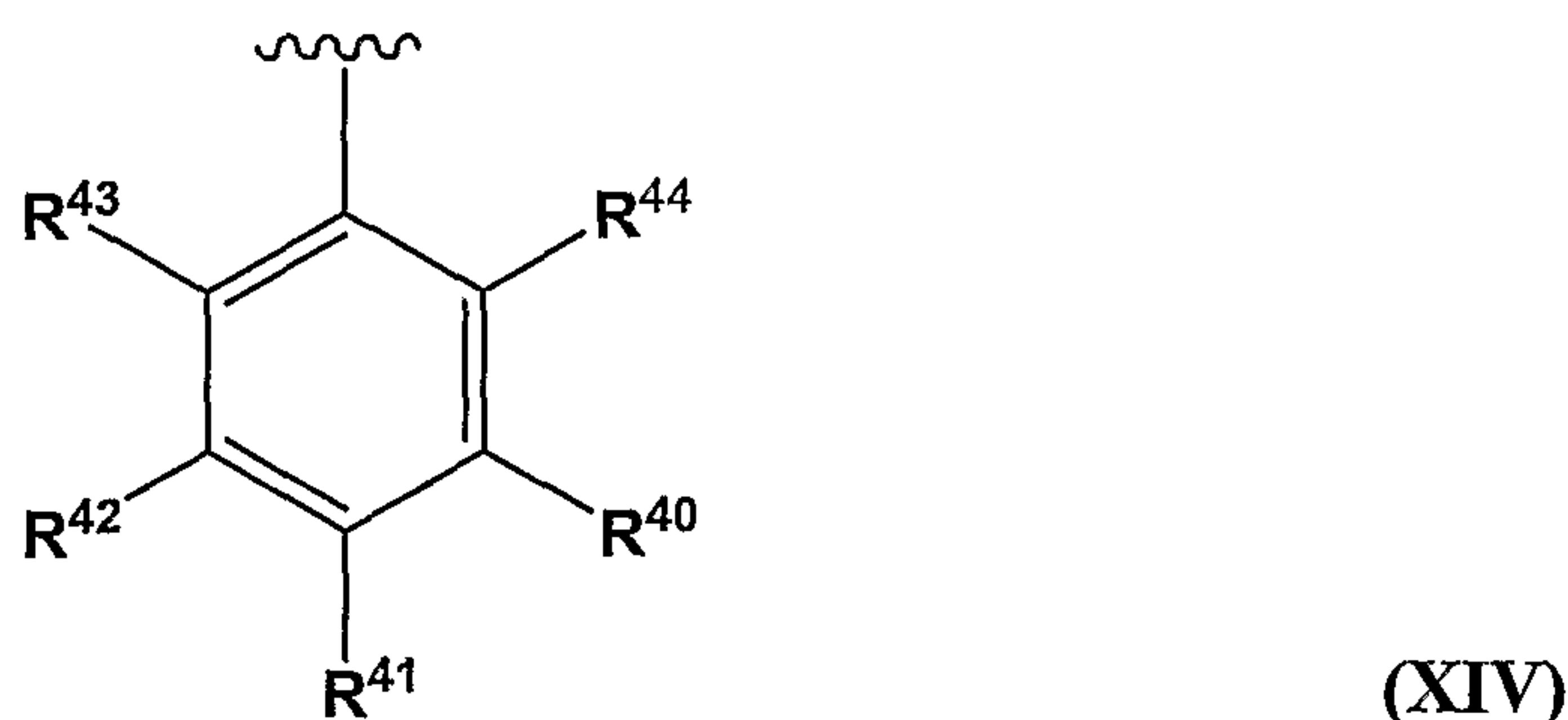
and its enantiomer. The method further comprises: c) subjecting the product of step b) to a deprotection reaction removing Y*, producing a compound according to Formula XII:



and its enantiomer. The method further comprises: d) subjecting the product of step c) to an arylation reaction, producing a compound according to Formula XIII:

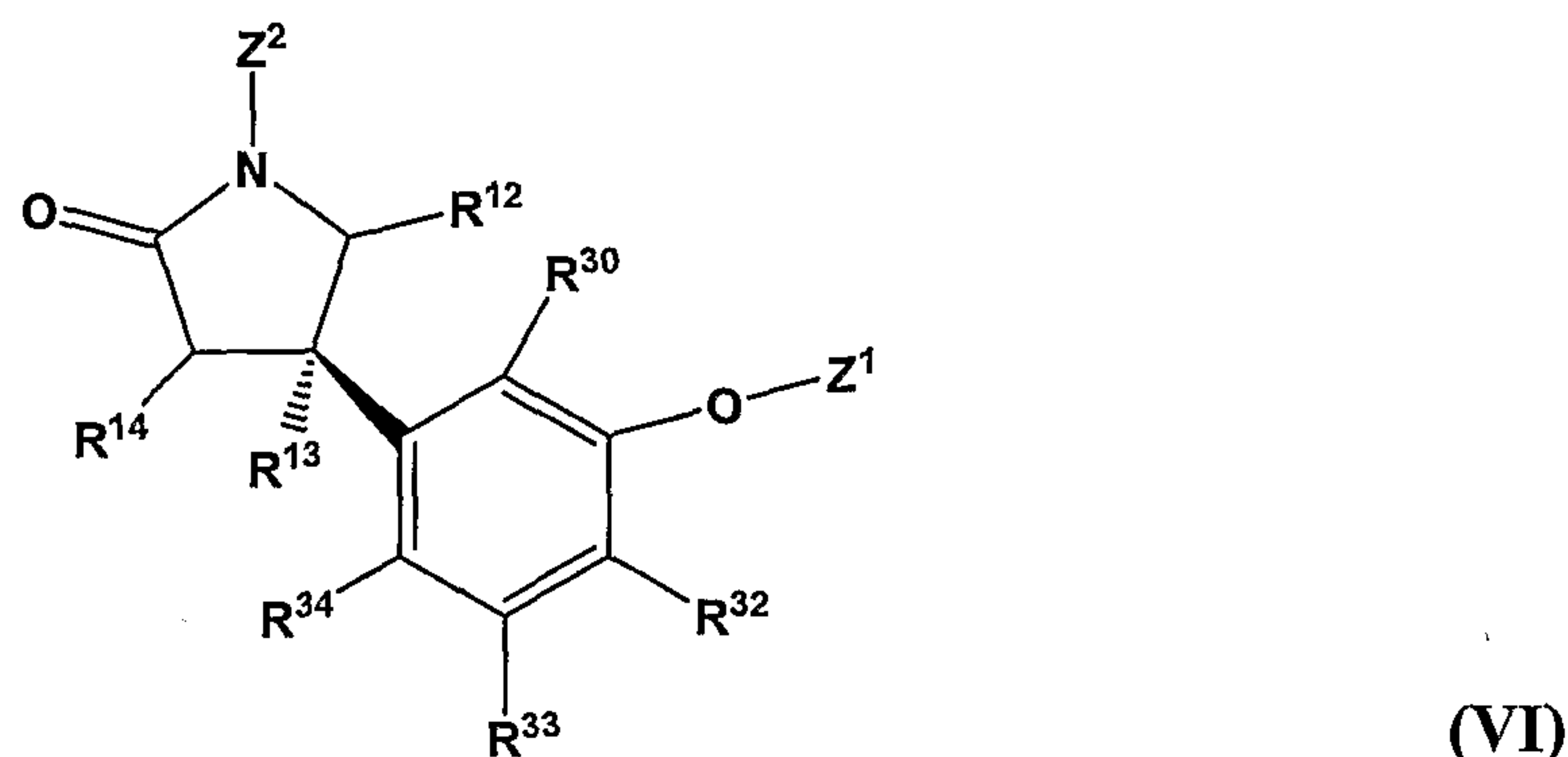


and its enantiomer. Z¹ is a moiety according to Formula XIV:



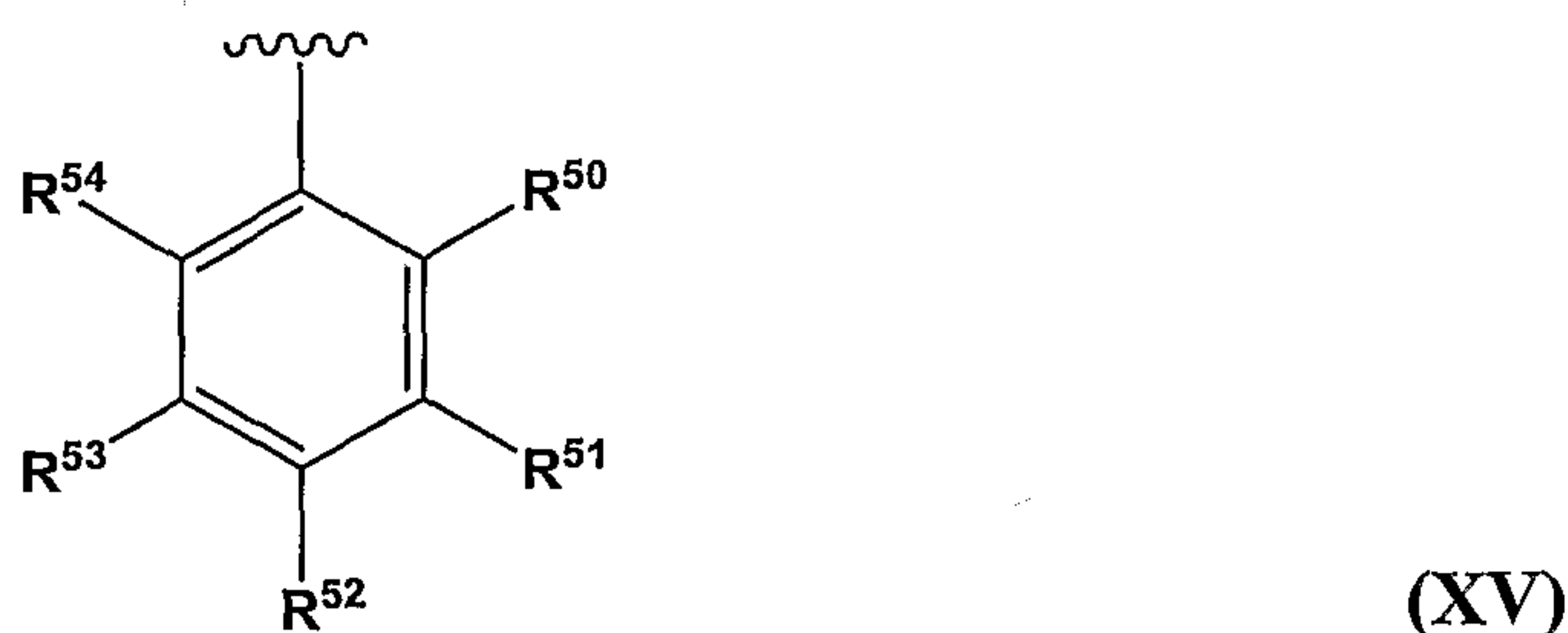
in which R⁴⁰, R⁴¹, R⁴², R⁴³, and R⁴⁴ are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR⁴⁶, NO₂, CN, halogen, C(O)R⁴⁶, NR⁴⁶R⁴⁷, C(O)NR⁴⁶R⁴⁷ and C(O)OR⁴⁶. R⁴⁶ is a member selected from H and substituted or unsubstituted alkyl. R⁴⁷ is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or

unsubstituted heteroaryl. The method further comprises: e) arylating the lactam nitrogen of the product of step d), producing a compound according to Formula VI:



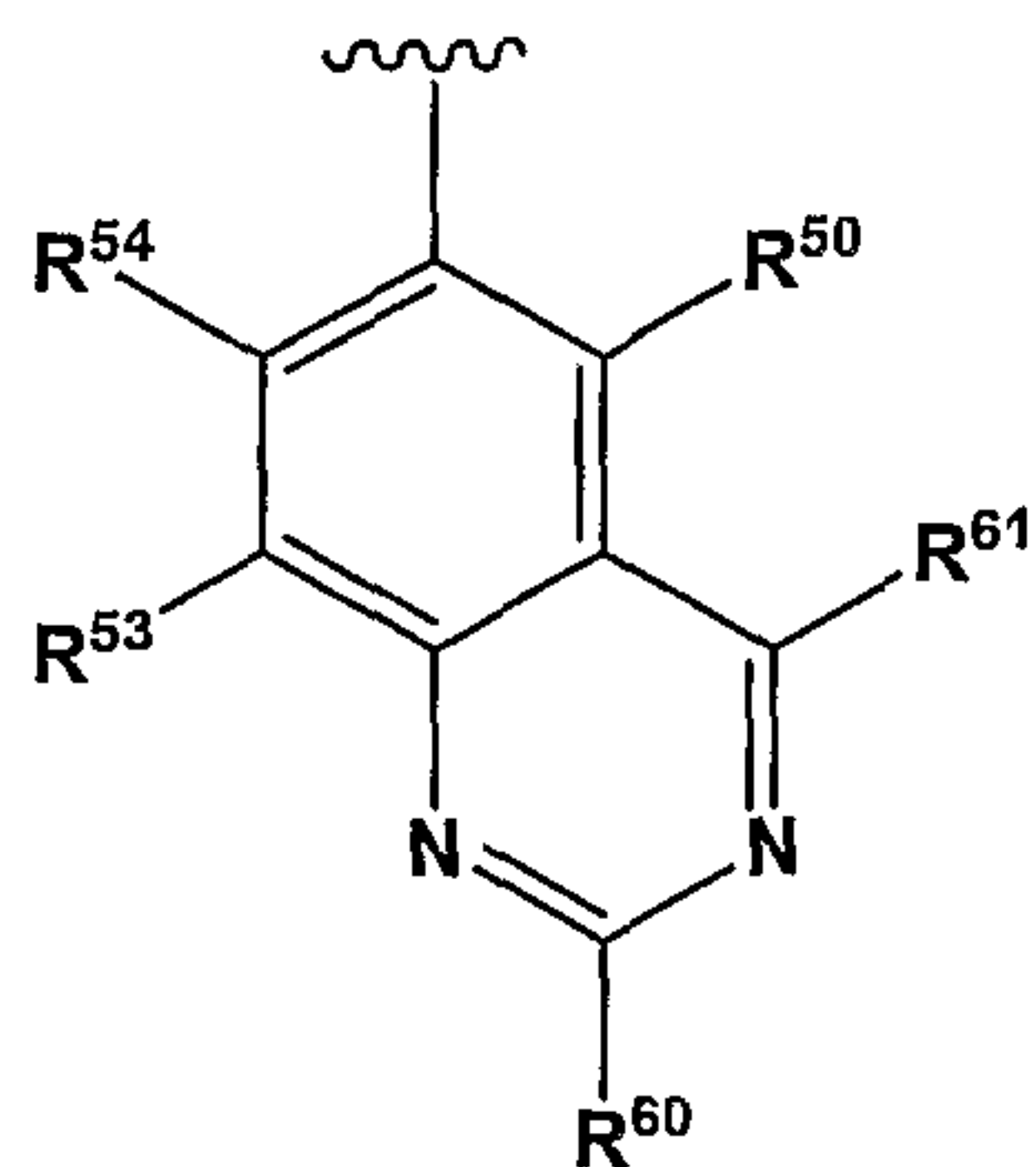
and its enantiomer. Z^2 is a member selected from substituted or unsubstituted-aryl, substituted or unsubstituted heteroaryl, thereby producing a compound having the formula according to Formula VI.

[0051] In an exemplary embodiment, Z^2 is a moiety according to Formula XV:

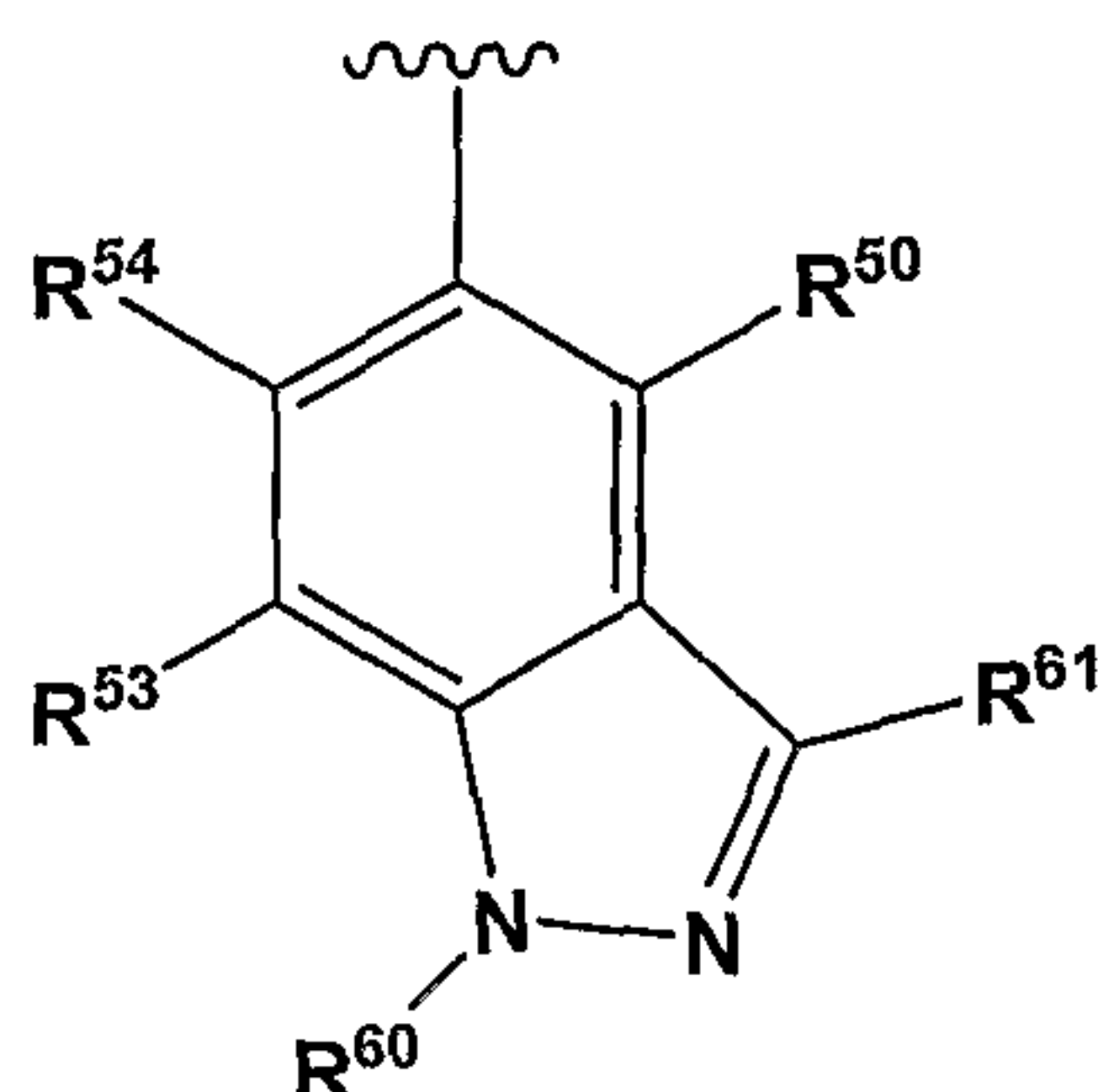


R^{50} , R^{51} , R^{52} , R^{53} and R^{54} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{55} , $SO_2NR^{55}R^{56}$, $CONR^{55}R^{56}$, $NR^{55}R^{56}$, NO_2 , CN, and halogen; and any two of R^{50} , R^{51} , R^{52} , R^{53} and R^{54} , taken together with the atoms to which they are joined, optionally form a substituted or unsubstituted 5- to 8- membered ring. R^{55} is a member selected from H and substituted or unsubstituted alkyl. R^{56} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. In another exemplary embodiment, R^{32} is halogen. In another exemplary embodiment, R^{30} , R^{33} , and R^{34} are H. In another exemplary embodiment, R^{40} , R^{41} , and R^{42} are H. In another exemplary embodiment, R^{51} and R^{52} , taken together with the atoms to which they are joined, can optionally form a substituted or unsubstituted 6-membered ring. In another exemplary

embodiment, Z^2 is a member selected from a moiety according to Formula XVI and a moiety according to Formula XVII:

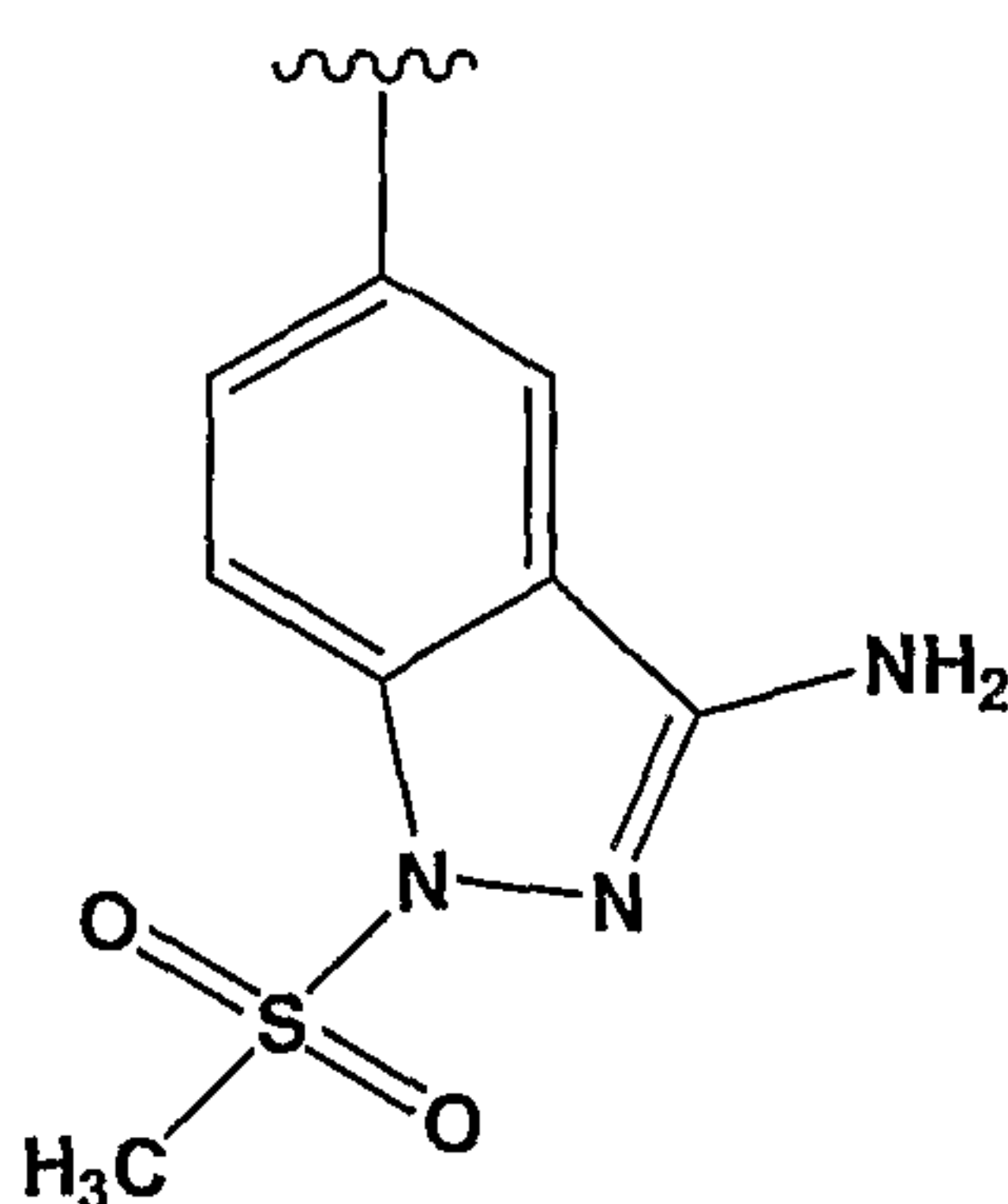


(XVI)



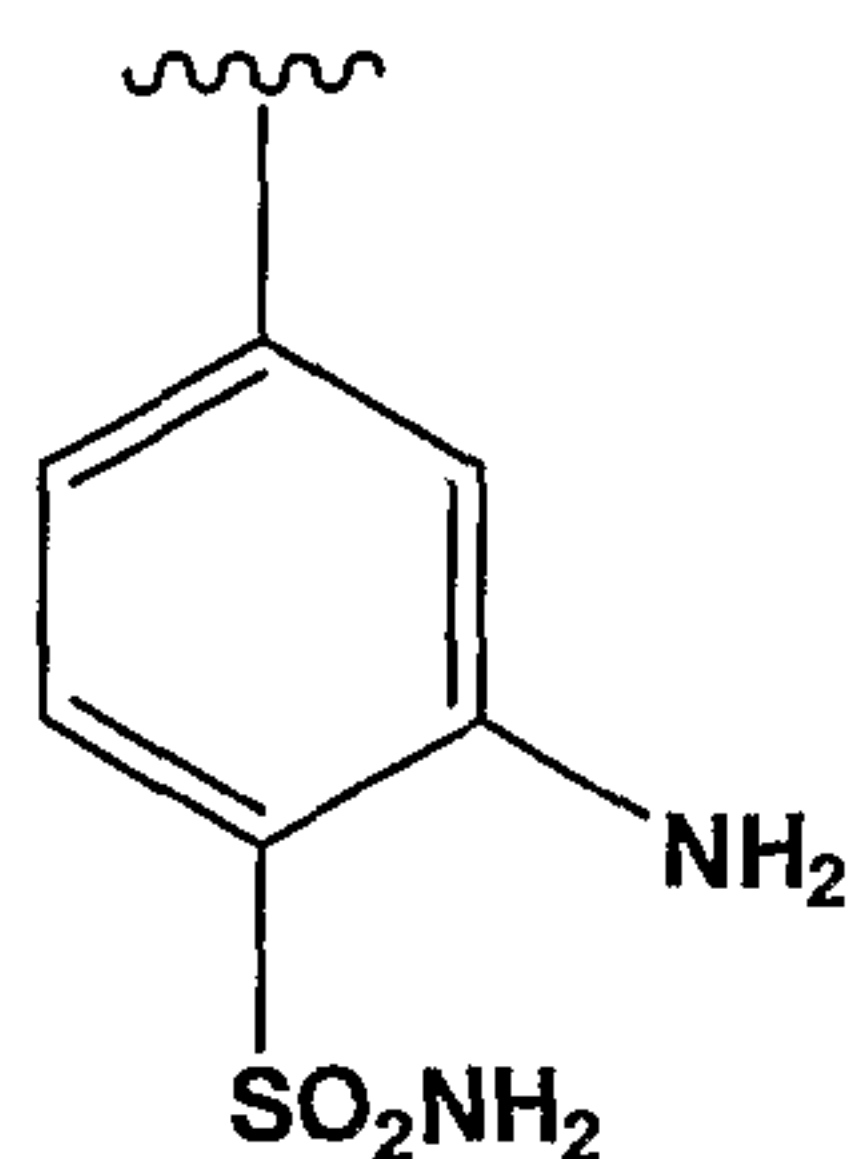
(XVII)

in which R^{60} and R^{61} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{62} , NO_2 , CN , $NR^{62}R^{63}$, $S(O)_2NR^{62}R^{63}$, $NR^{62}S(O)_2R^{63}$, $C(O)NR^{62}R^{63}$, $S(O)_2R^{62}$ and halogen. R^{62} is a member selected from H and substituted or unsubstituted alkyl. R^{63} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl. In an exemplary embodiment, Z^2 is a moiety according to Formula XVIII:



(XVIII).

In another exemplary embodiment, Z^2 is a moiety according to Formula XIX:



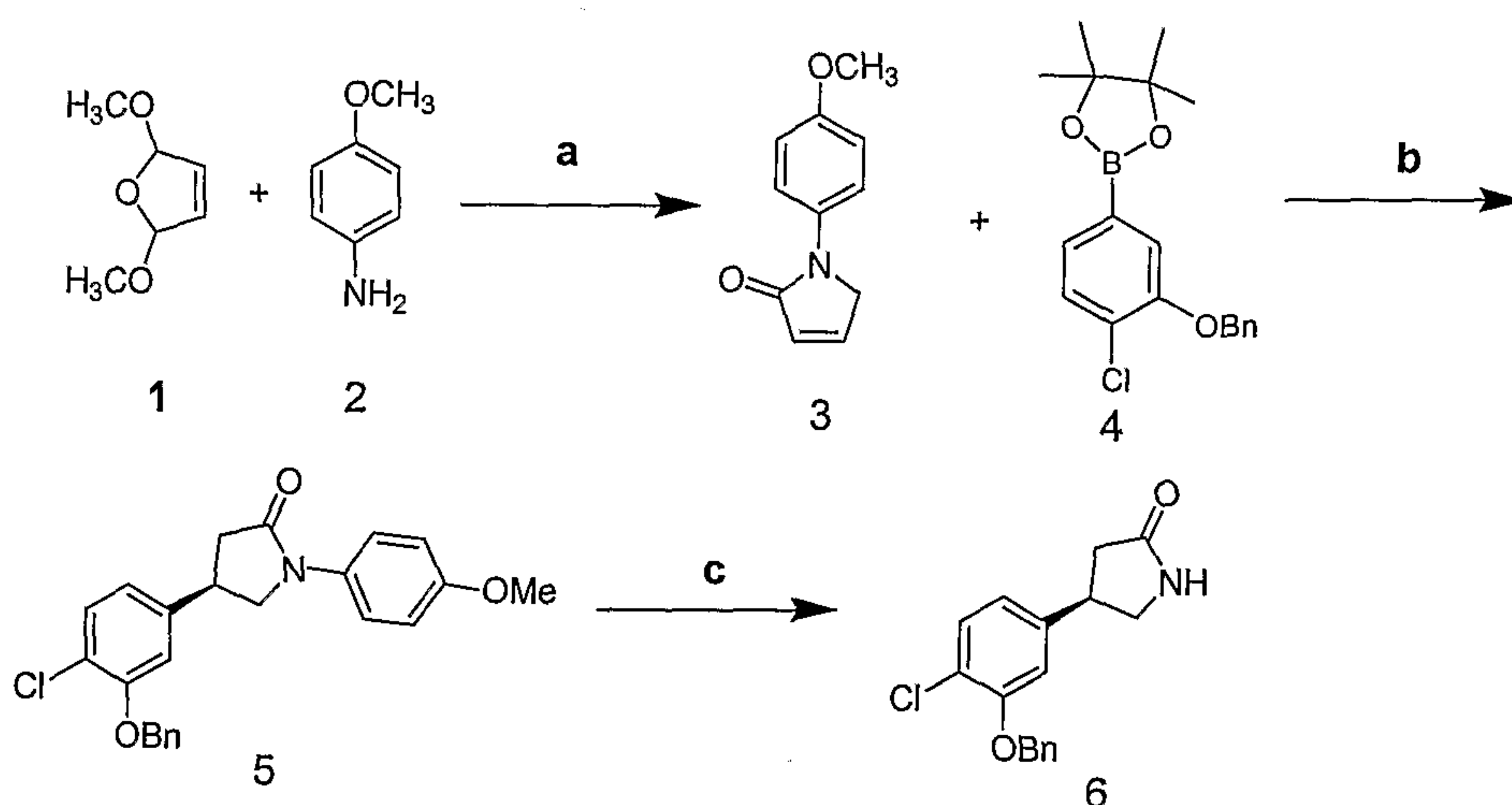
(XIX).

III. Reaction Conditions for the Methods

[0052] The discussion below is offered to illustrate certain of the diverse methods available for use in assembling the compounds and mixtures of the invention, it is not intended to define the scope of reactions or reaction sequences that are useful in preparing the compounds of the present invention.

[0053] The compounds utilized in this invention are synthesized according to Scheme 1.

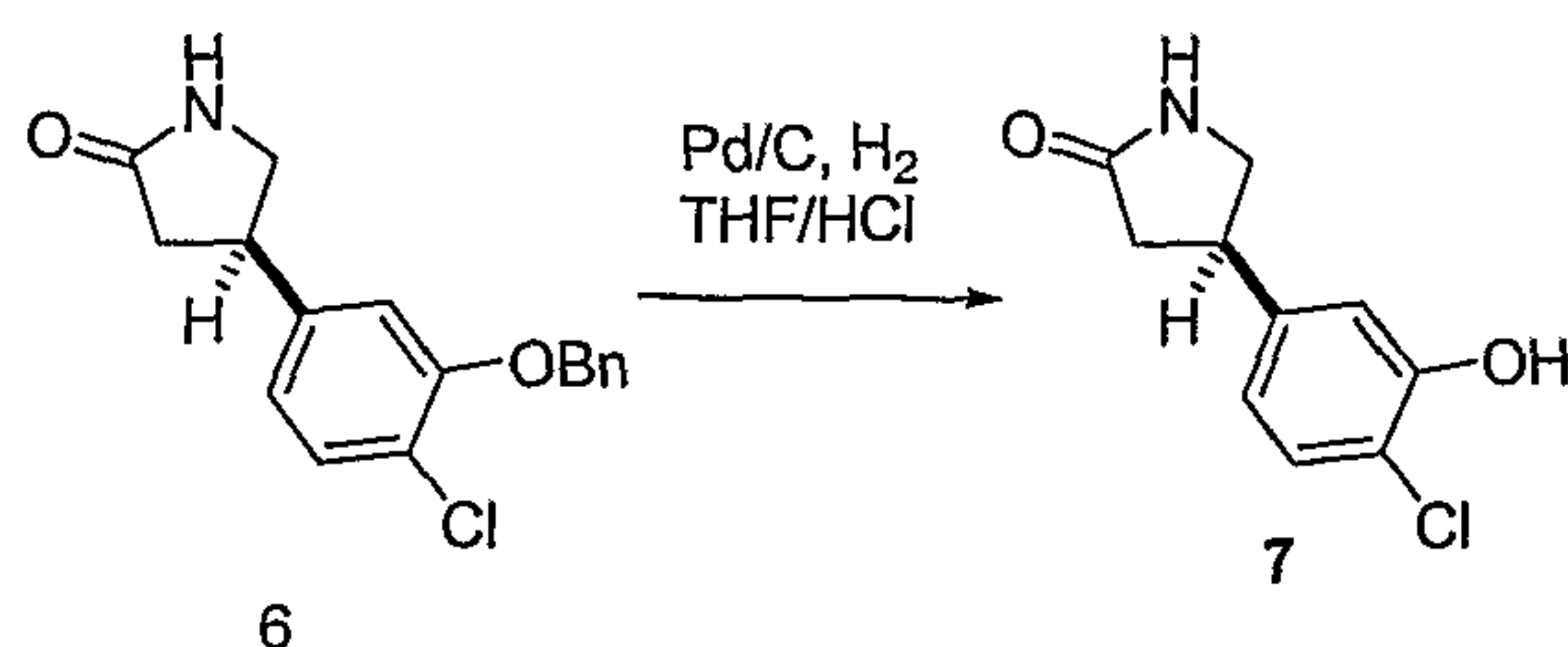
Scheme 1



Reagents and conditions: a) CH_3CN , 0.4N HCl, rt, 1 h; b) Rh(cat), (R)-BINAP, K_2CO_3 , Dioxane/ H_2O , 80C, 6 h; c) CAN, CH_3CN/H_2O OC 4 h.

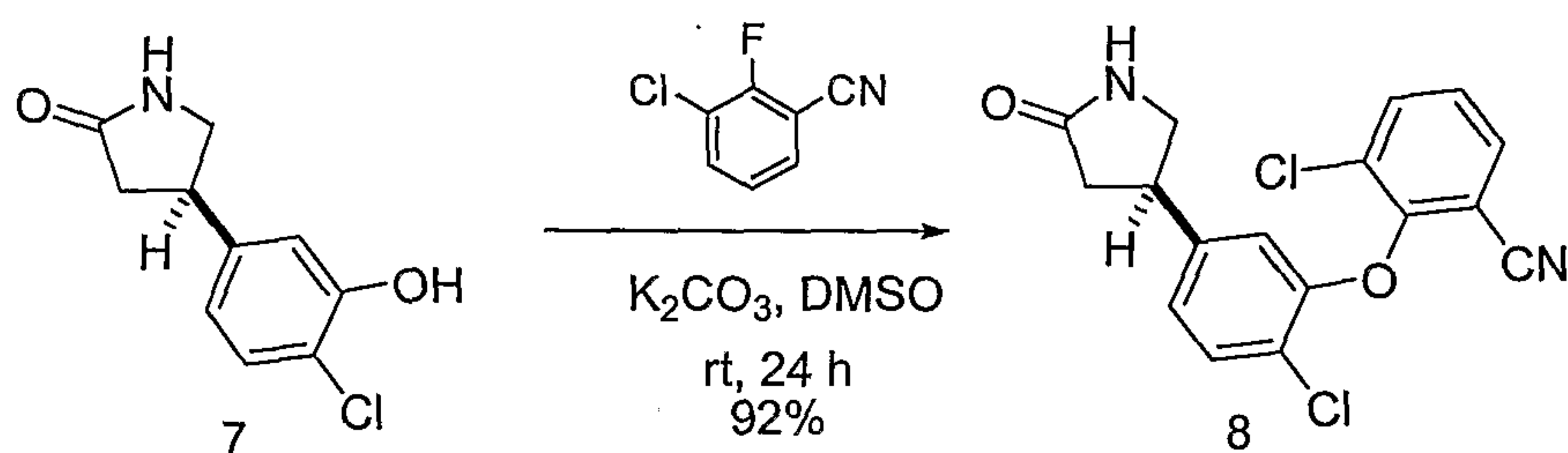
[0054] In the first step of Scheme 1, compounds 1 and 2 can be reacted under the conditions of step a in order to form compound 3. Compound 4 can be synthesized by mixing an aryl moiety and borate with a palladium catalyst. Compounds 3 and 4 can be reacted under the conditions of step b in order to form compound 5. Finally, the pyrrolidone nitrogen can be deprotected under the conditions of step c in order to form compound 6.

[0055] Another reaction involved in the methods of the invention is a deprotection reaction. In an exemplary embodiment, a protecting group is removed as shown in Scheme 2.

Scheme 2

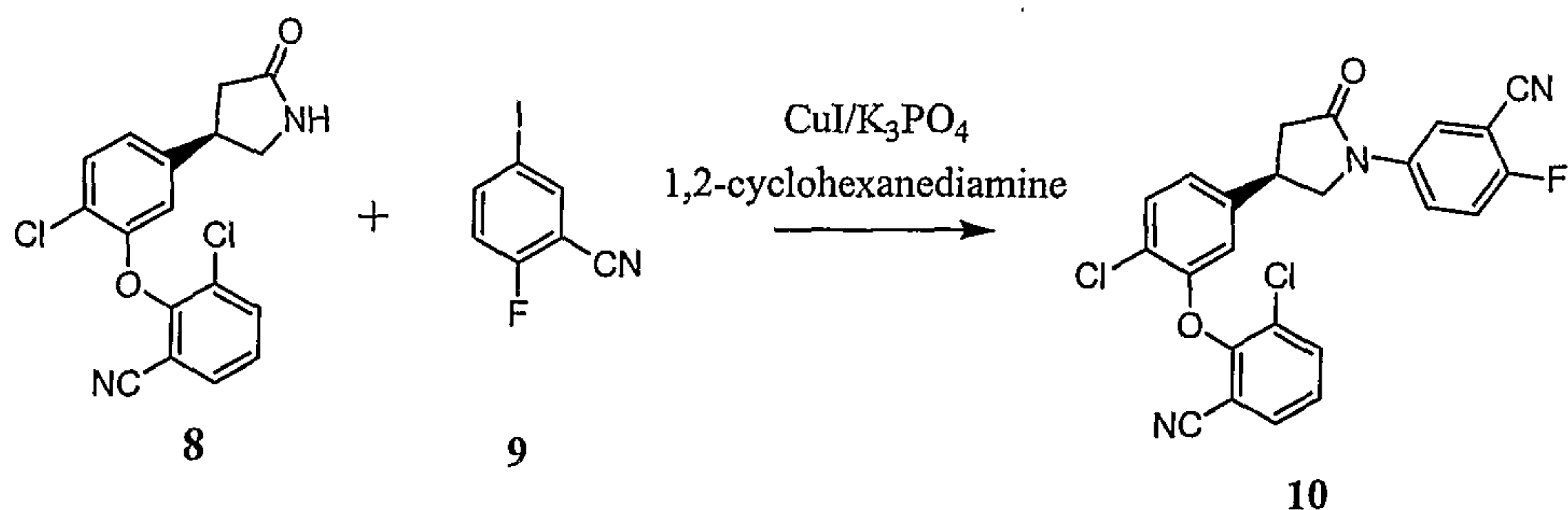
[0056] In Scheme 2, compound 6 is reacted with a palladium catalyst in order to remove the benzyl protecting group and produce compound 7.

[0057] Another reaction involved in the methods of the invention is an arylation reaction. In an exemplary embodiment, an aryl moiety is added as shown in Scheme 3.

Scheme 3

[0058] In Scheme 3, compound 7 is reacted with an aryl moiety and base in order to produce compound 8.

[0059] Another reaction involved in the methods of the invention is the attachment of an aryl moiety to the lactam nitrogen. In an exemplary embodiment, an aryl moiety is added as shown in Scheme 4.

Scheme 4

[0060] In Scheme 4, compound 8 is reacted with an aryl moiety 9 under the reaction conditions mentioned above in order to produce compound 10.

[0061] The compounds of the invention are synthesized by an appropriate combination of generally well known synthetic methods. Techniques useful in synthesizing the compounds of the invention are both readily apparent and accessible to those of skill in the relevant art.

[0062] While this invention has been disclosed with reference to specific embodiments, it is apparent that other embodiments and variations of this invention may be devised by others skilled in the art without departing from the true spirit and scope of the invention.

EXAMPLES

General

[0063] In the examples below, unless otherwise stated, temperatures are given in degrees Celsius ($^{\circ}\text{C}$); operations were carried out at room or ambient temperature, "rt," or "RT," (typically a range of from about 18-25 $^{\circ}\text{C}$; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (typically, 4.5-30 mm Hg) with a bath temperature of up to 60 $^{\circ}\text{C}$; the course of reactions was typically followed by thin layer chromatography (TLC) and reaction times are provided for illustration only; melting points are uncorrected; products exhibited satisfactory ^1H -NMR and/or microanalytical data; yields are provided for illustration only; and the following conventional abbreviations are also used: mp (melting point), L (liter(s)), mL (milliliters), mmol (millimoles), g (grams), mg (milligrams), min (minutes), and h (hours).

[0064] Unless otherwise specified, all solvents (HPLC grade) and reagents were purchased from suppliers and used without further purification. Reactions were conducted under a blanket of argon unless otherwise stated. Analytical TLC was performed on Whatman Inc. 60 silica gel plates (0.25 mm thickness). Compounds were visualized under UV lamp (254 nm) or by developing with KMnO_4/KOH , ninhydrin or Hanessian's solution. Flash chromatography was done using silica gel from Selectro Scientific (particle size 32-63). ^1H NMR, ^{19}F NMR and ^{13}C NMR spectra were recorded on a Varian 300 machine at 300 MHz, 282 MHz and 75.7 MHz, respectively. Melting points were recorded on an Electrothermal IA9100 apparatus and were uncorrected.

EXAMPLE 1

Preparation of 6

1.1 Synthesis of 3

[0065] To a solution of *p*-anisidine **2** (18.48 g, 0.15 mol, 1 eq) and 2,5-dimethoxy-2,5-dihydrofuran, **1** (39.04 g, 0.3 mol, 2 eq) in acetonitrile (750 mL) was added a solution of 0.4 N aq HCl (600 mL). The reaction mixture was stirred at rt for 1 h, quenched with NaHCO₃ (40.32 g, 0.48 mol, 2 eq to HCl), concentrated under reduced pressure at 27 °C and partitioned between EtOAc and H₂O. The aqueous phase was extracted with EtOAc and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated. The crude residue was purified by column chromatography with hexanes:EtOAc (1:1) to give 1-(4-Methoxy-phenyl)-1,5-dihydro-pyrrol-2-one, **3** (10.85 g, 38%).

1.2 Results

[0066] Analytical data for structure **3** is provided below.

1.2.a 1-(4-Methoxy-phenyl)-1,5-dihydro-pyrrol-2-one

[0067] ¹H NMR (CDCl₃): δ 7.57 (2 H, d, J = 9.2 Hz), 7.14 (1H, dt, J = 0.8, 6.0 Hz), .6.92 (2 H, d, J = 9.2 Hz), 6.26 (1 H, dt, J = 0.8, 6.0), 4.40 (2 H, t, J = 1.6), 3.80 (3 H, s) ppm.

1.3 Synthesis of 4

[0068] A mixture of 2-benzyloxy-4-bromo-1-chloro-benzene (120 g, 0.4 mol), diborate (107.5 g, 0.42 mol), KOAc (117.8 g, 3 eq), Pd(dppf)₂Cl₂ (1% mole) and 500 mL DMF was degassed, with stirring, and recharged with nitrogen. The mixture was heated to 80°C for 3 h. DMF was removed *in vacuo*, resulting in the formation of a residue. The residue was mixed with ethyl acetate and then filtered. After filtration, the solid was washed with ethyl acetate (3x20 mL) and re-crystallized in ethyl acetate to give 97 g of pure product. The mother solution was also concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexane) to give crude product, which is re-crystallized in ethyl acetate. Product was 2-(4-chloro-3-benzyloxy-phenyl)-4,4,5,5,-tetramethyl[1,3,2]dioxaborolane, **4**.

1.4 Results

[0069] Analytical data for structure **4** is provided below.

1.4.a (4-Chloro-3-benzyloxy-phenyl)-4,4,5,5,-tetramethyl[1,3,2]dioxaborolane

[0070] ^1H NMR (CDCl_3): δ 7.35 (2 H, d, $J = 7.6$ Hz), 7.28 (1 H, brs), 7.17-7.26 (5 H, m), 7.11 (1 H, s), 5.02 (2 H, s), 1.20 (12 H, s) ppm.

1.5 Synthesis of 5

[0071] A solution of **3** (9 g, 47.57 mmol, 1 eq), **4** (32.8 g, 95.14 mmol, 2 eq), chloro(1,5-cyclooctadiene)rhodium (I) dimer (352 mg, 0.7136 mmol, 0.015 eq), (R)-BINAP (1.04 g, 1.665 mmol, 0.035 eq) and K_2CO_3 (3.3 g, 23.8 mmol, 0.5 eq) in dioxane:water (10:1) was purged with nitrogen and heated in 80 °C in an oil bath for 26 h. The reaction mixture was partitioned between EtOAc and brine. The aqueous phase was extracted with EtOAc and the combined EtOAc extracts were washed with brine, dried over Na_2SO_4 , and evaporated. The residue was purified by column chromatography (5:4 hexanes:EtOAc) to give a solid product. Recrystallization in EtOAc and hexanes provided the product, (R)-4-(3-benzyloxy-4-chloro-phenyl)-1-(4-methoxy-phenyl)-pyrrolidin-2-one, **5**.

1.6 Results

[0072] Analytical data for structure **5** is provided below.

1.6.a (R)-4-(3-Benzyloxy-4-chloro-phenyl)-1-(4-methoxy-phenyl)-pyrrolidin-2-one

[0073] ^1H NMR (CDCl_3): δ 7.48 (2 H, d, $J = 9.2$ Hz), 7.44 (2 H, m), 7.32-7.39 (4 H, m), 6.92 (2 H, d, $J = 9.2$ Hz), 6.86 (1 H, d, $J = 1.6$ Hz), 6.83 (1 H, dd, $J = 0.8, 8.0$ Hz), 5.16 (2 H, s), 4.12 (1 H, dd, $J = 8.0, 9.6$ Hz), 3.81 (3 H, s), 3.75 (1 H, dd, $J = 6.8, 9.6$ Hz), 3.63 (1 H, dddd, $J = 8$ Hz), 2.98 (1 H, dd, $J = 8.8, 16.8$ Hz), 2.68 (1 H, dd, $J = 16.8, 8.4$ Hz) ppm.

1.7 Synthesis of 6

[0074] To a solution of **5** (16.5 g, 40 mmol, 1 eq) in CH_3CN (1400 mL) was added a solution of ammonium cerium nitrate (CAN) (65.8 g, 0.12 mol, 3 eq) in 50% aqueous CH_3CN at 0 °C dropwise. The reaction mixture was stirred at 0 °C for 1 h and $\text{Na}_2\text{S}_2\text{O}_3$ (45.4 g, 0.36 mol, 9 eq) is added. The reaction mixture was stirred at 0 °C for another hour and filtered through Celite to remove the precipitate. The filtrate was concentrated under reduced pressure and the residue was partitioned between 5% MeOH in EtOAc and H_2O . The aqueous phase was extracted with 5% MeOH in EtOAc and the combined extracts were washed with brine, dried over Na_2SO_4 , and evaporated. Purification through column chromatography (40:1 CH_2Cl_2 :MeOH) afforded the product, (R)-4-(3-benzyloxy-4-chloro-phenyl)-pyrrolidin-2-one, **6**.

1.8 Results

[0075] Analytical data for structure 6 is provided below.

1.8.a (R)-4-(3-Benzyloxy-4-chloro-phenyl)-pyrrolidin-2-one

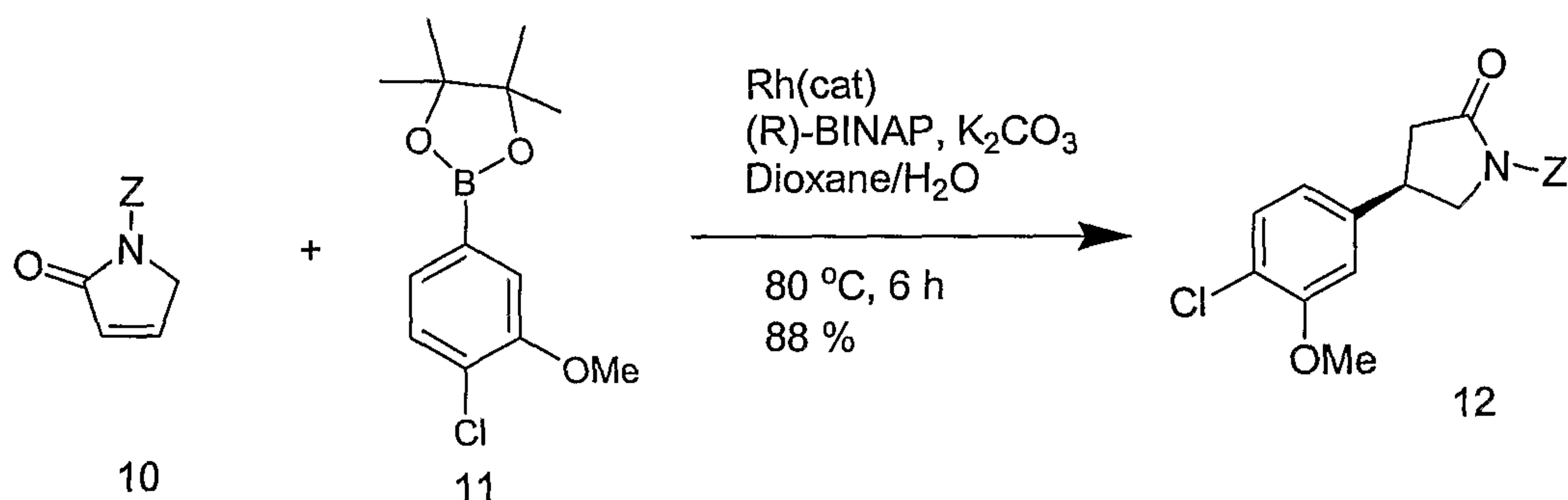
[0076] ^1H NMR (CDCl_3): δ 7.41 (d, 2H, $J = 7.6$ Hz), 7.35 (t, 2H, $J = 6.8$ Hz), 7.29 (d, 2H, $J = 8.0$ Hz), 6.78 (d, 1H, $J = 2.0$ Hz), 6.75 (dd, 1H, $J = 2.0, 8.0$ Hz), 5.58 (brs, 1H), 5.11 (s, 2H), 3.70 (t, 1H, $J = 8.4$ Hz), 3.62-3.56 (m, 1H), 2.27 (dd, 1H, $J = 6.8, 9.2$ Hz), 2.66 (dd, 1H, $J = 8.8, 16.8$ Hz), 2.36 (dd, 1H, $J = 9.2, 17.2$ Hz); LCMS m/z 302.20 $[\text{M}+\text{H}]^+$.

EXAMPLE 2

Determining the efficacy of R^1 substituents

[0077] A study of pyrrolidones with varying substituents on the endocyclic nitrogen was undertaken. The general reaction scheme is shown in Scheme 5. The different R^1 substituents are also listed. The results of these tests are as follows:

Scheme 5



<u>Z substituents</u>	% recovery	% ee
<i>p</i> -methoxybenzyl	35	--
<i>p</i> -N-acetyl phenyl	83	--
<i>p</i> -N-protected sulfonamidyl phenyl	82	83
<i>m</i> -N-protected phenyl	78	85
<i>p</i> -methoxyphenyl	90	86

[0078] Suprisingly, the percent recovery for these reactions increased from 35% to about 80% when a phenyl group was substituted for a benzyl group at the Z position. This is in

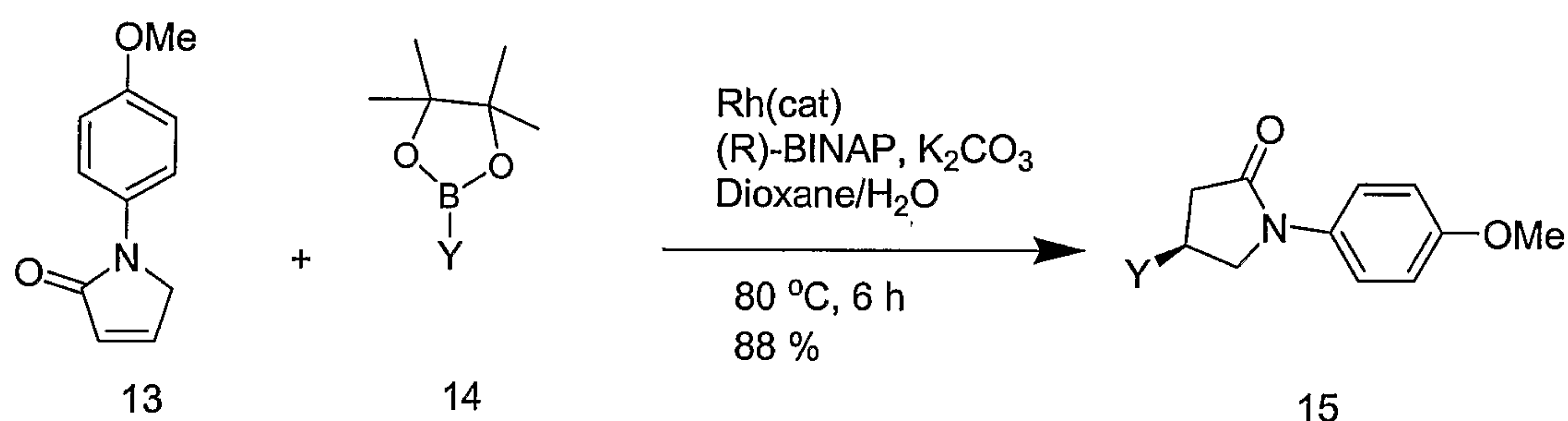
contrast with the asymmetric synthesis reactions described in Senda, where yields of up to 75% were recorded for piperidinones with benzyl groups at the equivalent of the Z position.

EXAMPLE 3

Determining the efficacy of boronic ester Y substituents

[0079] A study of boronic esters with varying Y substituents was undertaken. The general reaction scheme is shown in Scheme 6. The different boronic ester substituents are also listed. The results of these experiments are as follows:

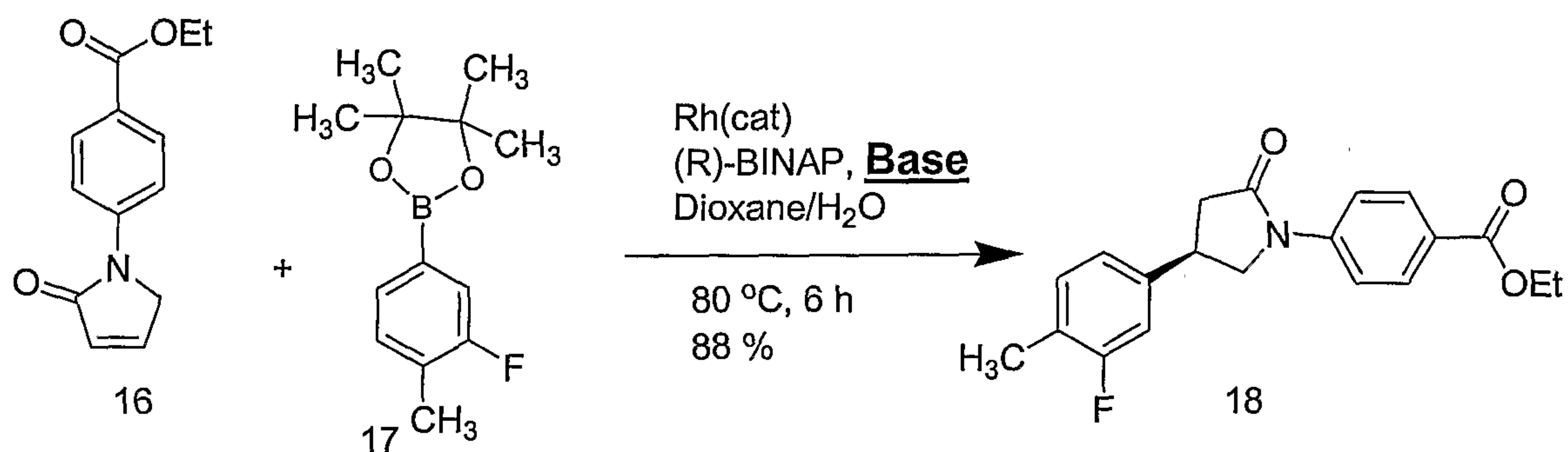
Scheme 6



<u>Y substituents</u>	<u>% recovery</u>	<u>% ee</u>
3-benzyoxy-4-chloro phenyl	93	86 (96 ee by recrystallization with EtOAc:Hex (1:1))
3-BOC phenyl	82	90
2-methoxy-4-chloro phenyl	70	84
3-benzyoxy-4-chloro-5-methoxymethoxymethylene phenyl	60	--
3-(2-chloro-5-cyano-phenoxy)-4-bromo phenyl	28	--
3-ethoxy-4-bromo phenyl	88	--
3-benzyoxy-4-chloro-2-methoxymethoxymethylene phenyl	52	--

EXAMPLE 4*Determining the efficacy of bases in the reaction conditions*

[0080] A study which varied the types of bases utilized was undertaken. The general reaction scheme is shown in Scheme 7. The different bases are also listed. The results of these experiments are as follows:

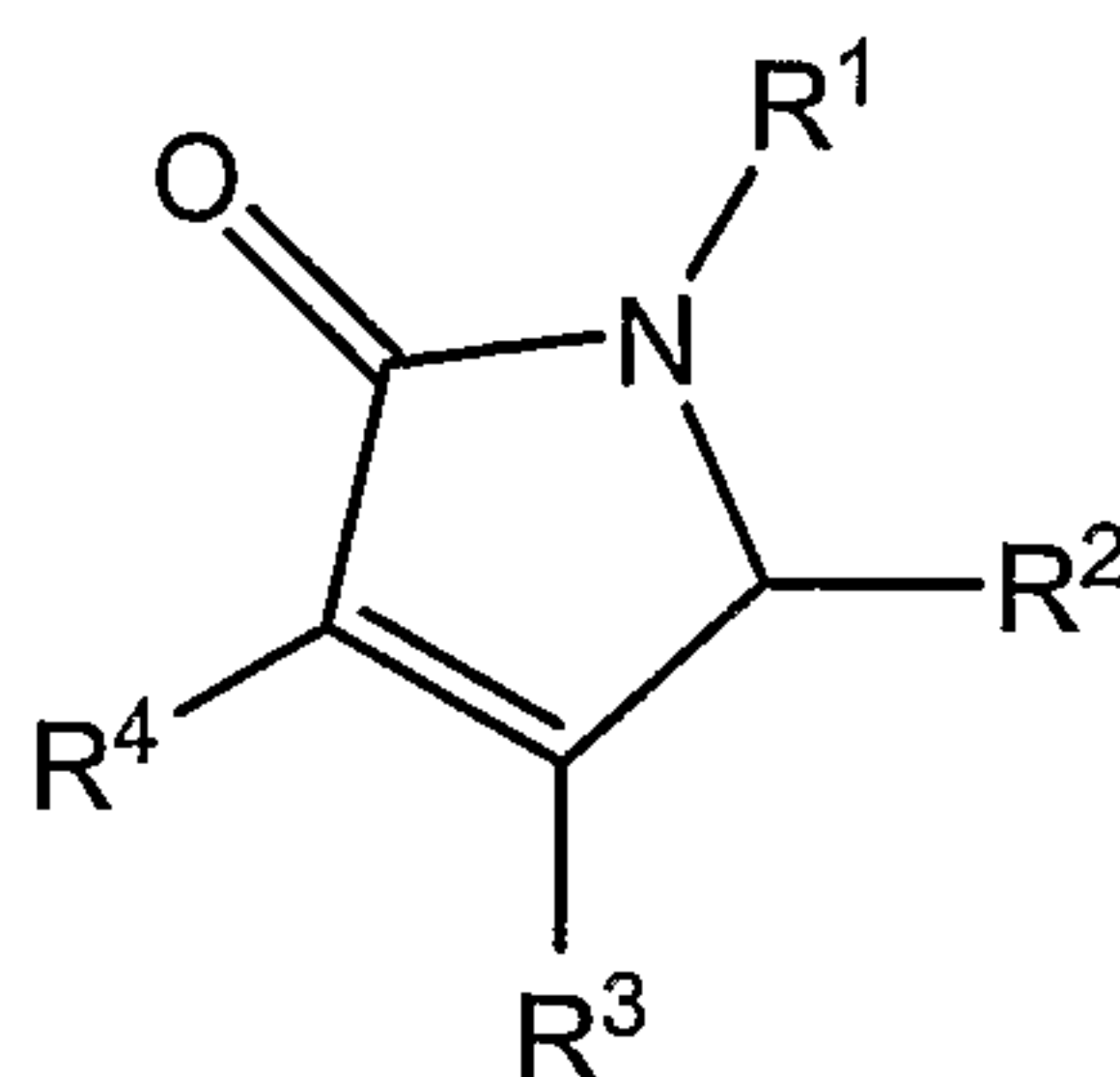
Scheme 7

<u>Base</u>	<u>Equivalents of Base</u>	<u>% Recovery</u>	<u>% ee</u>
KOH	4.5	15-25	94
NaOAc	2.5	<5	--
K ₂ CO ₃	0.5	83	88

[0081] All patents, patent applications, and other publications cited in this application are incorporated by reference in the entirety.

WHAT IS CLAIMED IS:

1. A method of synthesizing an amide-containing heterocycle or a pharmaceutically acceptable salt thereof, the method comprising:
 - a) contacting an organometallic rhodium (I) complex, a chiral ligand, an α,β unsaturated amide-containing heterocycle according to Formula I:

**(I)**

wherein

R^1 is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^2 , R^3 , and R^4 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{5a} , NO_2 , CN , halogen, $C(O)R^{5b}$, $NR^{5a}R^{5b}$, $C(O)NR^{5a}R^{5b}$ and $C(O)OR^{5b}$

wherein

R^{5a} is a member selected from H and substituted or unsubstituted alkyl;

R^{5b} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

and a boronic ester according to Formula II:



wherein

R^6 is a member selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

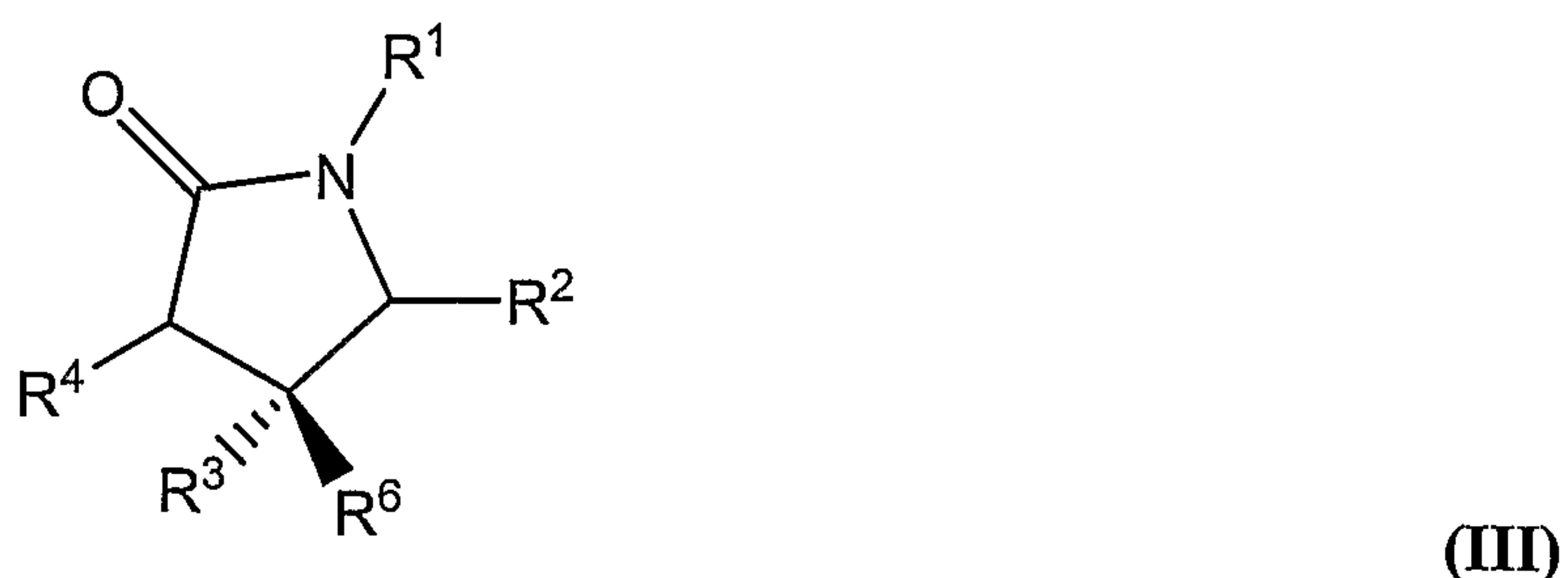
R^7 and R^8 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl

wherein R^7 and R^8 , taken together with the oxygen atoms to which they are joined, optionally form a substituted or unsubstituted 5- to 8- membered ring

wherein

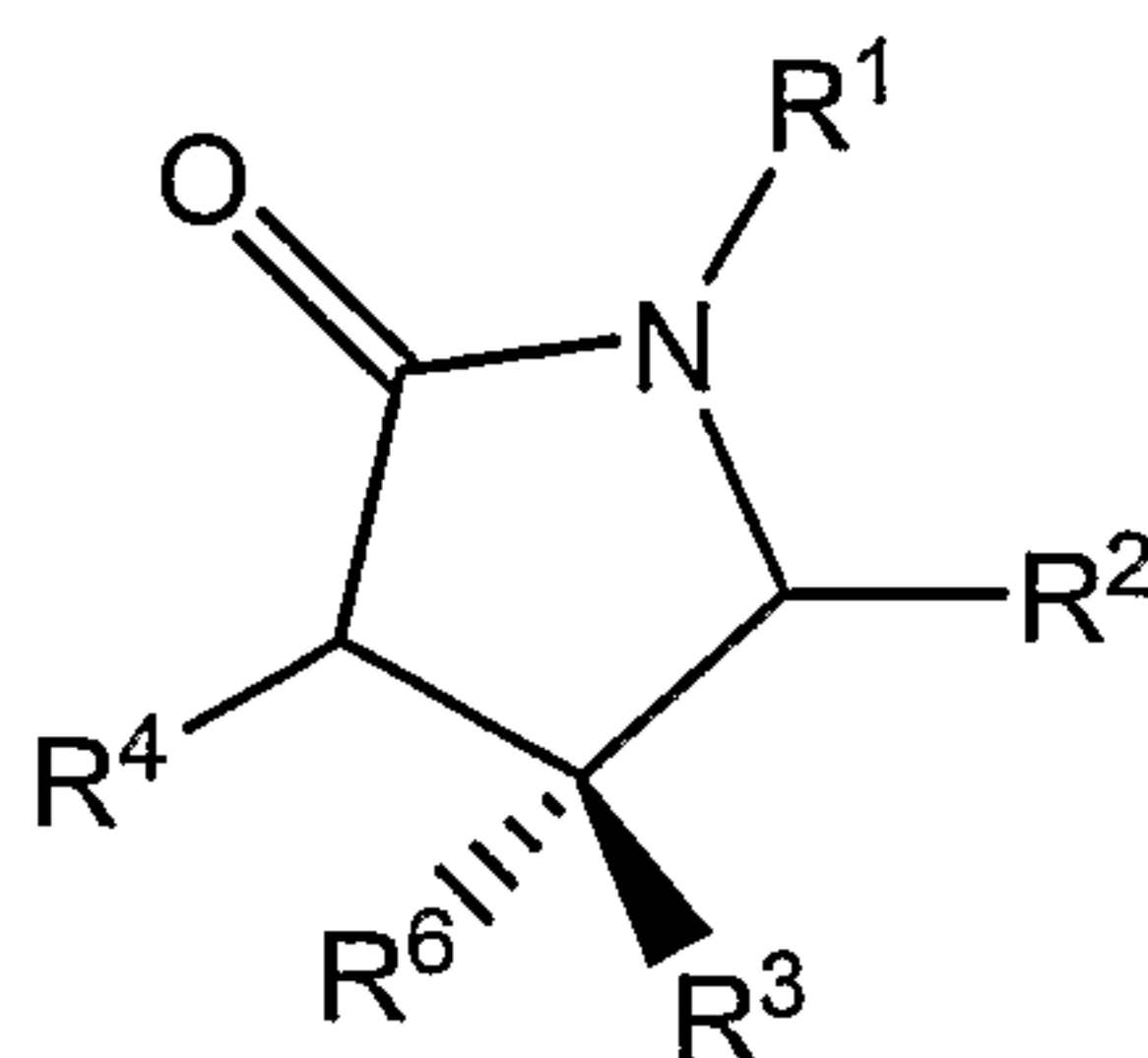
R^{10} is a member selected from H and substituted or unsubstituted alkyl

under conditions sufficient to form a product comprising an amide-containing heterocycle according to Formula III:



thereby synthesizing said amide-containing heterocycle or pharmaceutically acceptable salt thereof.

2. The method according to claim 1, wherein said product further comprises an amide-containing heterocycle according to Formula IIIa:



(IIIa).

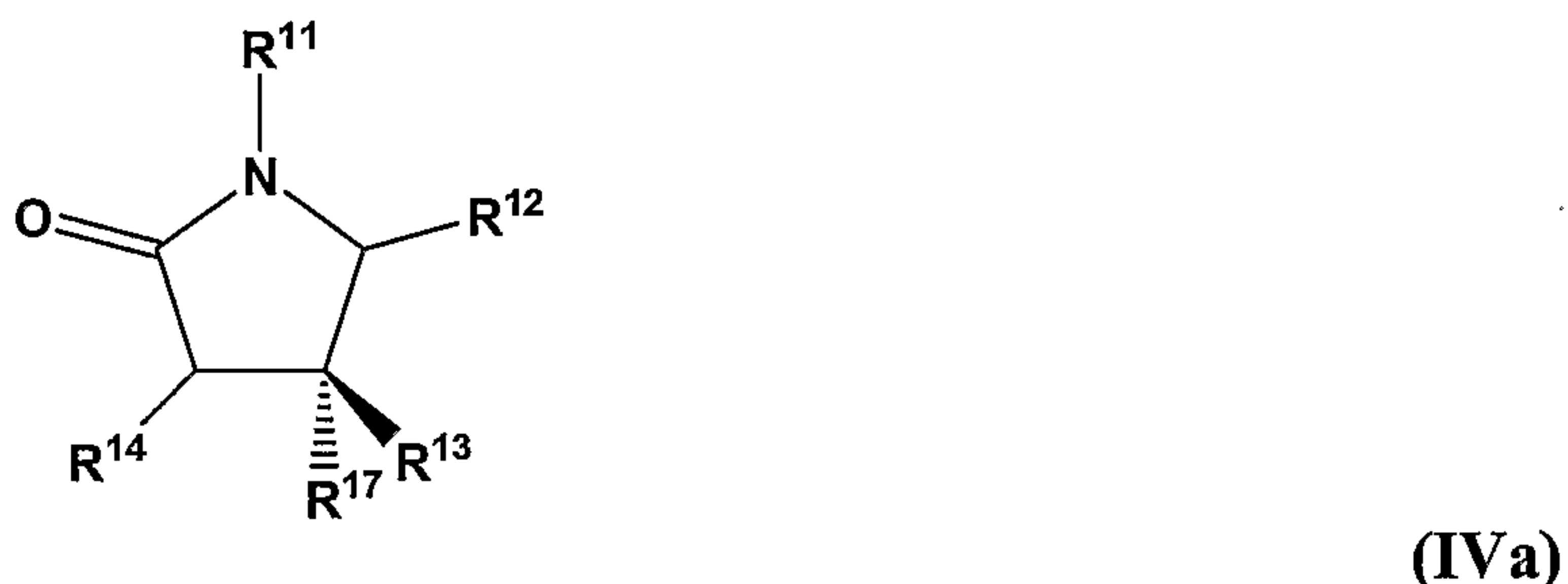
3. The method according to claim 2, wherein said product has an ee of about 60% or greater.
4. The method according to claim 1, wherein the organometallic rhodium (I) complex comprises a chiral ligand selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.
5. The method according to claim 1, wherein said chiral ligand comprises an aryl substituted phosphine.
6. The method according to claim 1, wherein R^6 is a member selected from substituted or unsubstituted phenyl, substituted or unsubstituted pyridinyl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted quinolinyl, substituted or unsubstituted isoquinolinyl, substituted or unsubstituted benzofuranyl, substituted or unsubstituted benzothiophenyl, substituted or unsubstituted benzoimidazolyl, substituted or unsubstituted quinazolinyl and substituted or unsubstituted quinoxalinyl.
7. The method according to claim 1, wherein R^1 is a member selected from substituted or unsubstituted phenyl and substituted or unsubstituted benzyl.
8. The method according to claim 1, wherein R^1 is substituted or unsubstituted phenyl.
9. The method according to claim 2, wherein said product has an ee of about 80% or greater.
10. The method according to claim 3, further comprising:
 - b) purifying the mixture of step a), thus producing a product with an ee that is greater than the ee after step a).

11. The method according to claim 10, wherein said purifying comprises subjecting the mixture to a recovery method comprising column chromatography and recrystallization.

12. A mixture comprising a compound according to Formula IV:



and a compound according to Formula IVa:



wherein

R^{11} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^{12} , R^{13} , and R^{14} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{15} , NO_2 , CN, halogen, $C(O)R^{15}$, $NR^{15}R^{16}$, $C(O)NR^{15}R^{16}$ and $C(O)OR^{15}$

wherein

R^{15} is a member selected from H and substituted or unsubstituted alkyl;

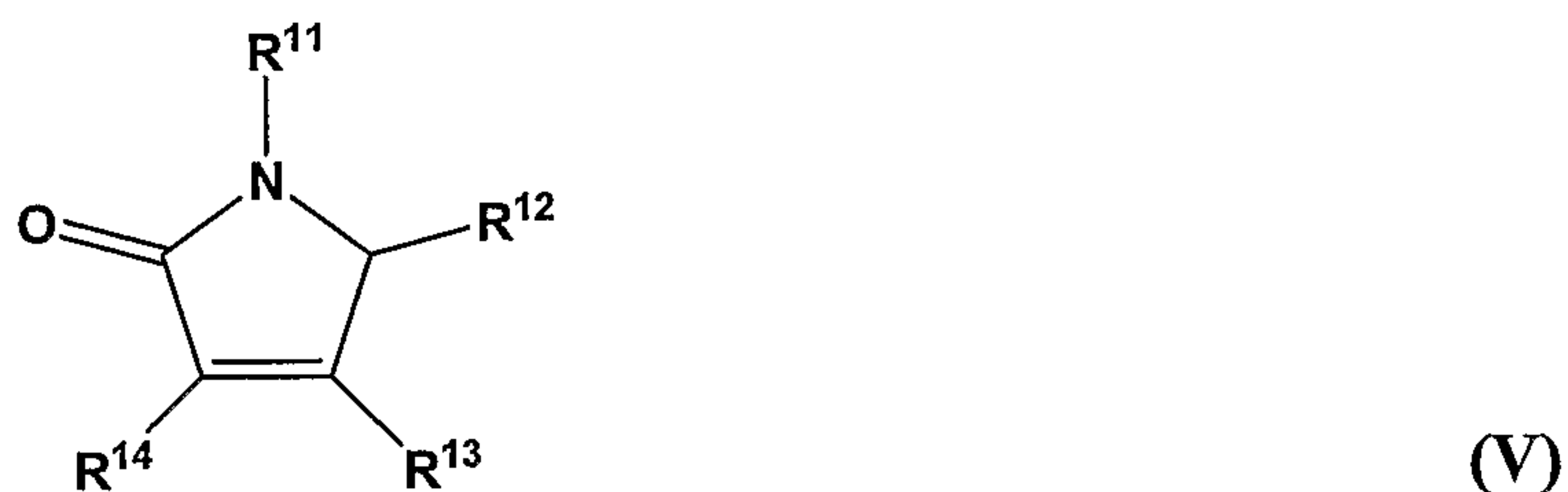
R^{16} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl

wherein

R^{17} is a member selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

13. The mixture of claim 12, wherein said mixture has an ee of about 60% or greater.

14. The mixture of claim 12, produced by a process comprising:
a) contacting an organometallic rhodium (I) complex, a chiral ligand, an α,β unsaturated N-substituted heterocycle according to Formula V:



wherein

R^{11} is a member selected from substituted or unsubstituted alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^{12} , R^{13} , and R^{14} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{15} , NO_2 , CN, halogen, $C(O)R^{15}$, $NR^{15}R^{16}$, $C(O)NR^{15}R^{16}$ and $C(O)OR^{15}$

wherein

R^{15} is a member selected from H and substituted or unsubstituted alkyl;

R^{16} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

and a boronic ester according to Formula II:



wherein

R^6 is a member selected from substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

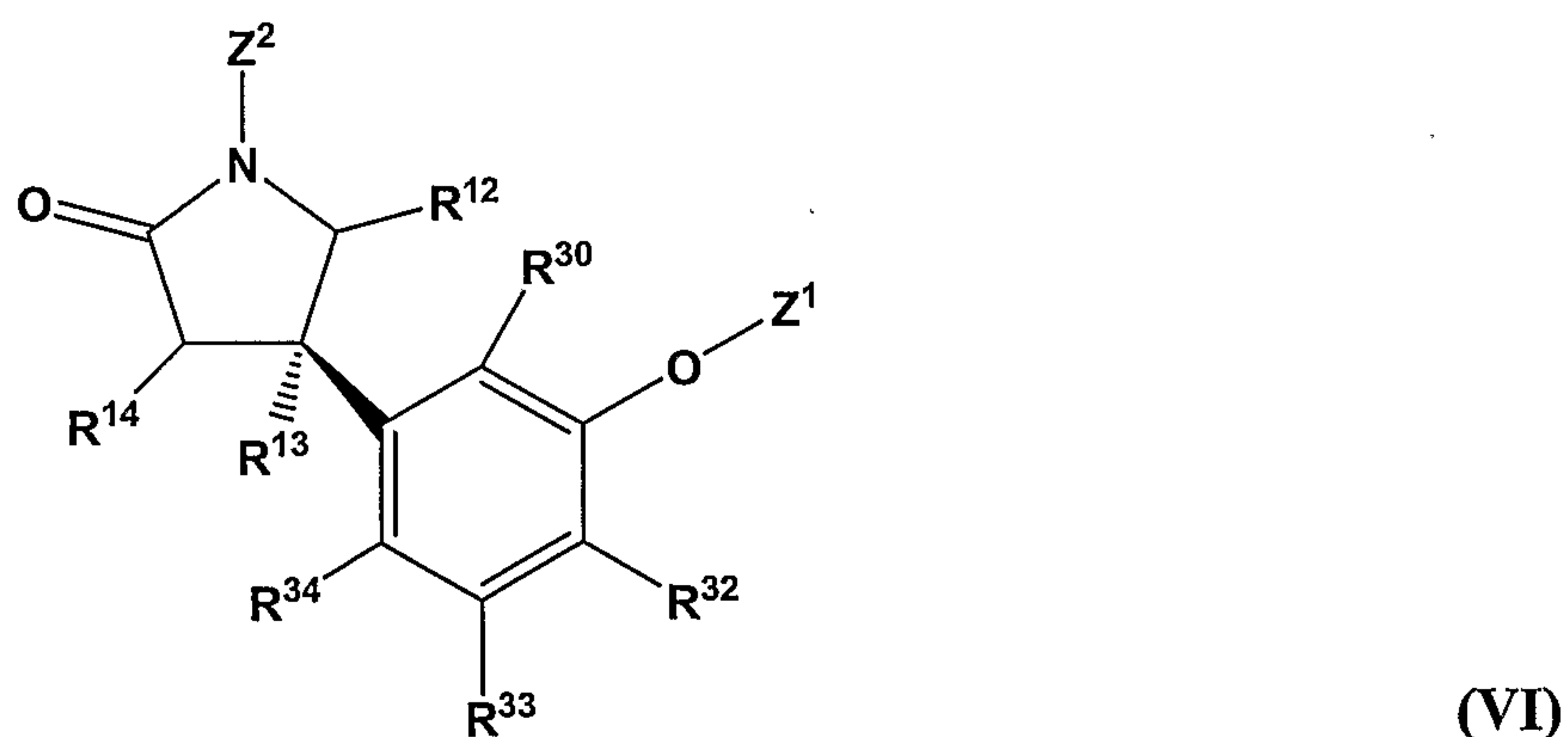
R^7 and R^8 are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl

wherein R^7 and R^8 , taken together with the oxygen atoms to which they are joined, optionally form a 5- to 8- membered ring under conditions sufficient to form said mixture.

15. The mixture of claim 12, wherein R^{11} is a member selected from substituted or unsubstituted phenyl and substituted or unsubstituted benzyl.

16. The mixture of claim 12, wherein R^{11} is substituted or unsubstituted phenyl.

17. A method of producing a compound having the formula according to Formula VI:



and its enantiomer

wherein

R^{12} , R^{13} , and R^{14} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{15} , NO_2 , CN, halogen, $C(O)R^{15}$, $NR^{15}R^{16}$, $C(O)NR^{15}R^{16}$ and $C(O)OR^{15}$

wherein

R^{15} is a member selected from H and substituted or unsubstituted alkyl;

R^{16} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^{30} , R^{32} , R^{33} , and R^{34} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{19} , NO_2 , CN, halogen, $C(O)R^{19}$, $NR^{19}R^{20}$, $C(O)NR^{19}R^{20}$ and $C(O)OR^{19}$

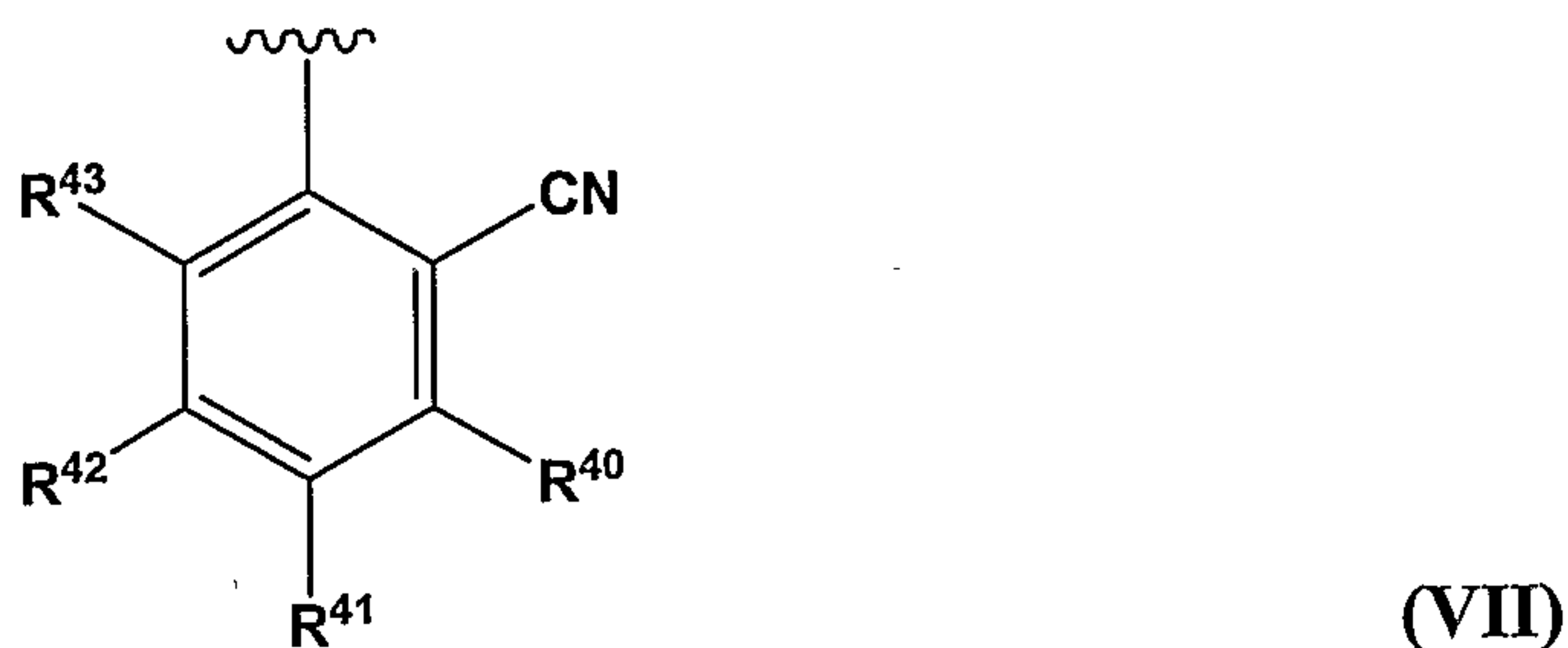
wherein

R^{33} and R^{34} or R^{33} and R^{32} or R^{32} and Z^1 together with the atoms to which they are attached form at least a 5-membered ring selected from substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

R^{19} is a member selected from H, substituted or unsubstituted aryl and substituted or unsubstituted alkyl;

R^{20} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

Z¹ is a moiety according to Formula VII:



wherein

R⁴⁰, R⁴¹, and R⁴² are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR⁴⁴, NO₂, CN, and halogen

wherein

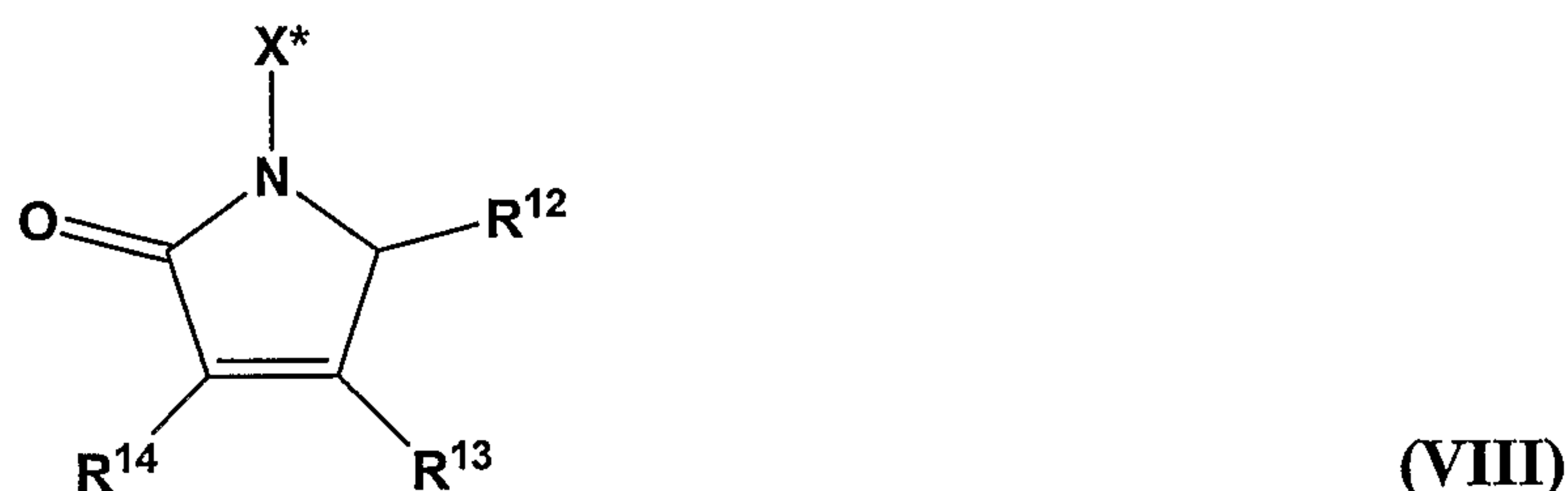
R⁴⁴ is a member selected from H and substituted or unsubstituted alkyl; and

R⁴³ is halogen;

Z² is a member selected from substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl;

said method comprising:

- a) contacting an organometallic rhodium (I) complex, a chiral ligand, an α,β unsaturated N-substituted heterocycle according to Formula VIII:



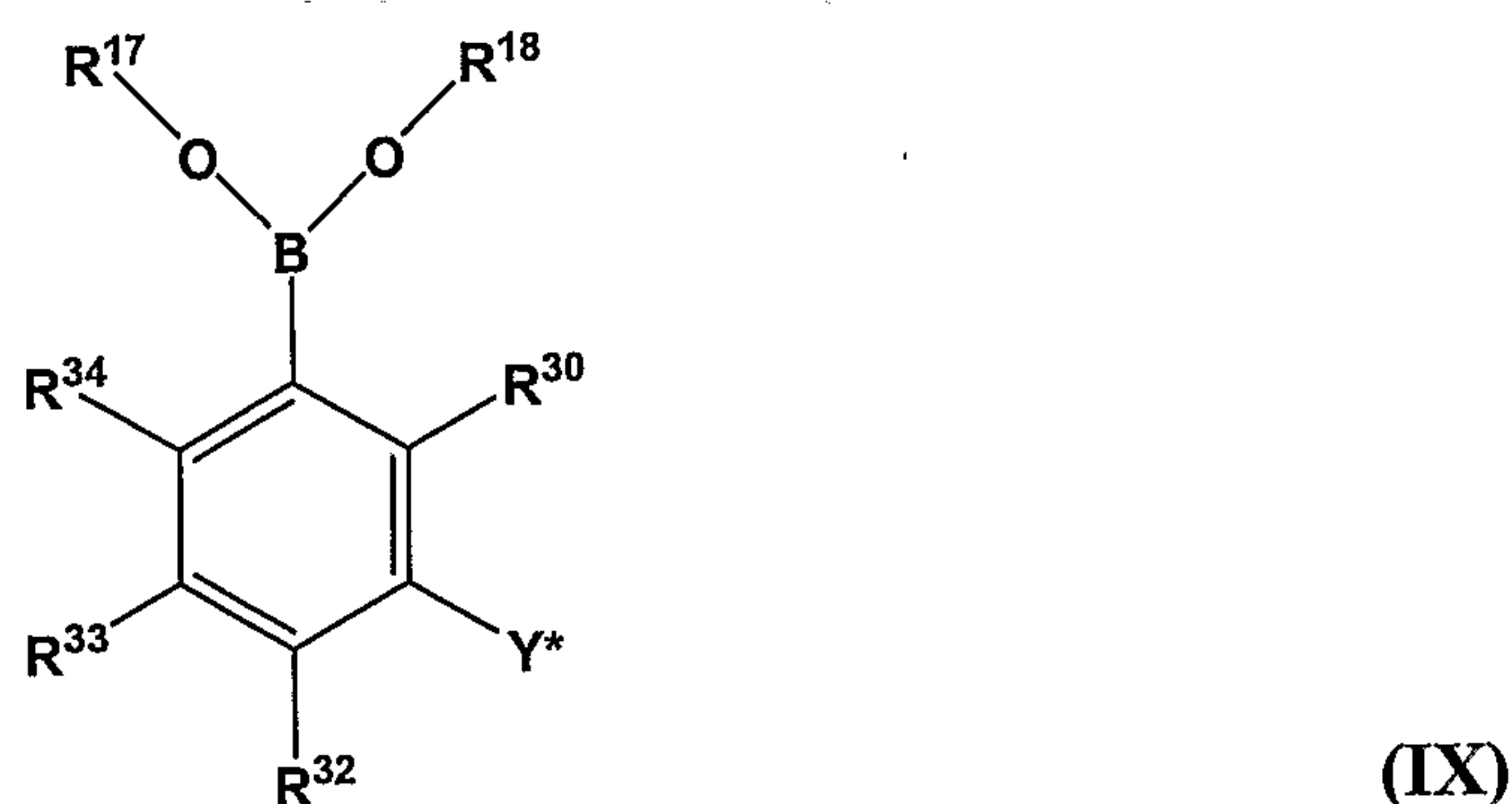
wherein

X* is a protecting group;

R¹², R¹³, and R¹⁴ are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR²⁵, NO₂, CN;

and a boronic ester according to Formula IX:



wherein

R³⁰, R³², R³³, and R³⁴ are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR¹⁹, NO₂, CN, and halogen;

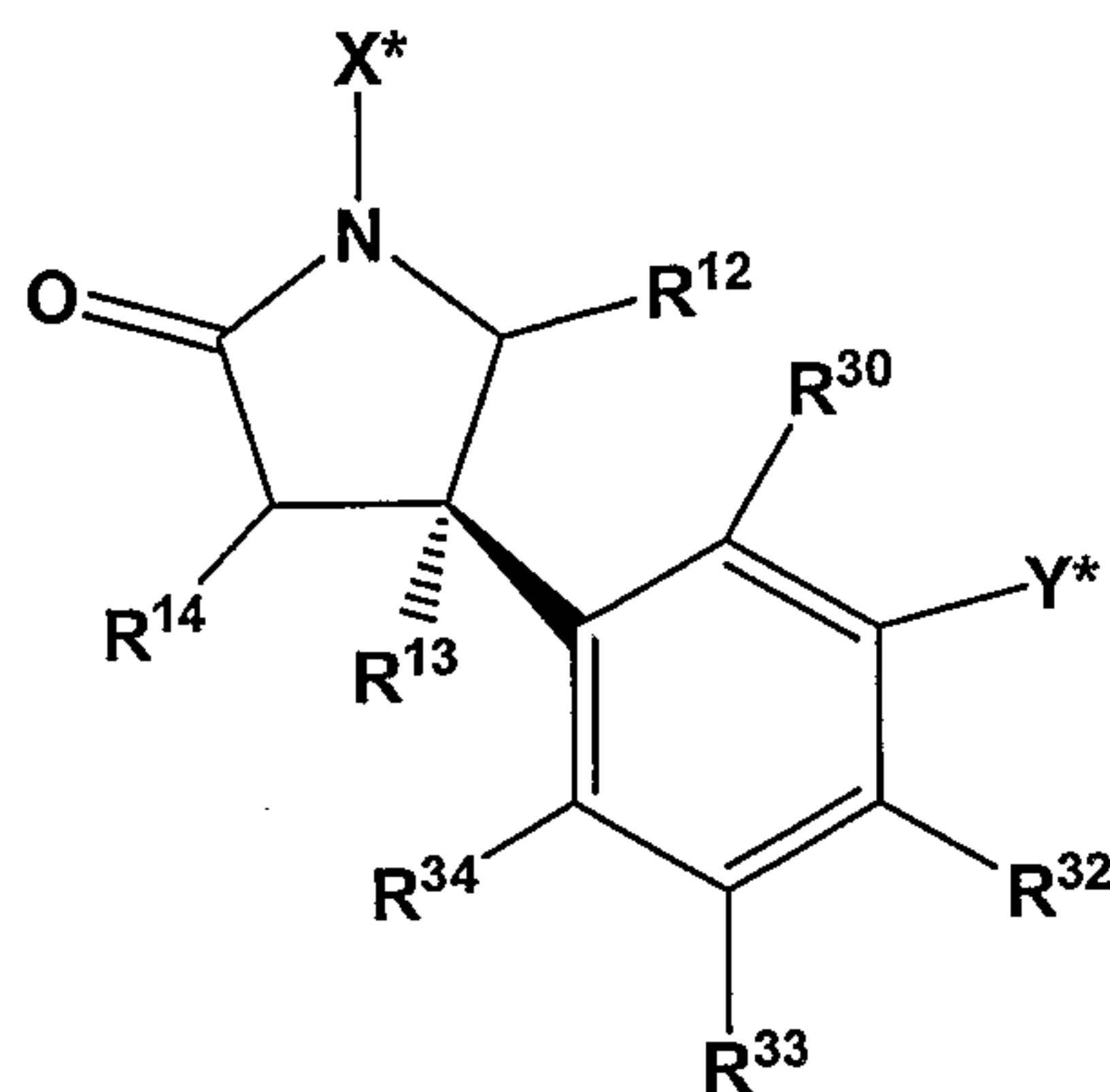
Y* is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR¹⁹, NO₂, CN, and halogen;

R¹⁷ and R¹⁸ are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and R¹⁷ and R¹⁸, taken together with the oxygen atoms to which they are joined, optionally form a substituted or unsubstituted 4- to 8- membered ring

wherein

R¹⁹ is a member selected from H, substituted or unsubstituted aryl and substituted or unsubstituted alkyl;

under conditions sufficient to form a mixture comprising an amide-containing heterocycle according to Formula X:

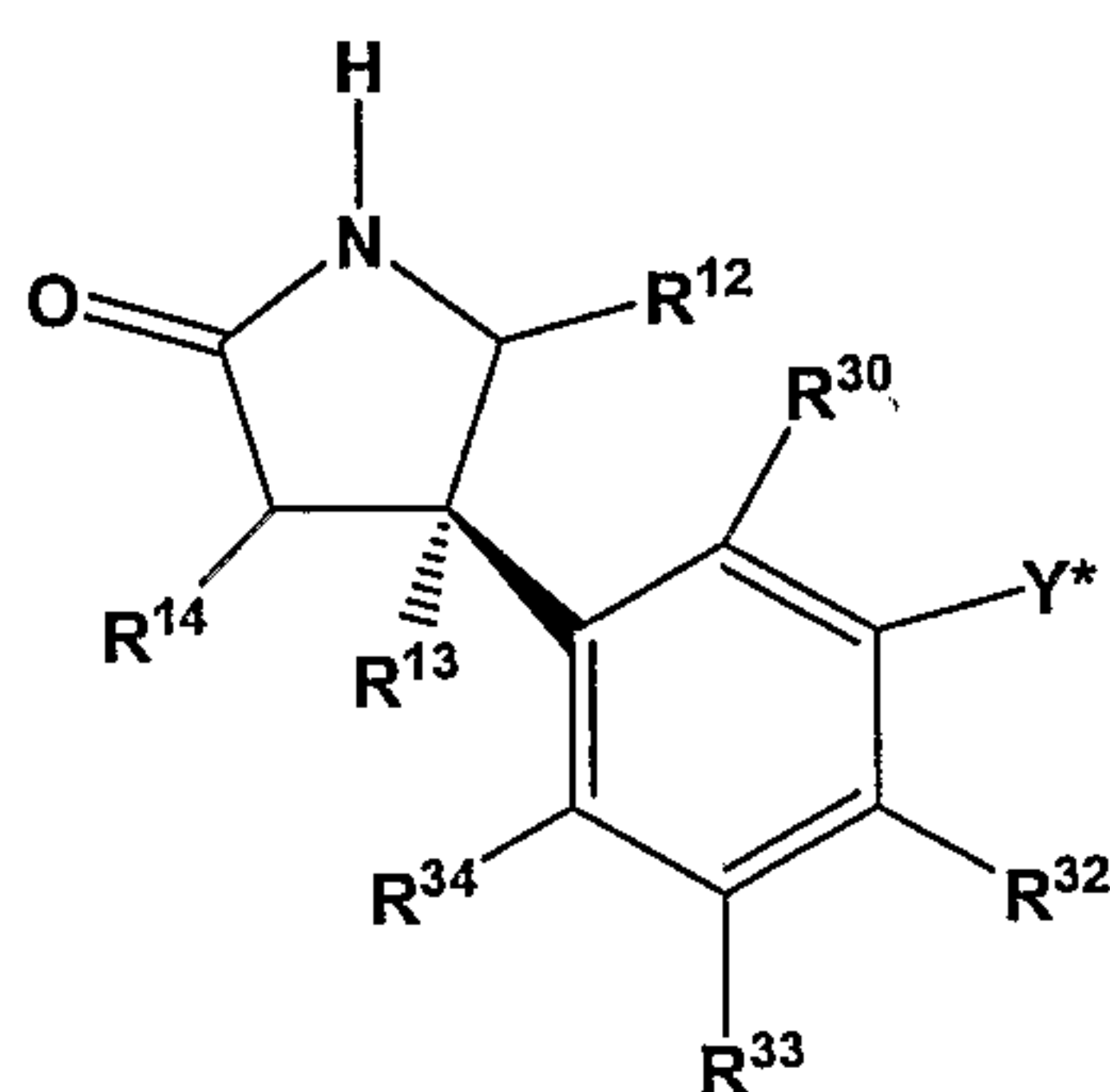


(X)

and its enantiomer

wherein said mixture has an ee of about 60% or greater;

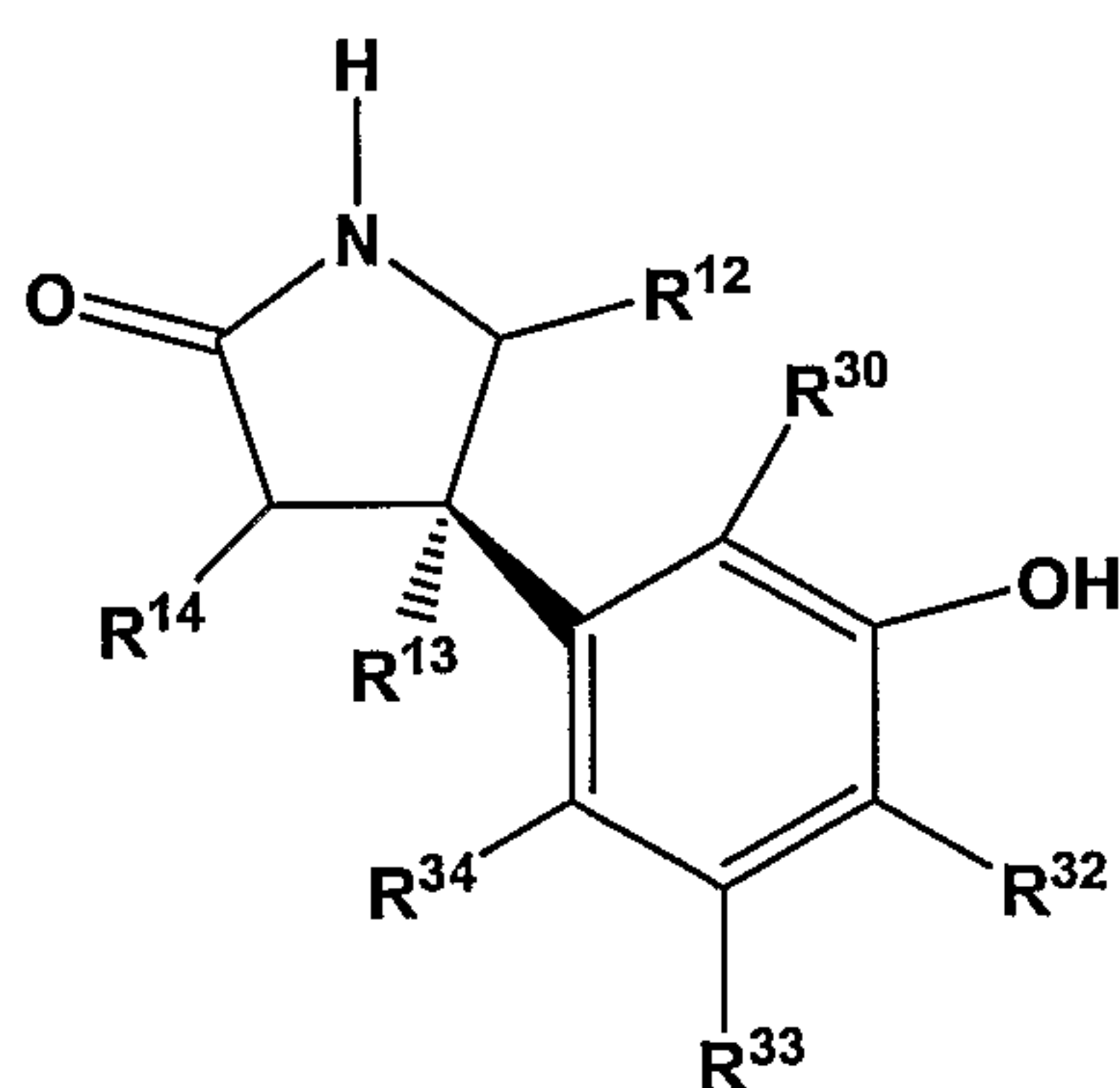
- b) subjecting the product of step a) to a deprotection reaction removing X*,
producing a compound according to Formula XI:



(XI)

and its enantiomer;

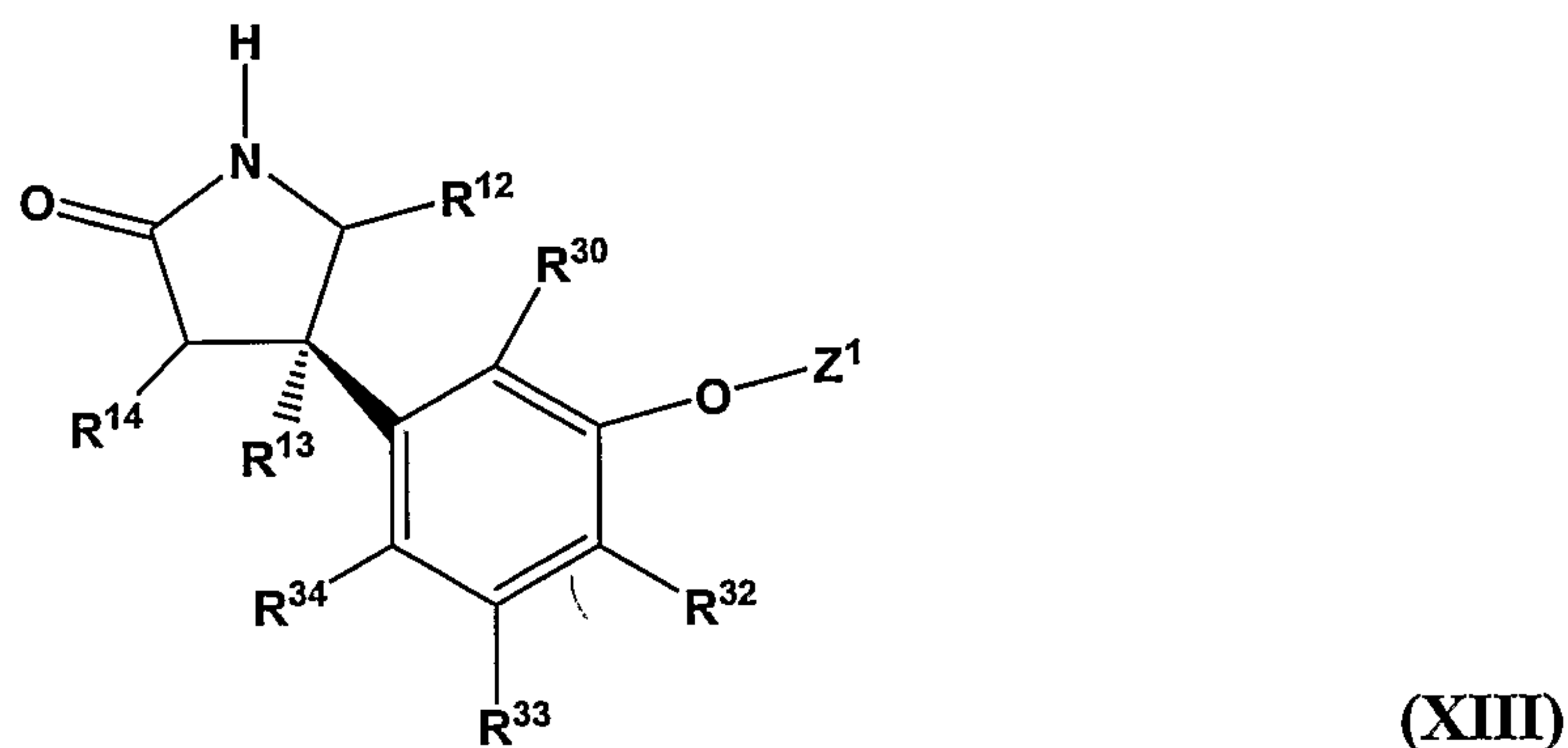
- c) subjecting the product of step b) to a deprotection reaction removing Y*,
producing a compound according to Formula XII:



(XII)

and its enantiomer;

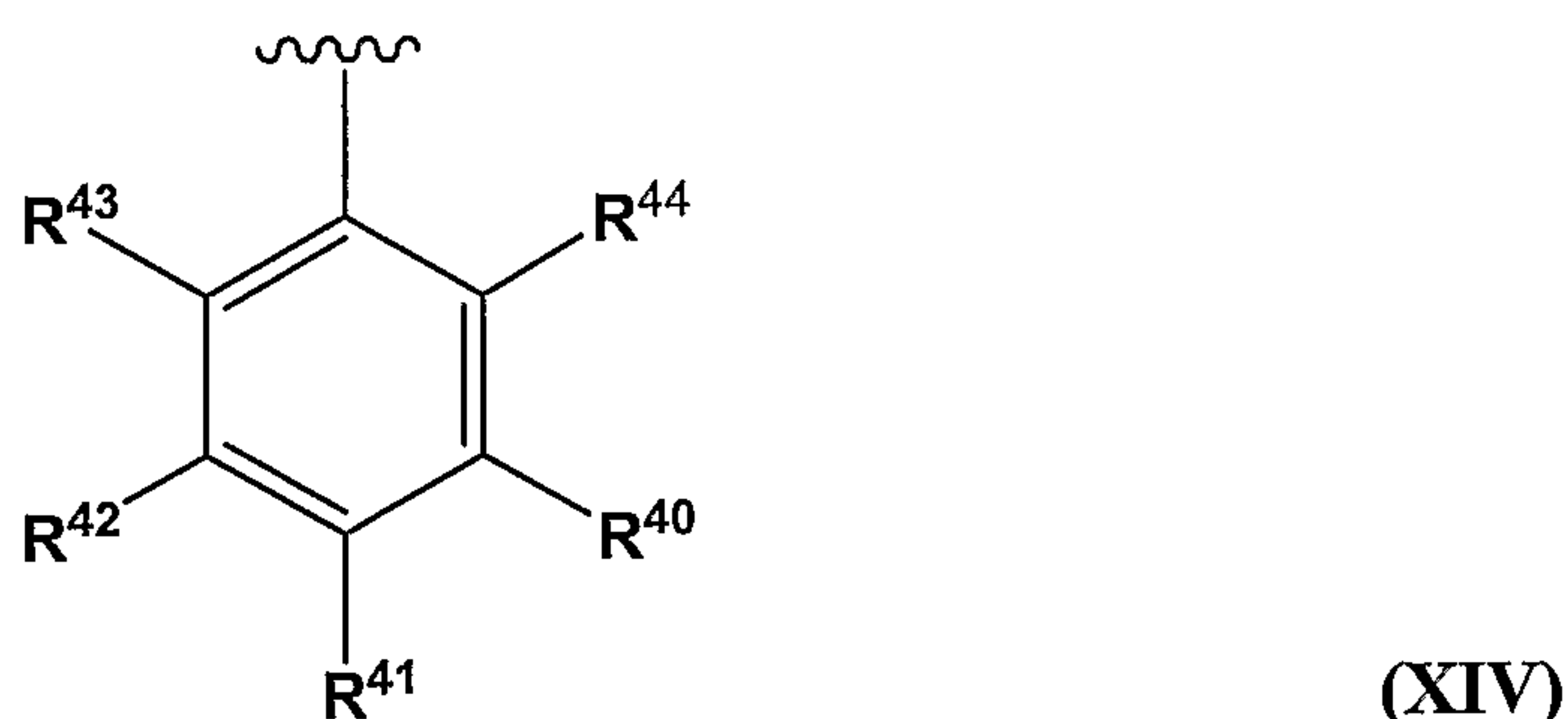
- d) subjecting the product of step c) to an arylation reaction, producing a compound
according to Formula XIII:



and its enantiomer

wherein

Z^1 is a moiety according to Formula XIV



wherein

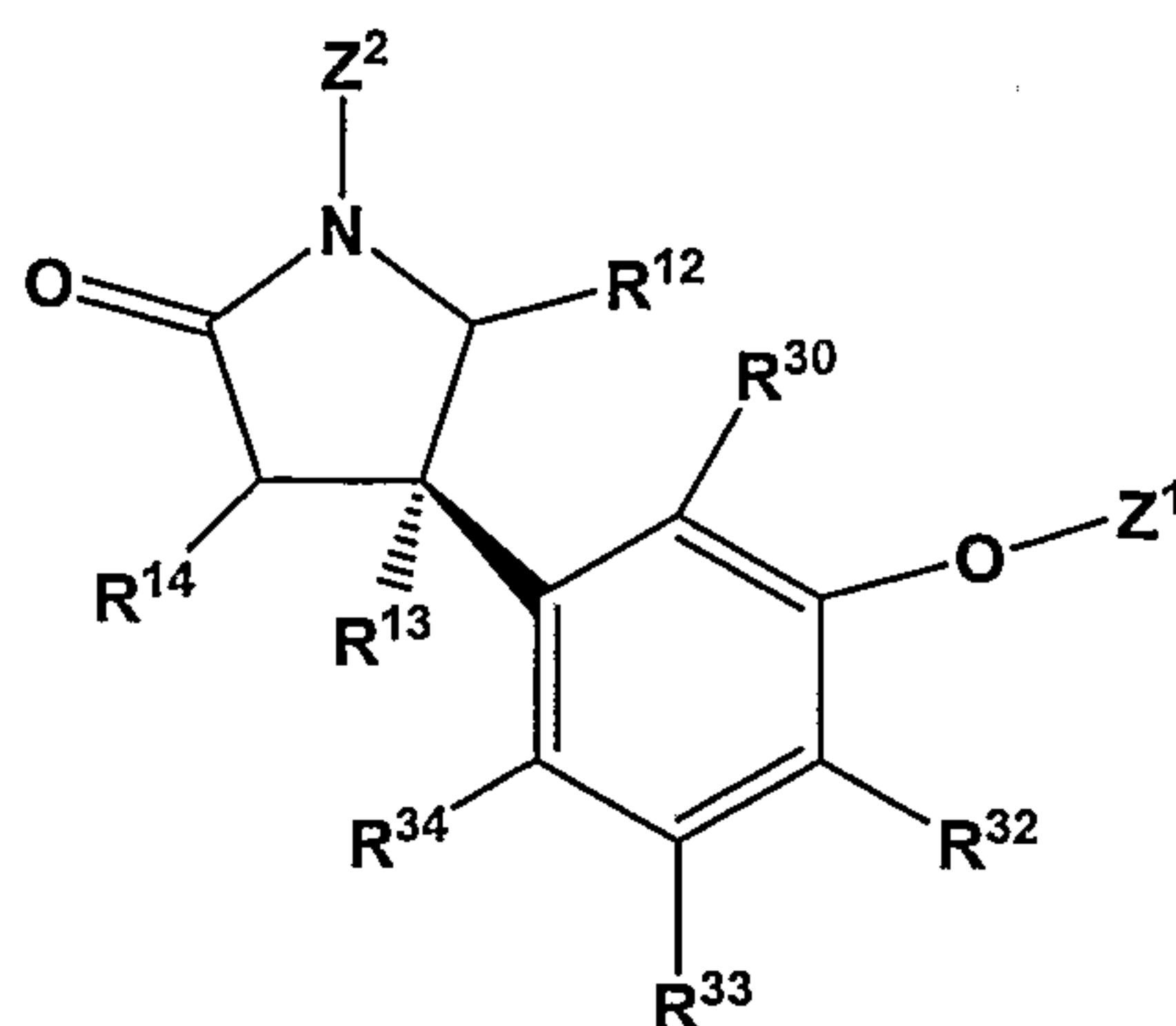
R^{40} , R^{41} , R^{42} , R^{43} , and R^{44} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{46} , NO_2 , CN, halogen, $C(O)R^{46}$, $NR^{46}R^{47}$, $C(O)NR^{46}R^{47}$ and $C(O)OR^{46}$

wherein

R^{46} is a member selected from H and substituted or unsubstituted alkyl;

R^{47} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

- e) arylating the lactam nitrogen of the product of step d), producing a compound according to Formula VI:



(VI)

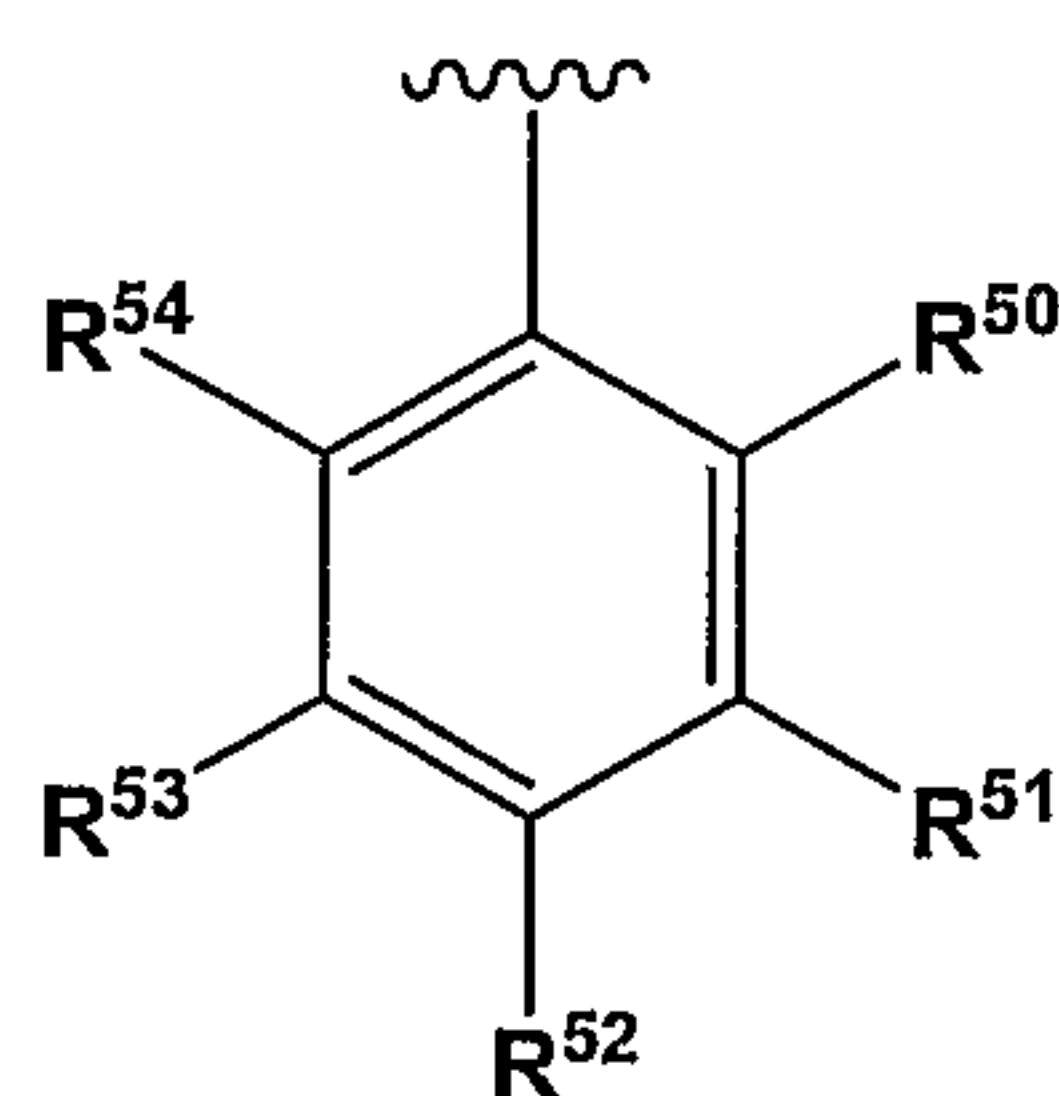
and its enantiomer

wherein

Z^2 is a member selected from substituted or unsubstituted-aryl, substituted or unsubstituted heteroaryl;

thereby producing said compound having the formula according to Formula VI.

18. The method according to claim 17, wherein Z^2 is a moiety according to Formula XV:



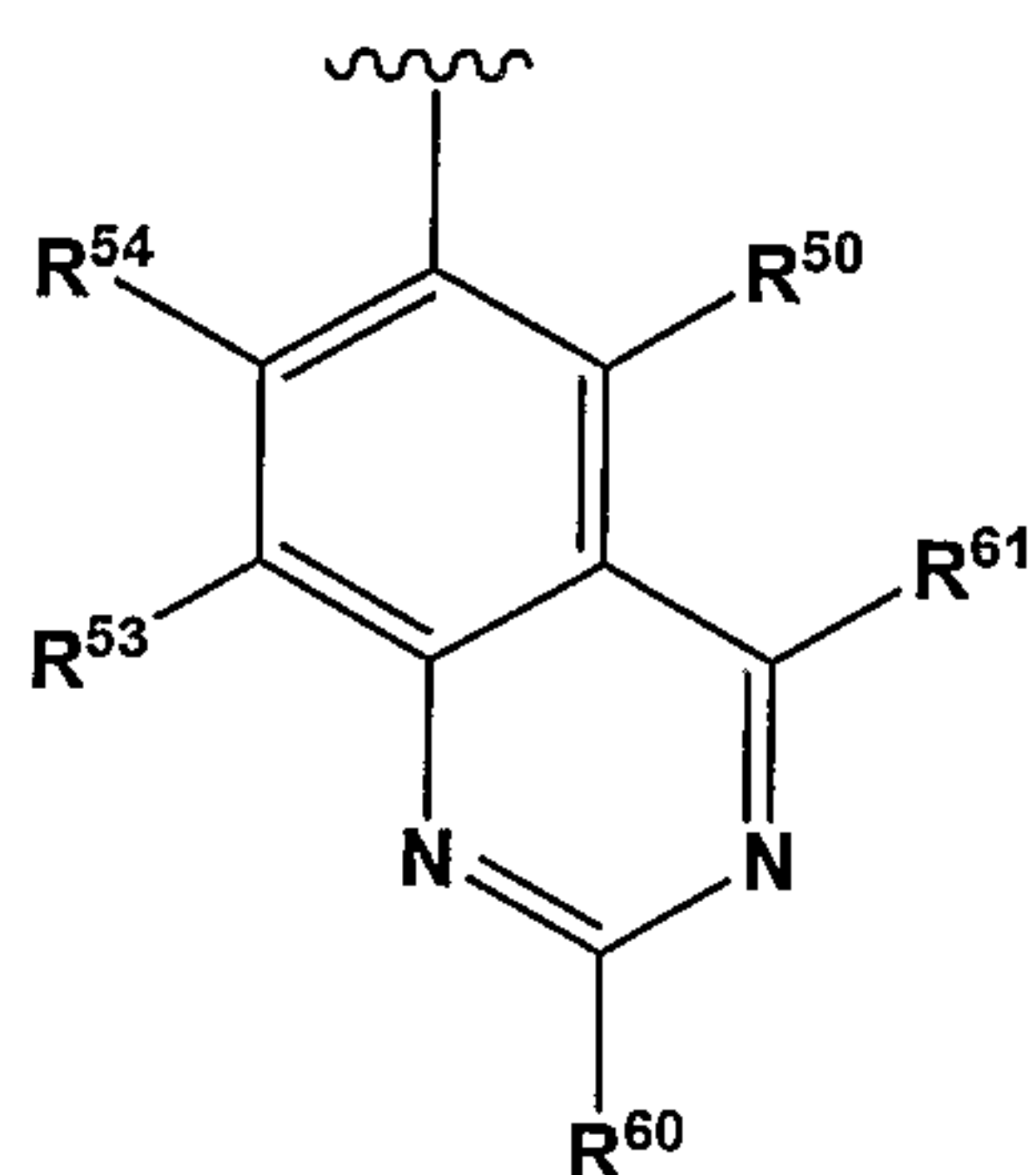
(XV)

R^{50} , R^{51} , R^{52} , R^{53} and R^{54} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{55} , $SO_2NR^{55}R^{56}$, $CONR^{55}R^{56}$, $NR^{55}R^{56}$, NO_2 , CN, and halogen; and any two of R^{50} , R^{51} , R^{52} , R^{53} and R^{54} , taken together with the atoms to which they are joined, optionally form a substituted or unsubstituted 5- to 8- membered ring wherein

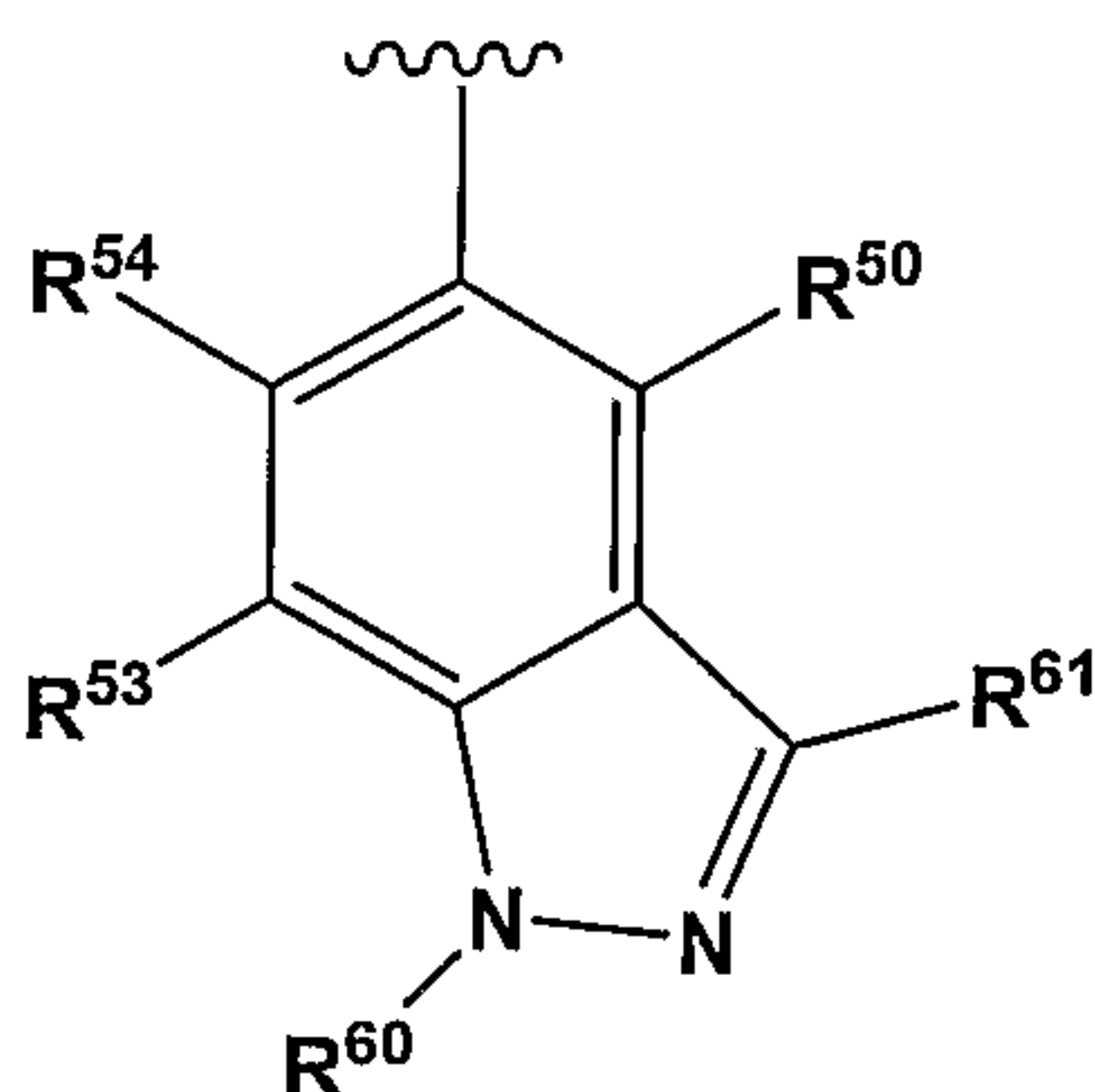
R^{55} is a member selected from H and substituted or unsubstituted alkyl;

R^{56} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

19. The method according to claim 17, wherein R^{32} is halogen.
20. The method according to claim 18, wherein R^{30} , R^{33} , and R^{34} are H.
21. The method according to claim 17, wherein R^{40} , R^{41} , and R^{42} are H.
22. The method according to claim 18, wherein R^{51} and R^{52} , taken together with the atoms to which they are joined, form a substituted or unsubstituted 6-membered ring.
23. The method according to claim 17, wherein Z^2 is a member selected from a moiety according to Formula XVI and a moiety according to Formula XVII:



(XVI)



(XVII)

wherein

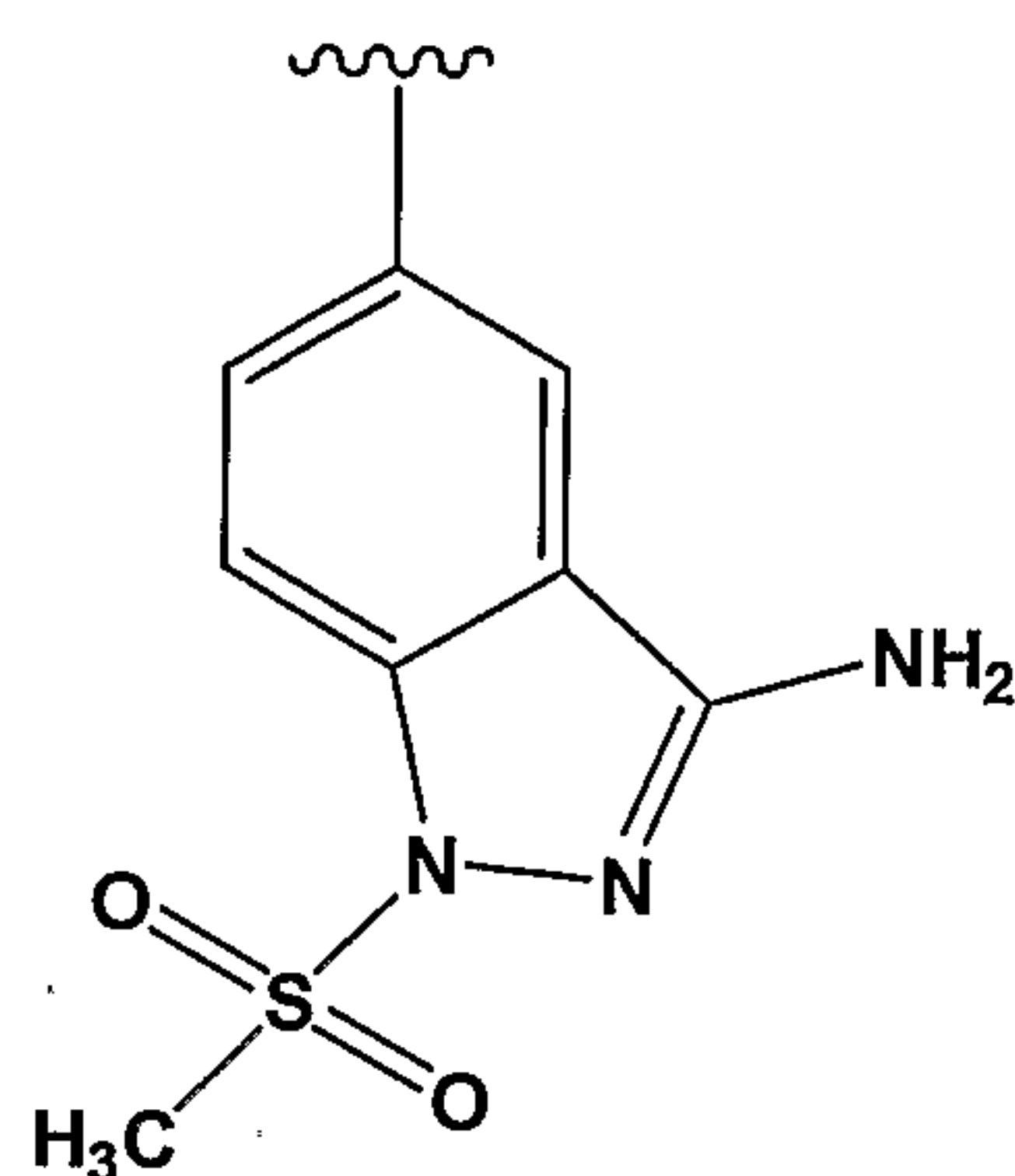
R^{60} and R^{61} are members independently selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, OR^{62} , NO_2 , CN , $NR^{62}R^{63}$, $S(O)_2NR^{62}R^{63}$, $NR^{62}S(O)_2R^{63}$, $C(O)NR^{62}R^{63}$, $S(O)_2R^{62}$ and halogen

wherein

R^{62} is a member selected from H and substituted or unsubstituted alkyl;
 R^{63} is a member selected from H, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or

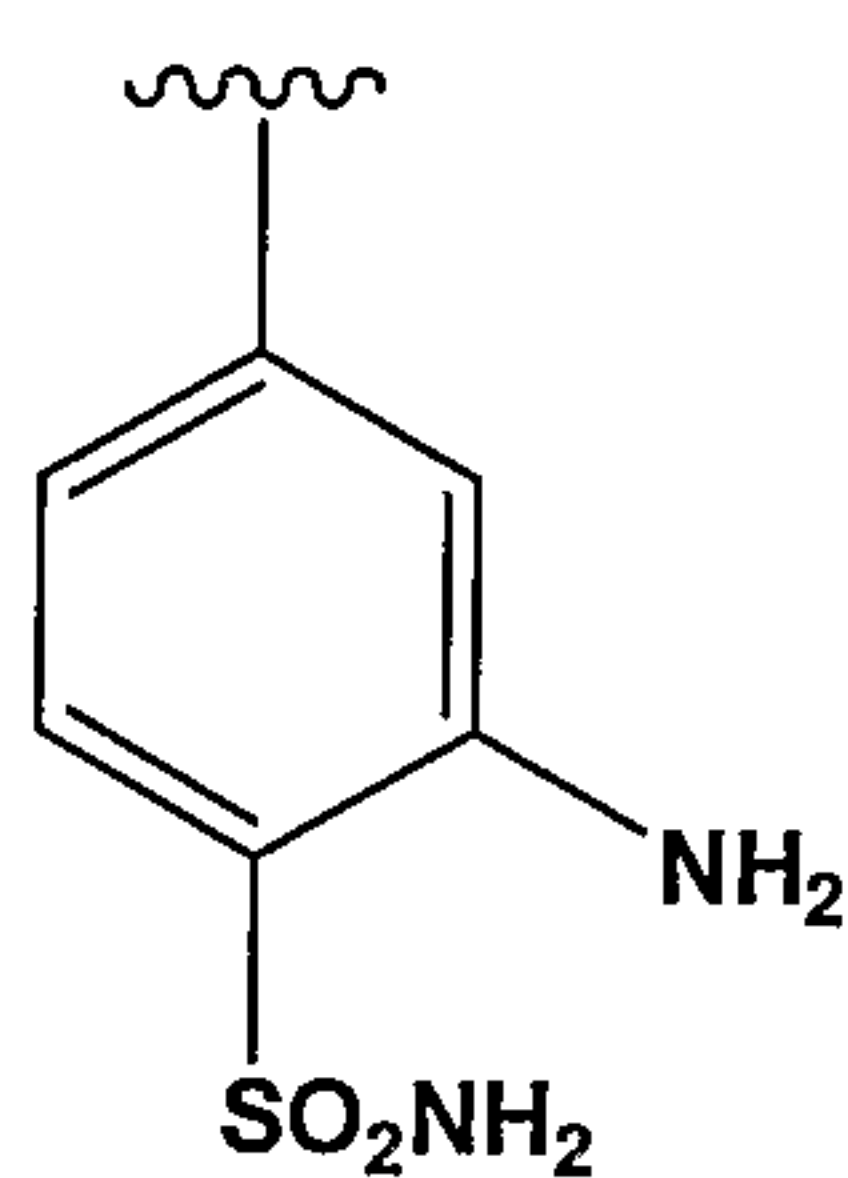
unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl.

24. The method according to claim 23, wherein Z^2 is a moiety according to Formula XVIII:



(XVIII).

25. The method according to claim 17, wherein Z^2 is a moiety according to Formula XIX:



(XIX).