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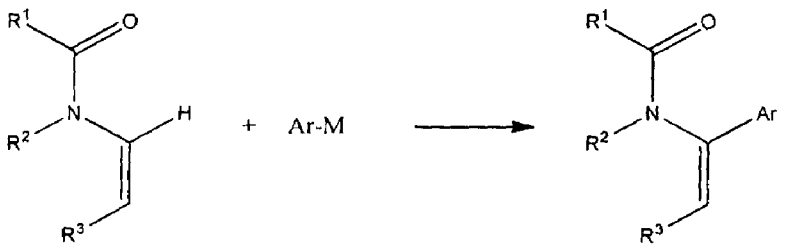
(54) **Title**: STEREOSELECTIVE SYNTHESIS OF HIGHLY SUBSTITUTED ENAMIDES



(II) (III) (I).

(57) **Abstract**: The disclosure provides new methods for the oxidative Heck cross-coupling reaction with electron-rich alkenes such as substituted β-amidoacrylate and other related substituted enamides. Previously, functionalization of enamides under Heck conditions has been limited to those with unsubstituted vinyl groups. By tuning the reaction parameters that allow for the balance between stability and reactivity of the reactants, the oxidative Heck cross-coupling reaction now provides highly substituted enamides in good to excellent yields. (II) (III) (I)·

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STEREOSELECTIVE SYNTHESIS OF HIGHLY SUBSTITUTED ENAMIDES

CROSS REFERENCE TO RELATED APPLICATIONS

[001] This application claims the benefit of priority under 35 U.S.C. §119(e) to United States Provisional Application No. 61/495,446, titled "STEREOSELECTIVE SYNTHESIS OF HIGHLY SUBSTITUTED ENAMIDES," filed on June 10, 2011, which is hereby incorporated by reference in its entirety for all purposes.

FIELD OF THE INVENTION

[002] The present invention is in the field of synthetic organic chemistry and more particularly, in the field of oxidative Heck cross-coupling reactions with electron-rich alkenes, such as substituted β-amidoacrylate and other related substituted enamides.

BACKGROUND OF THE DISCLOSURE

[003] The Heck arylation has proven to be among the most versatile reactions for C-C bond formation owing to its excellent chemoselectivity, wide functional group tolerability, and simplicity. This palladium (0)-mediated catalytic process allows for facile cross-coupling of alkenes with various aryl and heteroaryl halides/pseudohalides. The oxidative Heck reaction has drawn significant attention where arylpalladium (II) species are generated by transmetallation with organometallic counterparts followed by undergoing insertion with alkenes. Among the organometallic coupling partners, organoboronic acids have been extensively explored in various transition-metal-mediated reactions owing to their stability, wide availability, and low toxicity. Significant progress has been made since the first demonstration of the catalytic, oxidative Heck cross-coupling using arylboronic acids by Uemura and coworkers. Despite the recent advances in the field, the limited substrate scope including necessitating steric and/or electronic bias prompt further improvements. For example, a literature survey shows that examples of Heck cross-coupling with electron-rich alkenes such as enamides are limited to those with simple unsubstituted vinyl groups.

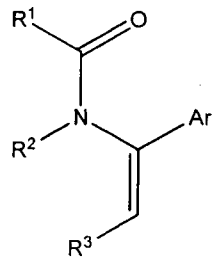
[004] β-Amidoacrylate is an important enamide moiety that has been widely utilized as a synthetic intermediate in the total synthesis of natural products as well as in the preparation of heterocycles and β-amino acids through asymmetric hydrogenation. These compounds are

typically prepared by condensation of β-ketoesters with amides, acylation of β-aminoacrylates, oxidative amidation of acrylates and addition of amides to terminal alkynes, which typically provide disubstituted enamides. While these methods offer various synthetic means for obtaining the β-amidoacrylate moiety, the limitations of these reactions include multiple synthetic steps, harsh reaction conditions, and narrow substrate scope including an intolerance for sterically demanding substrates, which leads to a lack of rapid access to structurally diverse compounds. Thus, there remains a need in the art for new and improved methods for the efficient synthesis of sterically hindered enamides, e.g. the β-amidoacrylate moiety.

SUMMARY OF THE INVENTION

[005] The present invention addresses these needs by providing new and improved methods for the synthesis of sterically hindered enamides including the β-amidoacrylate moiety, which can be utilized as a synthetic intermediate in the total synthesis of natural products as well as in the preparation of heterocycles and β-amino acids through asymmetric hydrogenation.

[006] Thus, in one embodiment the disclosure provides methods for preparing a compound of Formula I:



(I),

wherein R^1 and R^2 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or R^1 and R^2 are each independently selected from CH_2, C=O and O, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

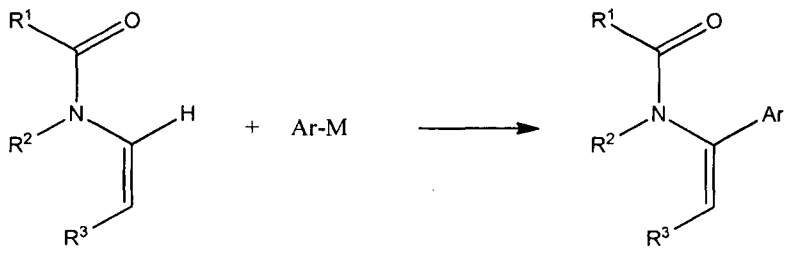
R^4 is selected H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring;

Ar is substituted or unsubstituted aryl,

the method comprising the steps of reacting a compound of Formula II with a compound of Formula III:



(II) (III) (I),

wherein the reaction occurs in the presence of:

about 1 mol % to about 20 mol % $Pd(OAc)_2$;

about 1 equivalent to about 3 equivalents of Ar-M, wherein Ar-M is an arylboron derivative selected from phenyl potassium trifluoroborate, substituted or unsubstituted phenylboronic acid, and substituted or unsubstituted pinacol phenylboronate;

optionally, about 5 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'- tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, $(p\text{-}CF_3C_6H_4)_3P$, $(p\text{-}CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos);

optionally, about 1 equivalent to about 10 equivalents of an additive fluoride source selected from silver fluoride (AgF), copper fluoride (CuF_2), cesium fluoride (CsF), and potassium bifluoride (KHF_2);

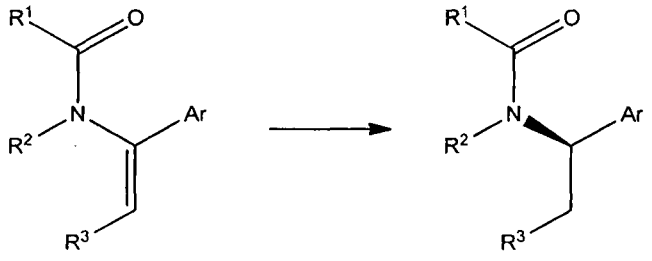
about 0.1 equivalent to about 10 equivalents of an oxidant selected from copper(II) acetate ($Cu(OAc)_2$), silver oxide (Ag_2O), silver fluoride (AgF), benzoquinone (BQ), potassium

persulfate ($K_2S_2O_8$), potassium ferricyanide ($K_3Fe(CN)_6$) and combinations thereof, either in the presence of absence of from about 1 atm oxygen to about 10 atm oxygen;

about 1 equivalent to about 10 equivalents of a base selected from sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof; and

a solvent selected from acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof, to provide the compound of Formula I.

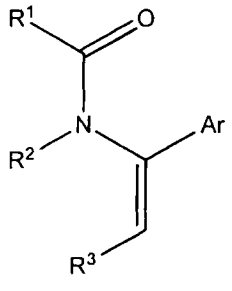
[007] In other embodiments the disclosure provides methods for preparing a compound of Formula IV, by asymmetrically hydrogenating the compound of Formula I to produce a β-amino acid derivative compound of Formula IV:



(I) (IV),

by exposing the compound of Formula I to asymmetric hydrogenation conditions employing the catalyst generated from bis(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate ($[Rh(cod)_2]BF_4$) and (R,R)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2′,1′-e)phosphepino]-benzene ((R)-BINAPHANE) in the presence of hydrogen to produce the compound of Formula IV.

[008] In other embodiments the disclosure provides a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently selected from H, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl, or

R^1 and R^2 are each independently selected from CH_2, C=O and O, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

R^4 is selected H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring; and

Ar is substituted or unsubstituted aryl.

DETAILED DESCRIPTION OF THE EMBODIMENTS

Definitions

[009] Unless otherwise defined, scientific and technical terms used in connection with the disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0010] The following terms, definitions and abbreviations further apply:

[0011] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight (i.e. unbranched) 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. $C_1\text{-}C_{10}$ 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-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-butynyl, and the higher homologs and isomers. Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl."

[0012] Specific values listed herein for groups, substituents, and ranges, are for illustration; they do not exclude other defined values or other values within defined ranges for the groups and substituents. For example, "alkyl" can be methyl, ethyl, propyl, isopropyl, butyl isobutyl, sec-butyl, pentyl, 3-pentyl, or hexyl; cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl; "-O(C_1-C_6)alkyl (alkoxy)" can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy.

[0013] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkyl, as exemplified, but not limited, by $-CH_2CH_2CH_2CH_2-$, $-CH_2CH=CHCH_2-$, $-CH_2CH=CCH_2-$, $-CH_2CH_2CH(CH_2CH_2CH_3)CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, which includes those groups having 10 or fewer carbon atoms. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

[0014] The terms "alkyl, alkoxy, alkenyl, alkynyl," etc. denote both straight and branched groups; but reference to an individual group such as "propyl" embraces the straight chain group, a branched chain isomer such as "isopropyl" being specifically referred to.

[0015] 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 at least one carbon atoms and at least one heteroatom selected from the group consisting of O, N, P, Si and S, and wherein the nitrogen, phosphorus, and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P and S and Si may be placed at any interior position of the heteroalkyl group or at the position at which alkyl group is attached to the remainder of the molecule. Examples include, but are not limited to, $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2$, $-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, $-CH=CH-N(CH_3)-CH_3$, $O-CH_3$, $-O-CH_2-CH_3$, and -CN. Up to two or three heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. 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, $-CH_2-CH_2-S-CH_2-CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxo, alkylenedioxo, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene 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 -C(O)OR'- includes both -C(O)OR'- and -R'OC(O)-. As described above, heteroalkyl groups, as used herein, include those groups that are attached to the remainder of the molecule through a heteroatom, such as -C(O)R', -C(O)NR', -NR'R', -OR', -SR', and/or $-SO_2R'$. Where "heteroalkyl" is recited, followed by recitations of specific heteroalkyl groups, such as -NR'R" or the like, it will be understood that the terms heteroalkyl and -NR'R" are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term "heteroalkyl" should not be interpreted herein as excluding specific heteroalkyl groups, such as -NR'R" or the like.

[0016] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, re, 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-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1-piperazinyl, 2-piperazinyl, and the like. The terms "cycloalkylene" and "heterocycloalkylene" refer to the divalent derivatives of cycloalkyl and heterocycloalkyl, respectively.

[0017] More specifically, the term "alkyl" refers to a branched or unbranched saturated hydrocarbon group of 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, pentyl, and the like. Alkyl groups herein contain 1 to 6 carbon atoms, such as, for example, methyl, ethyl, and the like. As used herein the term "alkyl" also includes the term "cycloalkyl," which refers to a cyclic alkyl group of three to eight, including three, five or six, carbon atoms. The term "cycloalkylene" as used herein refers to a divalent cyclic alkylene group, typically a 3-, 5-, 6-, or 8-membered ring.

[0018] The term "alkoxy" as used herein refers to an alkyl group bound through a single, terminal ether linkage, i.e., an "alkoxy" group may be defined as -OR, where R is alkyl as defined herein. A "lower alkoxy" group refers to an alkoxy group containing 1 to 6, carbon atoms.

[0019] The term "aryl" means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (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 (in each separate ring in the case of multiple rings) 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 carbon or heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pynolyl, 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, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below. The terms "arylene" and "heteroarylene" refer to the divalent radicals of aryl and heteroaryl, respectively.

[0020] For brevity, the term "aryl" when used in combination with other terms (e.g., aryloxo, arylthioxo, 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). However, the term "haloaryl," as used herein is meant to cover aryls substituted with one or more halogens.

[0021] The term "aryl" as used herein refers to an aromatic carbocyclic ring, typically 6- or 10-membered, wherein at least one ring is aromatic. For example, "aryl" denotes a phenyl group or an ortho-fused bicyclic carbocyclic group having about nine to ten ring atoms in which at least one ring is aromatic.

[0022] "Heteroaryl" encompasses a group attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each independently may be non-peroxide oxygen, sulfur, and N(X), where X is absent or is H, O, $(C_1$-$C_4)$alkyl, phenyl or benzyl, as well as a group of an ortho-fused bicyclic-heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene digroup thereto.

[0023] Where a heteroalkyl, heterocycloalkyl, or heteroaryl includes a specific number of members (e.g. "3 to 7 membered"), the term "member" referrers to a carbon or heteroatom.

[0024] 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$(C_1$-$C_4)$alkyl" is mean to include, but not be limited to, trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like. The term "halo" also refers to fluoro, chloro, bromo, or iodo.

[0025] The term "oxo" as used herein means an oxygen that is double bonded to a carbon atom.

[0026] Each of above terms (e.g., "alkyl," "heteroalkyl," "cycloalkyl, and "heterocycloalkyl", "aryl," "heteroaryl" as well as their divalent radical derivatives) are meant to include both substituted and unsubstituted forms of the indicated radical. Substituents for each type of radical are provided below.

[0027] Substituents for alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl monovalent and divalent derivative radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) 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', -CO_2R', -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"C(O)OR', -NR-C(NR'R")=NR"', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -$NRSO_2$R', -CN and -NO_2 in a number ranging from zero to (2 m'+1), where m' is the total number of carbon atoms in such radical. R', R", R"' and R"" each independently refer to hydrogen, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted

heterocycloalkyl, 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 disclosure 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. When R' and R"' are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 4-, 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., $-CF_3$ and $-CH_2CF_3$) and acyl (e.g., -C(O)CH-, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

[0028] Similar to the substituents described for alkyl radicals above, exemplary substituents for aryl and heteroaryl groups (as well as their divalent derivatives) are varied and are selected from, for example: halogen, -OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', $-CO_2R'$, -C(O)NR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"C(O)OR', -NR-C(NR'R"R"')=NR"", -NR-C(NR'R") =NR"', -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-NRSO_2R'$, -CN and $-NO_2$, -R', $-N_3$, $-CH(Ph)_2$, fluoro(C_1-C_4)alkoxy, and fluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on aromatic ring system; and where R', R", R"' and R"" are independently selected from hydrogen, 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. When a compound of the disclosure 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.

[0029] Two of the substituents on adjacent atoms of aryl or heteroaryl ring may optionally form a ring 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 aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, 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 aryl or heteroaryl ring may

optionally be replaced with a substituent of the formula $-(CRR')_s-X'-(C''R''')_d-$, 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 independently selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

[0030] As used herein, the term "heteroatom" or "ring heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S), phosphorus (P), and silicon (Si).

[0031] An "aminoalkyl" as used herein refers to an amino group covalently bound to an alkylene linker. The amino group is -NR'R'', wherein R' and R'' are typically selected from hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl.

[0032] A "substituent group," as used herein, means a group selected from the following moieties:

[0033] (A) -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, oxo, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0034] (B) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from:

[0035] (i) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0036] (ii) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl, substituted with at least one substituent selected from: (a) oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, unsubstituted heteroaryl, and

[0037] (b) alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl, substituted with at least one substituent selected from oxo, -OH, $-NH_2$, -SH, -CN, $-CF_3$, $-NO_2$, halogen, unsubstituted alkyl, unsubstituted heteroalkyl, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, and unsubstituted heteroaryl.

[0038] A "size-limited substituent" or "size-limited substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_{20} alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 20 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_4-C_8 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 4 to 8 membered heterocycloalkyl.

[0039] A "lower substituent" or "lower substituent group," as used herein means a group selected from all of the substituents described above for a "substituent group," wherein each substituted or unsubstituted alkyl is a substituted or unsubstituted C_1-C_8 alkyl, each substituted or unsubstituted heteroalkyl is a substituted or unsubstituted 2 to 8 membered heteroalkyl, each substituted or unsubstituted cycloalkyl is a substituted or unsubstituted C_5-C_7 cycloalkyl, and each substituted or unsubstituted heterocycloalkyl is a substituted or unsubstituted 5 to 7 membered heterocycloalkyl.

[0040] The compounds of the disclosure may exist as salts. The disclosure includes such salts. Examples of applicable salt forms include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates (eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures, succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in art. Also included are base addition salts such as sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the disclosure contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogen-carbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, mono-hydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methane-sulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like. Certain specific

compounds of the disclosure contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0041] The neutral forms of the compounds are regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents.

[0042] Certain compounds of the disclosure 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 disclosure. Certain compounds of the disclosure may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the disclosure and are intended to be within the scope of the disclosure.

[0043] Certain compounds of the disclosure possess asymmetric carbon atoms (optical or chiral centers) or double bonds; the enantiomers, racemates, diastereomers, tautomers, geometric isomers, stereoisometric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)- or, as (D)- or (L)- for amino acids, and individual isomers are encompassed within the scope of the disclosure. The compounds of the disclosure do not include those which are known in art to be too unstable to synthesize and/or isolate. The disclosure is meant to include compounds in racemic and optically pure forms. Optically active (R)- and (S)-, or (D)- and (L)-somers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. When the compounds described herein contain olefinic bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers.

[0044] The term "tautomer," as used herein, refers to one of two or more structural isomers which exist in equilibrium and which are readily converted from one isomeric form to another.

[0045] It will be apparent to one skilled in the art that certain compounds of this disclosure may exist in tautomeric forms, all such tautomeric forms of the compounds being within the scope of the disclosure.

[0046] Unless otherwise stated, structures depicted herein are also meant to include all stereochemical forms of the structure; i.e., the R and S configurations for each asymmetric

center. Therefore, single stereochemical isomers as well as enantiomeric and diastereomeric mixtures of the compounds are within the scope of the disclosure.

[0047] Unless otherwise stated, structures depicted herein are also meant to include compounds which differ in the presence of one or more isotopically enriched atoms. For example, compounds having the structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of this disclosure.

[0048] The compounds of the disclosure may also contain unnatural proportions of atomic isotopes at one or more of atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (3H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the disclosure, whether radioactive or not, are encompassed within the scope of the disclosure.

[0049] Throughout the present disclosure the term "about" a certain value means that a range of value±25%, and preferably a range of value±10%, and more preferably a range of value±5%, is contemplated. Thus, for example, about 20 mol % of a certain reagent includes the reagent being present between 15% and 25%, preferably between 18% and 22%, and more preferably between 19% and 73.5%.

[0050] The terms "a," "an," or "a(n)", when used in reference to a group of substituents herein, mean at least one. For example, where a compound is substituted with "an" alkyl or aryl, the compound is optionally substituted with at least one alkyl and/or at least one aryl. Moreover, where a moiety is substituted with an R substituent, the group may be referred to as "R-substituted." Where a moiety is R-substituted, the moiety is substituted with at least one R substituent and each R substituent is optionally different.

[0051] Description of compounds of the disclosure are limited by principles of chemical bonding known to those skilled in the art. Accordingly, where a group may be substituted by one or more of a number of substituents, such substitutions are selected so as to comply with principles of chemical bonding and to give compounds which are not inherently unstable and/or would be known to one of ordinary skill in the art as likely to be unstable under ambient conditions, such as aqueous, neutral, and several known physiological conditions. For example, a heterocycloalkyl or heteroaryl is attached to the remainder of the molecule via a ring

heteroatom in compliance with principles of chemical bonding known to those skilled in the art thereby avoiding inherently unstable compounds.

[0052] It will be appreciated by those skilled in the art that compounds of the disclosure having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the disclosure encompasses any racemic, optically active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the disclosure, which possesses the useful properties described herein. Also, if the named compound comprises a chiral center, the scope of the disclosure also includes compositions comprising the racemic mixture of the two enantiomers, as well as compositions comprising each enantiomer individually, substantially free of the other enantiomer. Thus, for example, contemplated herein is a composition comprising the S enantiomer substantially free of the R enantiomer, or a composition comprising the R enantiomer substantially free of the S enantiomer.

[0053] By "substantially free" it is meant that the composition comprises less than 10%, or less than 8%, or less than 5%, or less than 3%, or less than 1% of the minor enantiomer. If the named compound comprises more than one chiral center, the scope of the disclosure also includes compositions comprising a mixture of the various diastereomers, as well as compositions comprising each diastereomer substantially free of the other diastereomers.

[0054] It is well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine the anti cancer activity using the standard tests described herein, or using other similar tests which are well known in the art.

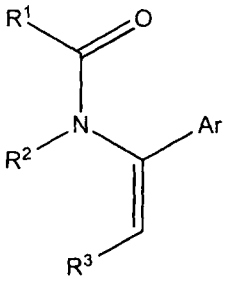
[0055] As used herein, "substantially pure" means an object species is the predominant species (i.e., on a molar basis it is more abundant than any other individual species in the composition), and a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species. Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species in the composition, for example, more than about 85%, 90%, 95%, and 99%. The object species may be also purified to essential homogeneity (contaminant species

cannot be detected in the composition by conventional detection methods), wherein the composition consists essentially of a single species.

Oxidative Heck Reaction

[0056] The present invention provides methods for the synthesis of sterically hindered enamides including the β-amidoacrylate moiety, which can be utilized as a synthetic intermediate in the total synthesis of natural products as well as in the preparation of heterocycles and β-amino acids through asymmetric hydrogenation.

[0057] Thus, in one embodiment the disclosure provides methods for preparing a compound of Formula I:



(I),

wherein R^1 and R^2 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or R^1 and R^2 are each independently selected from CH_2, C=O and O, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

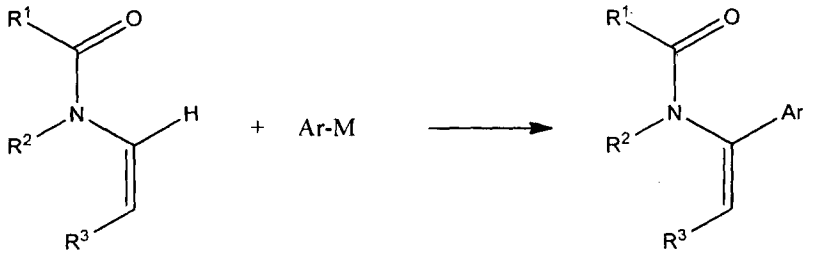
R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

R^4 is selected H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring;

Ar is substituted or unsubstituted aryl,

the method comprising the steps of reacting a compound of Formula II with a compound of Formula III:



(II) (III) (I),

wherein the reaction occurs in the presence of:

about 1 mol % to about 20 mol % $Pd(OAc)_2$;

about 1 equivalent to about 3 equivalents of Ar-M, wherein Ar-M is an arylboron derivative selected from phenyl potassium trifluoroborate, substituted or unsubstituted phenylboronic acid, and substituted or unsubstituted pinacol phenylboronate;

optionally, about 5 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'- tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, $(p\text{-}CF_3C_6H_4)_3P$, $(p\text{-}CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos);

optionally, about 1 equivalent to about 10 equivalents of an additive fluoride source selected from silver fluoride (AgF), copper fluoride (CuF_2), cesium fluoride (CsF), and potassium bifluoride (KHF_2);

about 0.1 equivalent to about 10 equivalents of an oxidant selected from copper(II) acetate ($Cu(OAc)_2$), silver oxide (Ag_2O), silver fluoride (AgF), benzoquinone (BQ), potassium persulfate ($K_2S_2O_8$), potassium ferricyanide ($K_3Fe(CN)_6$) and combinations thereof, either in the presence of absence of from about 1 atm oxygen to about 10 atm oxygen;

about 1 equivalent to about 10 equivalents of a base selected from sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof; and

a solvent selected from acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof,

to provide the compound of Formula I.

[0058] In other embodiments the disclosure provides methods for preparing a compound of Formula I, wherein:

R^1 and R^2, or the 5-, 6- or 7-membered ring they form, are each optionally independently substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

R^3 is optionally substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

R^4 is optionally substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

R^5 and R^6, or the 5-, 6- or 7-membered heterocyclic ring, or the 5-membered heteroaryl ring they form, are each optionally independently substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy; and

Ar is optionally substituted with halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy or $CO_2(C_1\text{-}C_6)$alkyl.

[0059] In other embodiments the disclosure provides methods for preparing a compound of Formula I, wherein the reaction occurs in the presence of:

about 10 mol % $Pd(OAc)_2$;

about 3 equivalents of Ar-M, wherein Ar-M is selected from phenyl potassium trifluoroborate, phenylboronic acid, ortho-, meta- or para-methyl phenylboronic acid, ortho-, meta- or para-methoxy phenylboronic acid, pinacol phenylboronate, pinacol ortho-, meta- or para-methyl phenylboronate, and pinacol phenylboronate ortho-, meta- or para-methoxy phenylboronate;

optionally, about 15 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and 1,1'-bis(diphenylphosphino)-ferrocene (DPPF);

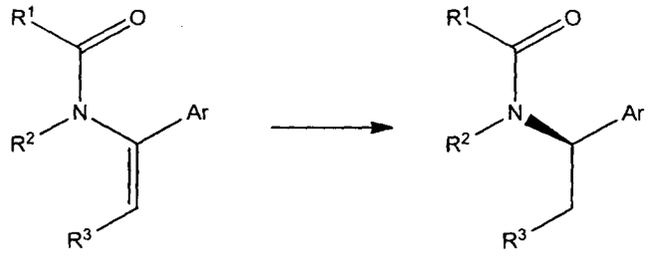
optionally, about 5 equivalent of an additive fluoride source of potassium bifluoride (KHF_2);

about 20 mol % of an oxidant selected from copper (II) acetate ($Cu(OAc)_2$) in conjunction with about 1 atm of oxygen;

about 5 equivalents of a base selected potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), and cesium carbonate (Cs_2CO_3); and

a solvent of about 20 % acetic acid (AcOH) in tert-butyl alcohol (tert-BuOH).

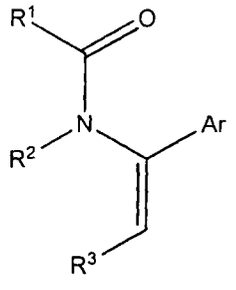
[0060] In other embodiments the disclosure provides methods for preparing a compound of Formula I, further comprising the step of asymmetrically hydrogenating the compound of Formula I to produce a β-amino acid derivative compound of Formula IV:



(I) (IV),

the method comprising the step exposing the compound of Formula I to asymmetric hydrogenation conditions employing the catalyst generated from bis(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate ($[Rh(cod)_2]BF_4$) and (R,R)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2′,1′-e)phosphepino]-benzene ((R)-BINAPHANE) in the presence of hydrogen to produce the compound of Formula IV.

[0061] In other embodiments the disclosure provides a compound of Formula I:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently selected from H, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl, or R^1 and R^2 are each independently selected from CH_2, C=O and O, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

R^4 is selected H, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl, or

R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring; and

Ar is substituted or unsubstituted aryl.

[0062] In other embodiments the disclosure provides a compound of Formula I, wherein:

R^1 and R^2, or the 5-, 6- or 7-membered ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

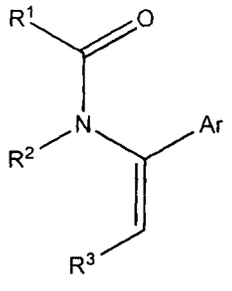
R^3 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy

R^4 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

R^5 and R^6, or the 5-, 6- or 7-membered heterocyclic ring, or the 5-membered heteroaryl ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

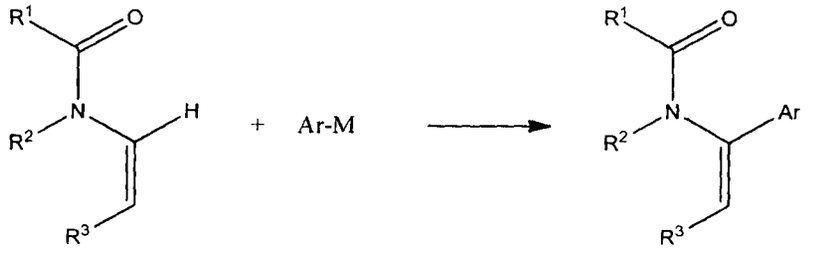
Ar is optionally substituted with halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or CO_2(C_1-C_6)alkyl.

[0063] In other embodiments the disclosure provides a compound of Formula I:



(I),

prepared by the method comprising the steps of reacting a compound of Formula II with a compound of Formula III:



(II) (III) (I),

wherein the reaction occurs in the presence of:

about 1 mol % to about 20 mol % $Pd(OAc)_2$;

about 1 equivalent to about 3 equivalents of Ar-M, wherein Ar-M is an arylboron derivative selected from phenyl potassium trifluoroborate, substituted or unsubstituted phenylboronic acid, and substituted or unsubstituted pinacol phenylboronate;

optionally, about 5 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'- tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, $(p\text{-}CF_3C_6H_4)_3P$, $(p\text{-}CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos);

optionally, about 1 equivalent to about 10 equivalents of an additive fluoride source selected from silver fluoride (AgF), copper fluoride (CuF_2), cesium fluoride (CsF), and potassium bifluoride (KHF_2);

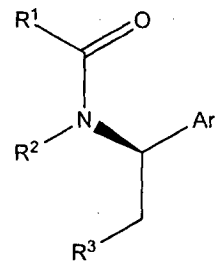
about 0.1 equivalent to about 10 equivalents of an oxidant selected from copper(II) acetate ($Cu(OAc)_2$), silver oxide (Ag_2O), silver fluoride (AgF), benzoquinone (BQ), potassium persulfate ($K_2S_2O_8$), potassium ferricyanide ($K_3Fe(CN)_6$) and combinations thereof, either in the presence of absence of from about 1 atm oxygen to about 10 atm oxygen;

about 1 equivalent to about 10 equivalents of a base selected from sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof; and

a solvent selected from acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof,

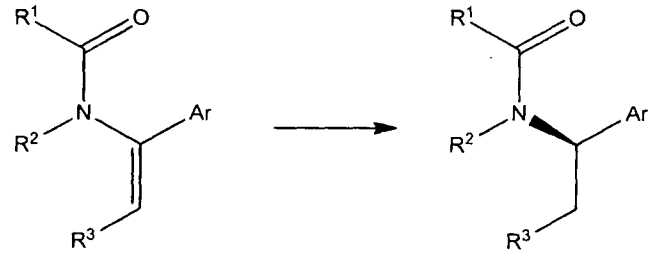
to provide the compound of Formula I.

[0064] In other embodiments the disclosure provides a compound of Formula IV:



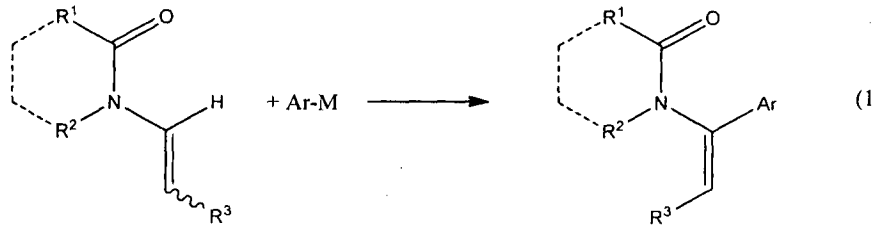
(IV),

prepared by the method of exposing the compound of Formula I to asymmetric hydrogenation conditions employing the catalyst generated from bis(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate ($[Rh(cod)_2]BF_4$) and (R,R)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2',1'-e)phosphepino]-benzene ((R)-BINAPHANE) in the presence of hydrogen to produce the compound of Formula IV:



(I) (IV).

[0065] In order to develop a synthetic route for the synthesis of structurally diverse β-amino acids, it was envisioned that Heck cross-coupling of β-amidoacrylates would provide β-aryl β-amidoacrylates, which could be subsequently converted into the corresponding β-amino acid derivatives by asymmetric hydrogenation [Eq. (1)].

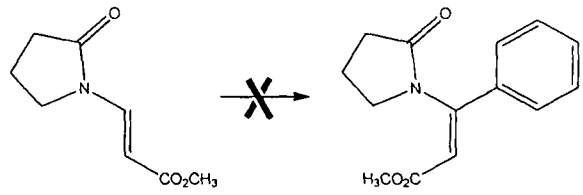


(1)

$R^3 = CO_2R$, CONRR', Ar

[0066] As shown below in Table 1, a survey of the various Heck conditions reported in the literature was undertaken, in which compound 1a was employed compound 1a a substrate. Surprisingly, none of the attempted reaction conditions afforded the Heck products possibly due to steric and/or electronic deactivation

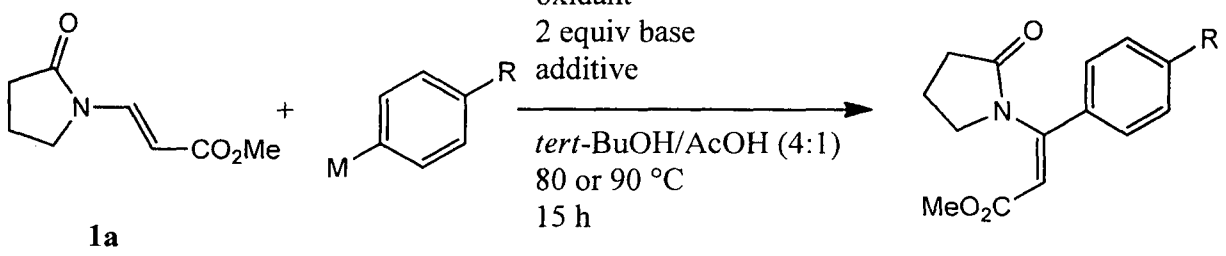
Table 1: Comparison to Reported Pd (II) Oxidative Heck Couplings



Reaction Conditions	%Yield	Reference
PhBr 3% $Pd(OAc)_2$ 6% DPPP 2 eq. Et_3N 10 eq. $[iPr_2NH_2][BF_4]$ Isopropanol, 90 °C	0	Liu, Z.; Xu, D.; Tang, W.; Xu, L.; Xiao, J. Tetrahedron Lett. 2008, 49, 2756.
$PhB(OH)_2$ 2% $Pd(OAc)_2$ 2 eq. NMM 2.4% DMPHEN Dioxane, 50 °C	0	Andappan, N.M.S.; Nilsson, p.; von Schench, H.; Larhed, M. J. Org. Chem. 2004, 69, 5212.
$PhB(OH)_2$ 5% $Pd(OAc)_2$ 2 eq. AgOAc 1 eq. CuF_2 2 eq. KHF_2 Acetone, 85 °C	0	Su, Y.; Jiao, N. Org. Lett. 2009, 11, 2980.

[0067] The failures of the above attempted reactions demonstrate the need for new reaction parameters for the oxidative Heck reaction of substituted enamides, e.g. the β-amidoacrylate moiety. These conditions should allow for the stereoselective synthesis of β-substituted β-amidoacrylates and their derivatives in high yields. Among the key factors in most catalytic cycles is the ability to tune the balance between the reactivity and stability of the reactants. Accordingly, the aryl metal species should possess sufficient stability under the given reaction conditions, yet have sufficient activation to provide the reactivity to participate in the catalytic cycle. Various reaction conditions, including the use of different boron derivatives, ligands, oxidants, bases, solvents, and temperature may influence the outcome of the oxidative Heck reaction. A survey of the various reaction conditions that were examined is provided in Table 2 below. °

Table 2. Oxidative Heck Cross-Coupling Reaction[a–d]



1a

3aa R = H; **3ab** R = OCH_3

Entry	R	M	Oxidant	Base	Ligand[f]	Additive	%Yield[e]
1	H	BF_3K	$Cu(OAc)_2$	Na_2CO_3	-	-	6
2	H	BF_3K	$Cu(OAc)_2$	K_3PO_4	-	-	30
3	H	BF_3K	$Cu(OAc)_2$	K_2CO_3	-	-	43
4	H	BF_3K	$Cu(OAc)_2$	Cs_2CO_3	-	-	39
5	H	BF_3K	Ag_2O	K_2CO_3	-	-	40
6	H	BF_3K	AgF	K_2CO_3	-	-	39
7	H	BF_3K	BQ	K_2CO_3	-	-	11
8	H	BF_3K	$K_2S_2O_8$	K_2CO_3	-	-	32
9	H	BF_3K	$K_3Fe(CN)_6$	K_2CO_3	-	-	4
10	H	BF_3K	$Cu(OAc)_2/O_2$	K_2CO_3	-	-	68
11	OCH_3	BF_3K	$Cu(OAc)_2/O_2$	K_2CO_3	-	-	38[j]
12	H	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	-	-	23
13	H	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	-	KHF_2	52
14	H	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	DMPHEN[g]	KHF_2	26
15	H	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	DPPF[g]	KHF_2	58
16	H	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	binap[g]	KHF_2	18
17	H	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	KHF_2	64
18	OCH_3	$B(OH)_2$	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	KHF_2	31[j]
19	H	B(Pin)	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	AgF[i]	61
20	H	B(Pin)	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	CuF_2[i]	48
21	H	B(Pin)	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	CsF[i]	61
22	H	B(Pin)	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	KHF_2	74

23	H	B(Pin)	$Cu(OAc)_2/O_2$	K_2CO_3	-	KHF_2	42
24	OCH_3	B(Pin)	$Cu(OAc)_2/O_2$	K_2CO_3	$bpPCy_2$	KHF_2	75[j]

[a] $ArBF_3K$ and ArB(Pin); 2 equiv used, and $ArB(OH)_2$; 1.5 equiv used.
[b] entries 1–9; 3 equiv of oxidant, 80 °C.
[c] entries 10–18; 20 mol % of $Cu(OAc)_2$, 1 atm of O_2, 80 °C.
[d] entries 19–24; 5 mol % of $Cu(OAc)_2$, 1 atm of O_2, 90 °C, 24 h.
[e] Yield determined by GC methods.
[f] 30 mol % of ligand.
[g] 15 mol % of ligand.
[h] 3 equiv of additive.
[i] 8 equiv of additive.
[j] Yield determined by ^1H NMR spectroscopy. Pin=pinacolate, DMPHEN = 2,9-dimethylphenanthroline, DPPF = 1,1'-bis(diphenylphosphanyl)ferrocene, BINAP = rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, bpPCy2=2-(dicyclohexylphosphino)biphenyl, BQ=benzoquinone.

[0068] Suitable boron derivatives for use in the oxidative Heck reaction include but are not limited to potassium trifluoroborate (BF_3K) and substituted or unsubstituted boronic acid derivatives ($RB(OH)_2$) including phenylboronic acid, 2-thienylboronic acid, methylboronic acid, propenylboronic acid and the like. Other suitable boron derivatives include substituted or unsubstituted boronate esters such as substituted or unsubstituted pinacol phenylboronate and the like. The arylboron derivatives may be substituted in the ortho, meta or para positions, with 1-3 functional groups selected from halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, and $CO_2(C_1\text{-}C_6)$alkyl. The use of arylboronic acids and arylboronates were examined because the different forms of these arylboron derivatives may lead to an improvement in the reaction by altering such factors as the stability of these compounds and the rate of the reaction of the transient intermediates in the catalytic cycle.

[0069] The use of ligands in the oxidative Heck reaction was also screened. Suitable ligands for use in this reaction include but are not limited to 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'-tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, $(p\text{-}CF_3C_6H_4)_3P$, $(p\text{-}CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2=dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) and the like. The use

of nitrogen-based ligands such as DMPHEN afforded the product in 26 % yield (Table 2, entry 14). Among the phosphine-based ligands screened, bpPCy$_2$ afforded the Heck product in 64 % yield (Table 2, entry 17). The corresponding phosphine oxide bpP(O)Cy$_2$, however, failed to give any product.

[0070] The electron-rich aryl trifluoroborate salts (e.g. ArBF$_3$K) and arylboronic acid (ArB(OH)$_2$) rapidly undergo protodeborylation under the oxidative Heck reaction conditions. To improve the lifespan of the arylboron species, the use of arylboronates were pursued in this reaction. For example, pinacol 4-methoxyphenylboronate (B(Pin)) improved the yield of the coupling product to 75% (Table 2, entry 24) in contrast to the corresponding trifluoroborate and boronic acids, which provided the coupled product in 38% and 31% (Table 2, entry 11 and 18 respectively). The use of pinacol 4-methoxyphenylboronate resulted in an improved 74% yield (Table 2, entry 22), whereas the use of pinacol phenylboronate resulted in a 42% yield (Table 2, entry 23).

[0071] Suitable fluoride sources for use in the oxidative Heck reaction include but is not limited to silver fluoride (AgF), copper fluoride (CuF$_2$), cesium fluoride (CsF), potassium bifluoride (KHF$_2$) and the like (Table 2, entries 19-22). Although use of the boronic acid derivatives alone afforded the desired product in 23% yield (Table 2, entry 12), the addition of KHF$_2$ improved the coupling yield to 52 % (Table 2, entry 13).

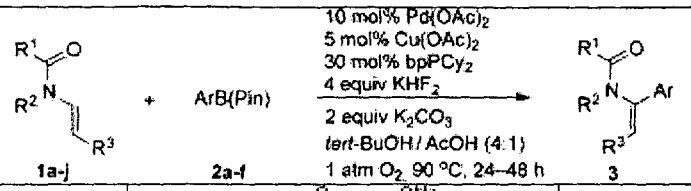
[0072] Suitable oxidants for use in the oxidative Heck reaction include but are not limited to copper(II) acetate (Cu(OAc)$_2$), silver oxide (Ag$_2$O), silver fluoride (AgF), benzoquinone (BQ), potassium persulfate (K$_2$S$_2$O$_8$), potassium ferricyanide (K$_3$Fe(CN)$_6$) and combinations thereof, either in the presence of absence of oxygen. Although common oxidants such as Ag$_2$O and AgF showed comparable results to Cu(OAc)$_2$ (Table 2, entries 5, 6 and 3, respectively), the use of a catalytic amount of Cu(OAc)$_2$ (20 mol %) in conjunction with oxygen (1 atm) as a terminal oxidant improved the product yield to 68 % (Table 2, entry 10). Careful analysis of the two reactions employing stoichiometric and catalytic amounts of Cu(OAc)$_2$ revealed that a large amount of Cu(OAc)$_2$ turns out to be detrimental, and promoted rapid protodeborylation (Table 2, entry 3). However, the reaction conditions employing a catalytic amount of Cu(OAc)$_2$ provided the desired product in 30% yield when the electron-rich 4-methoxyphenyltrifluoroborate was used as a coupling partner producing a large amount of the protodeborylation product (Table 2, entry 11).

[0073] Suitable bases for use in the oxidative Heck reaction include but are not limited to sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof (Table 2, entry 1, entry 3 and 5-24, entry 2, and entry 4, respectively).

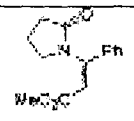
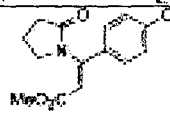
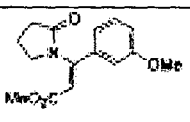
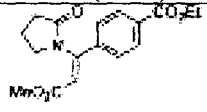
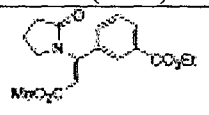
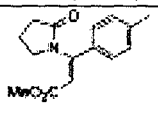
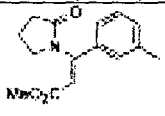
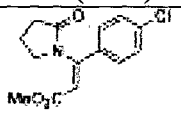
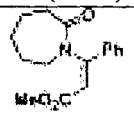
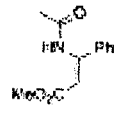
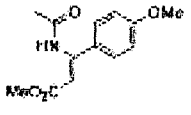
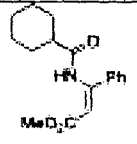
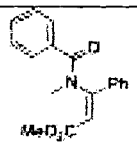
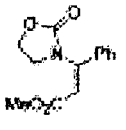
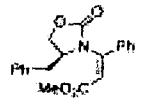
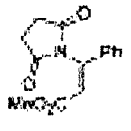
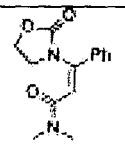
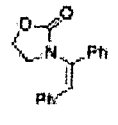
[0074] A brief screening of solvents employing compound 1 a and potassium phenyltrifluoroborate as the coupling partner in the presence of $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (3 equiv), and K_2CO_3 (2 equiv) identified suitable solvents for this reaction, including but not limited to acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof. One useful combination includes, for example, about 20 % AcOH in tert-BuOH. Interestingly, it was found that the use of either 1,4-dioxane or tert-BuOH afforded moderate yields of the desired product, i.e. 50 % and 54 %, respectively, when a stoichiometric amount of $Cu(OAc)_2$ was employed. For reactions when a catalytic amount of $Cu(OAc)_2$ under 1 atm oxygen was used, however, the use of these solvents provided decreased yields of product (18 % 1,4-dioxane and 0 % tert-BuOH). Pure AcOH as a solvent also resulted in a 23% yield of the coupled product.

[0075] A survey of the scope of the substrates that may be used in the oxidative Heck reaction was also examined. Substrates used in these reactions were the E alkene isomers except for compound 1 d. Regardless of the geometry of the alkenes in the substrates, the coupling reactions resulted in Z isomers. Examination of the electronic influence of different aryl groups revealed that those with both electron-donating and electron-withdrawing groups are well-tolerated and gave the coupled products in good to excellent yields (Table 3, entry 3 ab–ae).

Table 3. Scope of the Oxidative Heck Cross-coupling Reaction[a,b]



1a-j 2a-f 3

 3aa (70%)	 3ab (72%)	 3ac (81%)
 3ad (63%)	 3ae (52%)	 3af(80%)
 3ag (80%)	 3ah (52%)	 3ba (81%)
 3ca (57%)	 3cb (51%)	 3da (69%)
 3ea (81%)	 3fa (71%)	 3ga (59%)
 3ha (58%)	 3ia (77%)	 3ja (75%)

[a] 2equiv of pinacol arylboronates. [b] Yield of isolated products. [c] Reaction time was 4 days. [d] Z isomer used as the substrate. [e] 11 % of β,β-diphenyl product 3 ja' was also isolated.

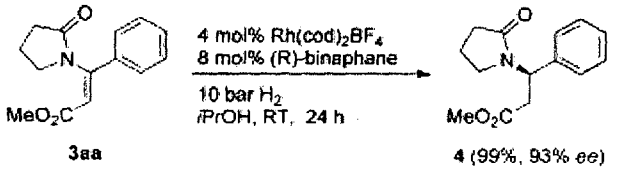
[0076] The reactions of arylboronates with ortho-substituents were sluggish. To gain access to more structurally diverse enamides, substitution of pyrrolidinone with a variety of amide groups including secondary, tertiary, cyclic, acyclic, and aromatic amides was examined.

[0077] As shown in Table 3, this method allows for the synthesis of diverse enamides in high yields. In addition, those containing oxazolidinones in place of amides also afforded products in high yields (Table 3, 3 fa, 3 ga, 3 ia, 3 ja). Moreover, despite the steric hindrance, the reaction of substrate 1 g with the Evans chiral oxazolidinone gave the product in 59 % yield. This outcome shows potential in an application of asymmetric reduction based on a chiral auxiliary. The reaction with highly deactivated alkene 1 h also proceeded smoothly to give product 3 ha in 59% yield.

[0078] The functional group tolerability of substrates with 1i bearing an amide group in place of ester groups was also examined. The reaction also proceeded smoothly and afforded compound 3ia in an excellent yield. Likewise, compound 1j with an aryl group gave the coupling product in a high yield. This result indicates that an electron-withdrawing group is not a requisite, although the regioselectivity of α/β decreases for those lacking an electron-withdrawing group (6.8:1 favoring α substitution in this case).

[0079] To probe if the amide carbonyl groups serve as directing groups in the reaction, a reaction by employing a substrate lacking a carbonyl group was attempted. The instability of the substrate in the acidic medium however, led to hydrolysis of the substrate. While directing groups are routinely employed to facilitate C-H bond activation, their presence is not required in the Heck reaction.

[0080] The transformation of enamides into β-amino acid derivatives proceeded smoothly. Enamide 3aa was exposed to asymmetric hydrogenation conditions employing the catalyst generated from bis(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate ($[Rh(cod)_2]BF_4$) and (R,R)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2′,1′-e)phosphepino]-benzene ((R)-BINAPHANE) smoothly produced compound 4 in 99 % yield and 93 % ee.



3aa 4 (99%, 93% *ee*) (2)

[0081] Other asymmetric hydrogenation conditions that are applicable here are well known to those of skill in the art.

[0082] In summary, the disclosure provides an efficient oxidative Heck cross-coupling reaction using conditions that allow for the synthesis of highly substituted enamides,

which are important synthetic intermediates with a broad utility in various applications. It is noted that modulation of the stability and reactivity of the arylboron species in this reaction was found to be the key for the reaction such that the increased life span of arylboron species leads to a decreased background reaction and yet sufficiently reactive to participate in the catalytic cycle upon activation.

EXAMPLES

[0083] The following examples are provided in order to demonstrate and further illustrate certain preferred embodiments and aspects of the present invention and are not to be construed as limiting the scope thereof.

General Information

[0084] ^1H NMR (400MHz) spectra were recorded at room temperature on a Bruker AV 300MHz, Bruker AVIII 400MHz or a JEOL ECA 400NMR spectrometer in $CDCl_3$ [using $(CH_3)_4Si$ (for ^1H, $\delta = 0.00$) as internal standard]. ^{13}C NMR (100 MHz) spectra on a Bruker AVIII 400MHz spectrometers in $CDCl_3$ [using $CDCl_3$ (for 13C, $\delta = 77.00$) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, m = multiplet, bd = broad of doublet, bs = broad of singlet. HRMS (ESI) spectra were recorded on a Waters Q-Tof premier™ mass spectrometer. X-ray crystallographic data were collected by using a Bruker X8Apex diffractometer with Mo K/α radiation (graphite monochromator).

[0085] Flash column chromatography was performed with silica gel 60 (230-400 mesh) or aluminium oxide (type CG-20, Sigma-Aldrich). Chromatograms were visualized by fluorescence quenching with UV light at 254 nm or by staining using base solution of potassium permanganate and molybdate.

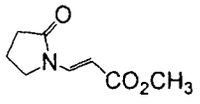
Materials

[0086] Unless otherwise noted, commercial reagents were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. *tert*-Butanol and acetic acid were purchased from Merck and used without further purification. $Pd(OAc)_2$ (98%) was purchased from Sigma-Aldrich, all the phosphine ligands were purchased from Strem, KHF_2 (97%) was purchased from Alfa Aesar, anhydrous $Cu(OAc)_2$ (98%) was purchased from Sigma-

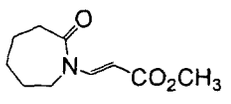
Aldrich, K_2CO_3 was ground to fine power which was dried under vacuum at 100 °C for 4 h. Arylboronic acids were purchased from Sigma-Aldrich and used without further purification. The corresponding pinacol boronates were prepared according to the literature procedure, and their spectroscopic data were confirmed by comparison with those reported previously.

Substrate Structures:

[0087] β-Amidoacrylates



1a



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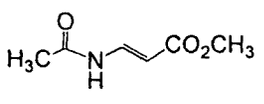

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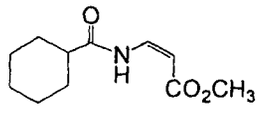

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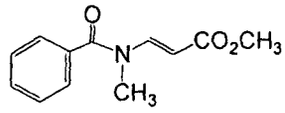

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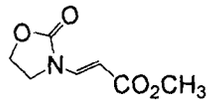

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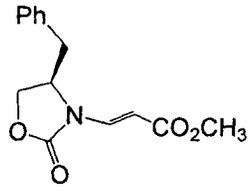

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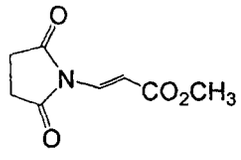
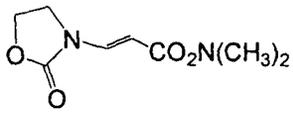


1h



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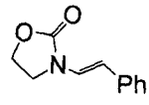
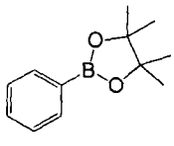


1j

[0088] Aryl Pinacol Boronic Esters



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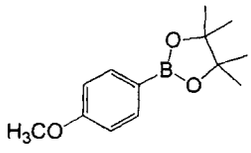

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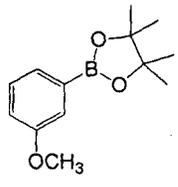

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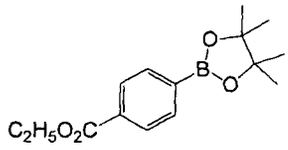

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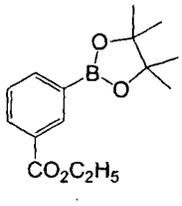

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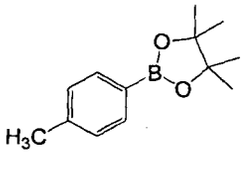

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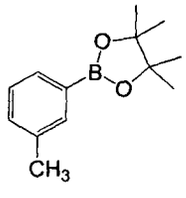

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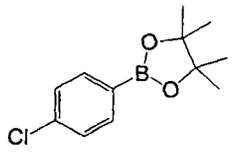
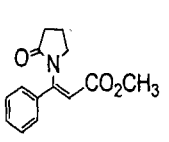


2h

Product Structures

[0089] β-Substituted β-Amidoacrylates



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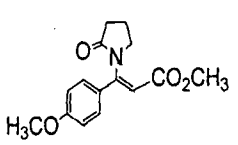

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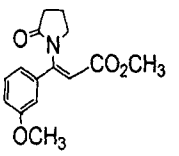

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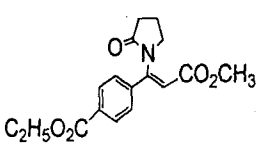

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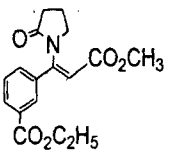

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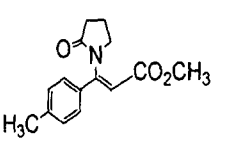

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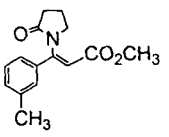

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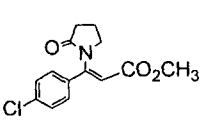

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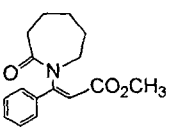

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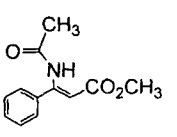

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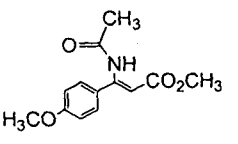

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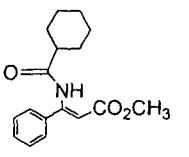

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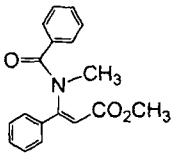

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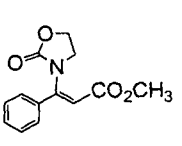

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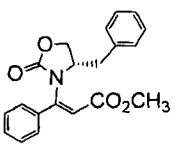

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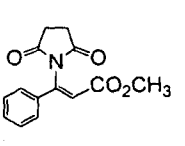

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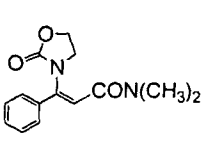

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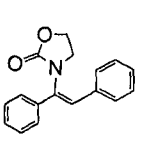


3ja

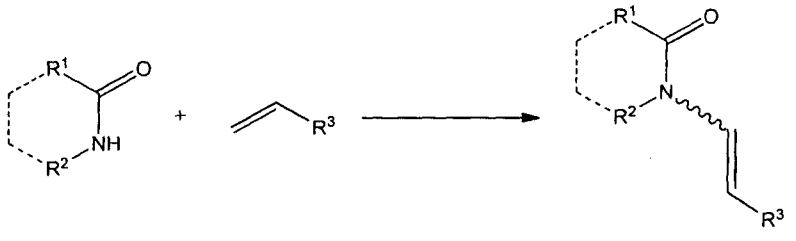
Example 1: General Procedure for the Preparation of Compound 3ab

[0090] Compound 1a (42 mg, 0.25 mmol), 4-methoxyphenylboronic acid pinacol ester 2 b (117 mg, 0.50 mmol), $Pd(OAc)_2$ (5.6 mg, 10 mol %), $Cu(OAc)_2$ (2.3 mg, 5 mol %), 2-(dicyclohexylphosphino)-biphenyl (26 mg, 30 mol %), K_2CO_3 (69 mg, 2 equiv), and KHF_2 (78 mg, 4 equiv). tert-BuOH/AcOH (4:1, 2.5 mL) were added to a flask that was subsequently evacuated and back-filled with O_2 three times before being heated to 90 °C under O_2 (1 atm). The progress of the reaction was monitored by TLC and GC analysis. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of CELITE®. The filtrate was concentrated in vacuo, and the crude material was purified by flash chromatography on silica gel (eluent: 40 % hexanes/ethyl acetate) to afford the product 3 ab (50 mg, 72 %, white solid, mp 88-89 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, J=8.8 Hz, 2 H), 6.91 (d, J=8.8 Hz, 2 H), 6.21 (s, 1 H), 3.84 (s, 3 H), 3.74 (s, 3 H), 3.56 (t, J=7.0 Hz, 2 H), 2.60 (t, J=8.0 Hz, 2 H), 2.23-2.15 ppm (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.44,

165.13, 161.68, 148.32, 128.56, 126.94, 114.38, 112.38, 55.42, 51.46, 49.26, 31.72, 19.21; HRMS (ESI): m/z calcd for $C_{15}H_{18}NO_4$ [M+H]+: 276.1236; found: 276.1239.

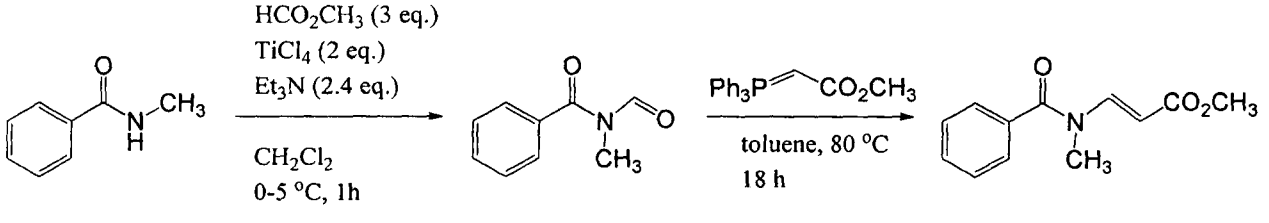
Example 2: General Procedures for the Synthesis of β-Amidoacrylates

[0091] The β-amidoacrylates 1a, 1b, 1c, 1d, 1f, 1g, 1i, 1j were synthesized according to the Murahashi's method:



[0092] All the reactions were performed in 2 mmol scale. In a dried 10 mL Schlenk tube were placed $PdCl_2(CH_3CN)_2$ (5 mol%), CuCl (5 mol%), dry DME (1M), and amide under O_2 (balloon) at 60 °C. At this temperature, the olefin (3 equiv) was added slowly. Upon completion of the reaction (24 h), the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of CELITE®. The filtrate was concentrated in vacuo. The crude residue was purified by flash chromatography on a short silica gel (ethyl acetate/hexanes) to afford the product (both *E* and *Z* isomers, only one isomer was used in the subsequent oxidative Heck reaction).

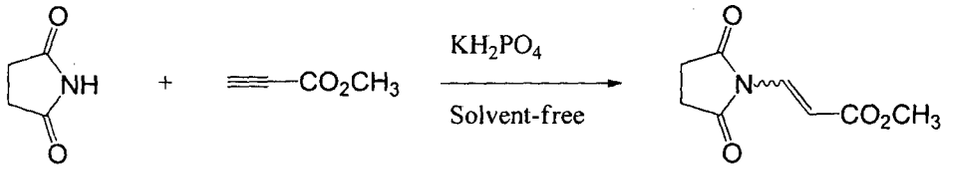
Example 3: The β-amidoacrylates 1e was synthesis according to the Marquez's method.



[0093] $TiCl_4$ (2 mmol) and triethylamine (2.4 mmol) were successively added dropwise to a stirring solution of *N*-methylbenzamide (1 mmol) and HCO_2CH_3 (3 mmol) in methylene chloride (2 mL) at 0-5 °C under a N_2 atmosphere. The mixture was stirred at the same temperature for 1 h and at 20-25 °C for 1 h. Water was added to the mixture, which was extracted twice with ethyl acetate. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The obtained crude material was used directly for the next step.

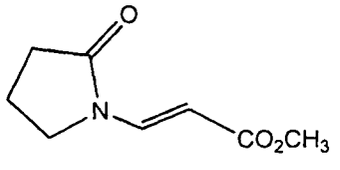
[0094] A solution of the crude *N*-formyl-*N*-methylbenzamide (1.0 mmol) in benzene (10 mL) was treated with methyl 2-(triphenylphosphoranylidene)acetate (3.0 mmol) and the resulting homogeneous mixture heated to 80 °C for 18 hours. Once the reaction was complete by TLC analysis, the solvent was then removed in vacuo to generate a semi-solid crude residue. Purification of the crude product by flash column chromatography (silica gel, 30% EtOAc/Hexane) proceeded to generate the desired 1e (*E*-isomer) in 60% overall yield.

Example 4: The β-amidoacrylates 1h was synthesis according to the Ramazani's method.



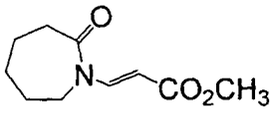
[0095] A heterogeneous mixture of succinimide (1 mmol), methyl propiolate (1 mmol), and powdered dipotassium hydrogen phosphate (0.8 g amount of the catalyst) was heated (without stirring) in an oven at 95 °C for 45 min and then placed over a column of silica gel. The column was washed using ethyl acetate/hexane as the eluent. The solvent was removed under reduced pressure, and the product was obtained as a mixture of *E* and *Z* isomer.

(*E*)-methyl 3-(2-oxopyrrolidin-1-yl)acrylate (*1a*)



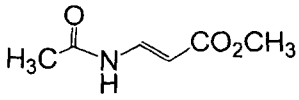
[0096] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 14.4 Hz, 1H), 5.21 (d, J = 14.4 Hz, 1H), 3.74 (s, 3H), 3.57 (t, J = 7.2 Hz, 2H), 2.56 (t, J = 8.2 Hz, 2H), 2.23-2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.25, 167.61, 137.44, 100.20, 51.40, 44.92, 30.91, 17.39; HRMS (ESI) m/z [M+H]+: Calcd for $C_8H_{12}NO_3$: 170.0817 Found: 170.0823

(*E*)-methyl 3-(2-oxoazepan-1-yl)acrylate (*1b*)



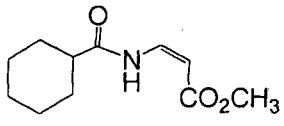
[0097] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 14.4 Hz, 1H), 5.24 (dd, J = 14.4 Hz, 1H), 3.66 (m, 3H), 3.57 (m, 2H), 2.64 (m, 2H), 1.7-1.64 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.91, 168.22, 140.91, 98.33, 51.29, 45.43, 36.94, 29.08, 27.14, 23.38; HRMS (ESI) m/z [M+H]+: Calcd for $C_{10}H_{16}NO_3$: 198.1130 Found: 198.1134.

(*E*)-methyl 3-acetamidoacrylate (*1c*)



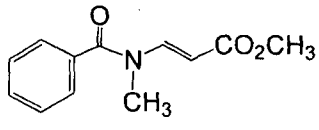
[0098] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (bs, 1H), 8.06-7.99 (m, 1H), 5.46(d, J = 14.0 Hz, 1H), 3.73 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.54, 168.10, 137.93, 100.87, 51.50, 23.36; HRMS (ESI) m/z [M+H]+: Calcd for $C_6H_{10}NO_3$: 144.0661 Found: 144.0655.

(Z)-methyl 3-(cyclohexanecarboxamido)acrylate (*1d*)



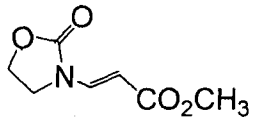
[0099] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (bd, J = 8.0 Hz, 1H), 7.56-7.50 (m, 1H), 5.14 (d, J = 8.8 Hz, 1H), 3.74 (s, 3H), 2.31-2.23 (m, 1H), 1.97-1.94 (m, 2H), 1.84-1.81 (m, 2H), 1.71-1.69 (m, 1H), 1.53-1.43 (m, 2H), 1.36-1.18 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.21, 169.78, 138.62, 95.64, 51.23, 45.34, 29.15, 25.58, 25.50; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{18}NO_3$: 212.1287 Found: 212.1290.

(*E*)-methyl 3-(*N*-methylbenzamido)acrylate (*1e*)



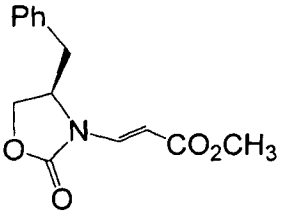
[00100] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 14.2 Hz, 1H), 7.55-7.45 (m, 5H), 5.35 (d, J = 13.8 Hz, 1H), 3.68 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.57, 167.79, 144.82, 133.67, 131.61, 128.94, 128.56, 99.06, 51.60, 31.55; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{14}NO_3$: 220.0974 Found: 220.0978.

(*E*)-methyl 3-(2-oxooxazolidin-3-yl)acrylate (*1f*)



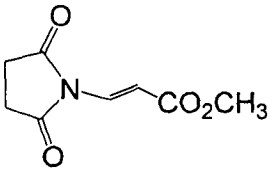
[00101] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 14.0 Hz, 1H), 5.16 (d, J = 14.0 Hz, 1H), 4.56-4.52 (m, 2H), 3.79 (t, J = 8.0 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.92, 154.52, 138.32, 100.06, 62.43, 51.50, 42.07; HRMS (ESI) m/z [M+H]+: Calcd for $C_7H_{10}NO_4$: 172.0610 Found: 172.0612.

(S)-(*E*)-methyl 3-(4-benzyl-2-oxooxazolidin-3-yl)acrylate (*1g*)



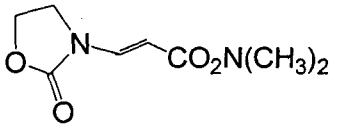
[00102] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 14.4 Hz, 1H), 7.37-7.27 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 5.44 (d, J = 14.4 Hz, 1H), 4.32-4.25 (m, 3H), 3.77 (s, 3H), 3.20 (d, J = 13.6 Hz, 1H), 2.86-2.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.12, 154.34, 137.67, 134.26, 129.32, 129.15, 127.69, 100.14, 66.81, 54.78, 51.58, 36.03; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{16}NO_4$: 262.1079 Found: 262.1079.

(*E*)-methyl 3-(2,5-dioxopyrrolidin-1-yl)acrylate (*1h*)



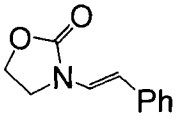
[00103] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 14.8 Hz, 1H), 7.00 (d, J = 14.8 Hz, 1H), 3.78 (s, 3H), 2.83 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.37, 167.21, 131.04, 110.44, 51.85, 27.77; HRMS (ESI) m/z [M+H]+: Calcd for $C_8H_{10}NO_4$: 184.0610 Found: 184.0608.

(*E*)-*N*,*N*-dimethyl-3-(2-oxooxazolidin-3-yl)acrylamide (*1i*)



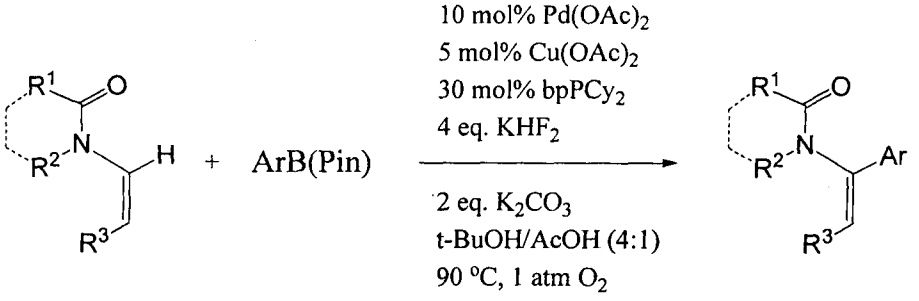
[00104] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 13.2 Hz, 1H), 5.60 (d, J = 13.2 Hz, 1H), 4.53-4.49 (m, 2H), 3.82-3.78 (m, 2H), 3.05 (bs, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.12, 154.75, 136.72, 99.78, 62.19, 42.66, 37.42, 35.77; HRMS (ESI) m/z [M+H]+: Calcd for $C_8H_{13}N_2O_3$: 185.0926 Found: 185.0929.

(*E*)-3-styryloxazolidin-2-one (*1j*)



[00105] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 9.2 Hz, 1H), 7.34-7.26 (m, 4H), 7.21-7.16 (m, 1H), 5.76 (d, J = 14.8 Hz, 1H), 4.51-4.46 (m, 2H), 3.85-3.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.44, 135.86, 128.77, 126.70, 125.52, 123.99, 111.07, 62.30, 42.53; HRMS (ESI) m/z [M+H]+: Calcd for $C_{11}H_{12}NO_2$: 190.0868 Found: 190.0872.

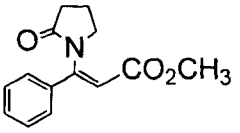
General Procedures for the Oxidative Heck Reaction



[00106] A flask equipped with a magnetic stir was charged with 1 (0.25 mmol), 2 (0.50 mmol), $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (5 mol%), 2-(dicyclohexylphosphino)biphenyl (30 mol%), K_2CO_3 (2 equiv), and 4 equiv KHF_2. t-BuOH/AcOH (4:1, 2.5 mL) was added subsequently. The flask was evacuated and backfilled with O_2 (3 times, balloon), and was heated to 90°C with vigorous stirring. The progress was monitored by TLC and GC analysis. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a small pad of CELITE®. The filtrate was concentrated in vacuo. The NMR yield of a desired product was determined using an internal standard (1,1,2,2-tetrachloroethane). The

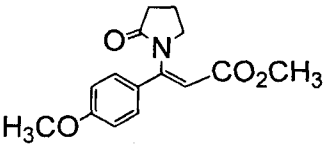
crude material was purified by flash chromatography on a short column of silica gel (hexane/ethyl acetate) to afford the product.

(*Z*)-methyl 3-(2-oxopyrrolidin-1-yl)-3-phenylacrylate (*3aa*)



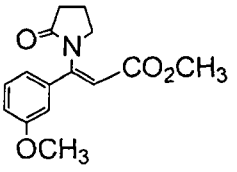
[00107] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47-7.38 (m, 5H), 6.27 (s, 1H), 3.75 (s, 3H), 3.55 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.22-2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.35, 165.02, 148.23, 134.75, 130.60, 128.95, 127.06, 114.46, 51.59, 49.12, 31.68, 19.18; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{16}NO_3$: 246.1130 Found: 246.1139.

(*Z*)-methyl 3-(4-methoxyphenyl)-3-(2-oxopyrrolidin-1-yl)acrylate (*3ab*)



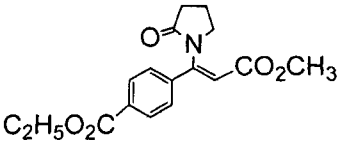
[00108] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.21 (s, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.56 (t, *J* = 7.0 Hz, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.23-2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.44, 165.13, 161.68, 148.32, 128.56, 126.94, 114.38, 112.38, 55.42, 51.46, 49.26, 31.72, 19.21; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{18}NO_4$: 276.1236 Found: 276.1239.

(*Z*)-methyl 3-(3-methoxyphenyl)-3-(2-oxopyrrolidin-1-yl)acrylate (*3ac*)



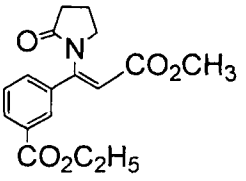
[00109] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (m, 1H), 7.05-7.03 (m, 1H), 6.98-6.96 (m, 2H), 6.26 (s, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.55 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.21-2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.24, 165.00, 159.99, 148.03, 136.29, 129.98, 119.51, 116.01, 114.55, 112.64, 55.38, 51.59, 49.11, 31.69, 19.19; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{18}NO_4$: 276.1236 Found: 276.1248.

(*Z*)-ethyl 4-(3-methoxy-3-oxo-1-(2-oxopyrrolidin-1-yl)prop-1-en-1-yl)benzoate (*3ad*)



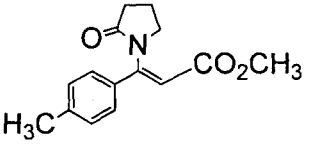
[00110] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H), 6.32 (s, 1H), 4.42-4.37 (m, 2H), 3.76 (s, 3H), 3.55 (t, *J* = 6.8 Hz, 2H), 2.61 (t, *J* = 8.0 Hz, 2H), 2.24-2.17 (m, 2H), 1.41 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.47, 165.81, 164.72, 147.08, 139.03, 132.23, 130.12, 127.00, 116.12, 61.30, 51.74, 49.08, 31.58, 19.18, 14.29; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{20}NO_5$: 318.1341 Found: 318.1347.

(*Z*)-ethyl 3-(3-methoxy-3-oxo-1-(2-oxopyrrolidin-1-yl)prop-1-en-1-yl)benzoate (*3ae*)



[00111] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.10 (m, 2H), 7.64-7.62 (m, 1H), 7.54-7.48 (m, 1H), 6.32 (s, 1H), 4.43-4.31 (m, 2H), 3.76 (s, 3H), 3.56 (t, *J* = 7.0 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.25-2.17 (m, 2H), 1.43-1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.53, 165.83, 164.80, 147.24, 135.25, 131.45, 131.40, 131.14, 129.10, 128.14, 115.35, 61.37, 51.69, 49.11, 31.64, 19.20, 14.31; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{20}NO_5$: 318.1341 Found: 318.1350.

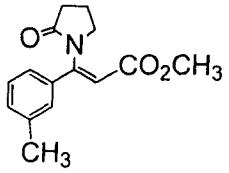
(*Z*)-methyl 3-(2-oxopyrrolidin-1-yl)-3-(p-tolyl)acrylate (*3af*)



[00112] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.24 (s, 1H), 3.74 (s, 3H), 3.55 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.38 (s, 3H), 2.22-2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.31, 165.09, 148.42, 141.03, 131.86,

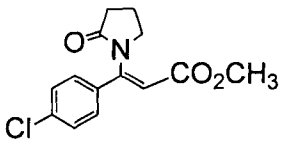
129.68, 126.99, 113.47, 51.51, 49.18, 31.72, 21.37, 19.19; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{18}NO_3$: 260.1287 Found: 260.1289.

(*Z*)-methyl 3-(2-oxopyrrolidin-1-yl)-3-(*m*-tolyl)acrylate (*3ag*)



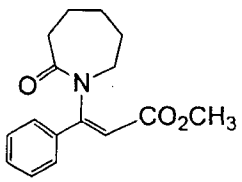
[00113] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.23 (m, 4H), 6.25 (s, 1H), 3.75 (s, 3H), 3.55 (t, *J* = 6.8 Hz, 2H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.37 (s, 3H), 2.22-2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.27, 165.05, 148.49, 138.69, 134.79, 131.41, 128.82, 127.65, 124.25, 114.26, 51.54, 49.14, 31.71, 21.43, 19.18; HRMS (ESI) m/z [M+H]+: Calcd for $C_{15}H_{18}NO_3$: 260.1287 Found: 260.1293.

(*Z*)-methyl 3-(4-chlorophenyl)-3-(2-oxopyrrolidin-1-yl)acrylate (*3ah*)



[00114] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 4H), 6.24 (s, 1H), 3.75 (s, 3H), 3.54 (t, *J* = 7.0 Hz, 2H), 2.59 (t, *J* = 8.0 Hz, 2H), 2.23-2.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.38, 164.79, 147.21, 136.71, 133.36, 129.26, 128.33, 114.81, 51.67, 49.08, 31.61, 19.20; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{15}NO_3Cl$: 280.0740 Found: 280.0748.

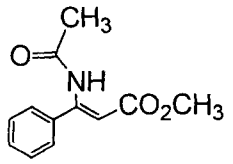
(*Z*)-methyl 3-(2-oxoazepan-1-yl)-3-phenylacrylate (*3ba*)



[00115] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.48 (m, 2H), 7.43-7.35 (m, 3H), 6.24 (s, 1H), 3.74 (s, 3H), 3.46 (bs, 2H), 2.76-2.73 (m, 2H), 1.92 (bs, 2H), 1.80 (bs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.96, 164.74, 153.38, 135.88, 130.35, 128.83, 127.36, 114.19, 51.44, 51.42,

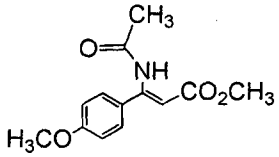
38.04, 30.30, 28.31, 22.65; HRMS (ESI) m/z [M+H]+: Calcd for $C_6H_{20}NO_3$: 274.1443 Found: 274.1449.

(*Z*)-methyl 3-acetamido-3-phenylacrylate (*3ca*)



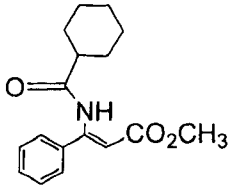
[00116] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (bs, 1H), 7.42-7.33 (m, 5H), 5.29 (s, 1H), 3.77 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.02, 168.45, 154.74. 135.85, 129.64, 128.08, 127.08, 100.59, 51.43, 24.80; HRMS (ESI) m/z [M+H]+: Calcd for $C_{12}H_{14}NO_3$: 220.0974 Found: 220.0981.

(*Z*)-methyl 3-acetamido-3-(4-methoxyphenyl)acrylate (*3cb*)



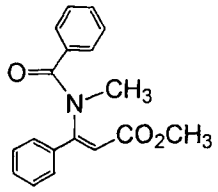
[00117] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.27 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.13, 168.67, 160.95, 154.40, 128.68, 127.92, 113.54, 99.52, 55.31, 51.34, 24.92; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{16}NO_4$: 250.1079 Found: 250.1072.

(*Z*)-methyl 3-(cyclohexanecarboxamido)-3-phenylacrylate (*3da*)



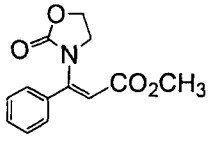
[00118] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 7.40-7.30 (m, 5H), 5.28 (s, 1H), 3.76 (s, 3H), 2.35-2.27 (m, 1H), 2.01-1.94 (m, 2H), 1.84-1.79 (m, 2H), 1.70-1.66 (m, 1H), 1.54-1.40 (m, 2H), 1.37-1.16 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.46, 169.18, 155.21, 136.12, 129.51, 128.04, 126.91, 100.38, 51.41, 46.41, 29.33, 25.69, 25.61; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{22}NO_3$: 288.1600 Found: 288.1590.

(*Z*)-methyl 3-(*N*-methylbenzamido)-3-phenylacrylate (*3ea*)



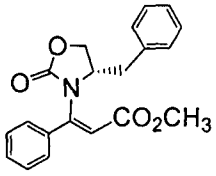
[00119] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.47-7.41 (m, 5H), 7.39-7.25 (m, 1H), 7.21-7.16 (m, 2H), 5.95 (bs, 1H), 3.67 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.56, 164.76, 154.82, 135.93, 135.47, 130.88, 130.26, 129.18, 128.07, 127.68, 127.47, 113.40, 51.55, 36.49; HRMS (ESI) m/z [M+H]+: Calcd for $C_{18}H_{18}NO_3$: 296.1287 Found: 296.1296.

(*Z*)-methyl 3-(2-oxooxazolidin-3-yl)-3-phenylacrylate (*3fa*)



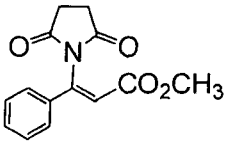
[00120] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.41 (m, 5H), 6.21 (s, 1H), 4.54-4.50 (m, 2H), 3.81-3.77 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.05, 156.24, 147.82, 134.47, 130.95, 129.08, 127.31, 114.04, 62.66, 51.76, 46.37; HRMS (ESI) m/z [M+H]+: Calcd for $C_{13}H_{14}NO_4$: 248.0923 Found: 248.0916.

(S)-(*Z*)-methyl 3-(4-benzyl-2-oxooxazolidin-3-yl)-3-phenylacrylate (*3ga*)



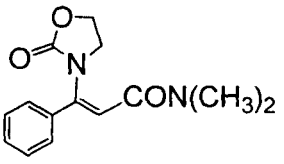
[00121] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.40 (m, 5H), 7.22-7.16 (m, 3H), 6.92-6.88 (m, 2H), 6.18 (s, 1H), 4.39-4.20 (m, 3H), 3.81 (s, 3H), 2.97-2.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.04, 155.44, 146.30, 135.46, 134.62, 130.85, 129.05, 128.89, 128.75, 127.50, 127.06, 115.54, 67.83, 57.85, 51.73, 39.36; HRMS (ESI) m/z [M+H]+: Calcd for $C_{20}H_{20}NO_4$: 338.1392 Found: 338.1394.

(*Z*)-methyl 3-(2,5-dioxopyrrolidin-1-yl)-3-phenylacrylate (*3ha*)



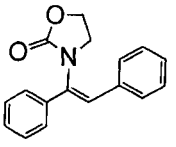
[00122] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.38 (m, 5H), 6.61 (s, 1H), 3.73 (s, 3H), 2.95 (d, *J* = 6.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.88, 164.21, 144.53, 133.75, 131.16, 129.08, 126.21, 116.69, 51.86, 29.14, 24.85; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{14}NO_4$: 260.0923 Found: 260.0923.

(*Z*)-*N*,*N*-dimethyl-3-(2-oxooxazolidin-3-yl)-3-phenylacrylamide (*3ia*)



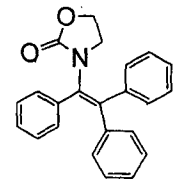
[00123] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.46 (m, 2H), 7.44-7.38 (m, 3H), 6.39 (s, 1H), 4.48-4.44 (m, 2H), 3.78-3.74 (m, 2H), 3.09 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.47, 156.64, 142.25, 134.91, 129.95, 128.95, 126.99, 118.52, 62.43, 46.40, 37.82, 34.98; HRMS (ESI) m/z [M+H]+: Calcd for $C_{14}H_{17}N_2O_3$: 261.1239 Found: 261.1245.

(*Z*)-3-(1,2-diphenylvinyl)oxazolidin-2-one (*3ja*)



[00124] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.28 (m, 10H), 6.87 (s, 1H), 4.44 (t, *J* = 6.4 Hz, 2H), 3.68 (t, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.40, 136.38, 135.27, 134.56, 128.88, 128.81, 128.34, 128.19, 126.99, 125.92, 62.60, 45.42; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{16}NO_2$: 266.1181 Found: 266.1185.

3-(2,2-diphenylvinyl)oxazolidin-2-one (*3ja'*)

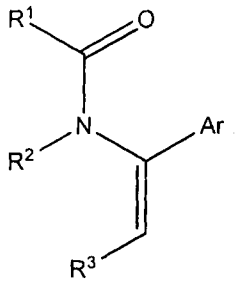


[00125] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.33 (m, 3H), 7.29-7.22 (m, 5H), 7.21-7.16 (m, 2H), 7.15 (s, 1H), 4.20 (t, J = 8.2 Hz, 2H), 3.14 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.27, 140.87, 138.06, 130.90, 128.27, 128.24, 127.85, 127.07, 126.14, 122.46, 62.63, 44.91; HRMS (ESI) m/z [M+H]+: Calcd for $C_{17}H_{16}NO_2$: 266.1181 Found: 266.1190.

[00126] Although the disclosure has been described with reference to the above examples, it will be understood that modifications and variations are encompassed within the spirit and scope of the disclosure. Accordingly, the disclosure is limited only by the following claims.

WHAT IS CLAIMED IS:

1. A method for preparing a compound of Formula I:



(I),

wherein:

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^1 and R^2 are each independently selected from CH_2, C=O and oxygen, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

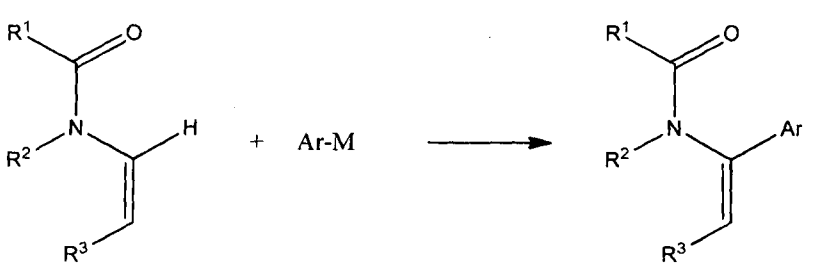
R^4 is selected H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring;

Ar is substituted or unsubstituted aryl,

the method comprising the steps of reacting a compound of Formula II with a compound of Formula III:



(II) (III) (I),

wherein the reaction occurs in the presence of:

about 1 mol % to about 20 mol % $Pd(OAc)_2$;

about 1 equivalent to about 3 equivalents of Ar-M, wherein Ar-M is an arylboron derivative selected from phenyl potassium trifluoroborate, substituted or unsubstituted phenylboronic acid, and substituted or unsubstituted pinacol phenylboronate;

optionally, about 5 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'- tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, $(p\text{-}CF_3C_6H_4)_3P$, $(p\text{-}CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos);

optionally, about 1 equivalent to about 10 equivalents of an additive fluoride source selected from silver fluoride (AgF), copper fluoride (CuF_2), cesium fluoride (CsF), and potassium bifluoride (KHF_2);

about 0.1 equivalent to about 10 equivalents of an oxidant selected from copper(II) acetate ($Cu(OAc)_2$), silver oxide (Ag_2O), silver fluoride (AgF), benzoquinone (BQ), potassium persulfate ($K_2S_2O_8$), potassium ferricyanide ($K_3Fe(CN)_6$) and combinations thereof, either in the presence of absence of from about 1 atm oxygen to about 10 atm oxygen;

about 1 equivalent to about 10 equivalents of a base selected from sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof; and

a solvent selected from acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof,

to provide the compound of Formula I.

2. The method of claim 1, wherein:

R^1 and R^2, or the 5-, 6- or 7-membered ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

R^3 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy

R^4 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

R^5 and R^6, or the 5-, 6- or 7-membered heterocyclic ring, or the 5-membered heteroaryl ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

Ar is optionally substituted with halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or $CO_2(C_1-C_6)$alkyl.

3. The method of claim 1, wherein the reaction occurs in the presence of:

about 10 mol % $Pd(OAc)_2$;

about 3 equivalents of Ar-M, wherein Ar-M is selected from phenyl potassium trifluoroborate, phenylboronic acid, ortho-, meta- or para-methyl phenylboronic acid, ortho-, meta- or para-methoxy phenylboronic acid, pinacol phenylboronate, pinacol ortho-, meta- or para-methyl phenylboronate, and pinacol phenylboronate ortho-, meta- or para-methoxy phenylboronate;

optionally, about 15 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and 1,1'-bis(diphenylphosphino)-ferrocene (DPPF);

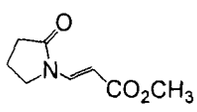
optionally, about 5 equivalent of an additive fluoride source of potassium bifluoride (KHF_2);

about 20 mol % of an oxidant selected from copper (II) acetate ($Cu(OAc)_2$) in conjunction with about 1 atm of oxygen;

about 5 equivalents of a base selected potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), and cesium carbonate (Cs_2CO_3); and

a solvent of about 20 % acetic acid (AcOH) in tert-butyl alcohol (tert-BuOH).

4. The method of claim 1, wherein the compound of Formula II is a β-amidoacrylate selected from the group consisting of



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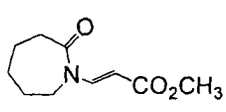

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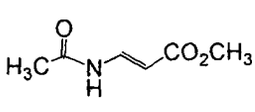

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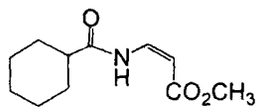

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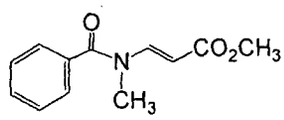

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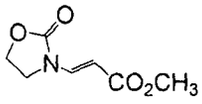

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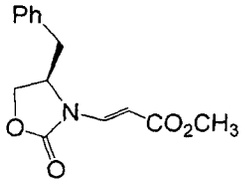

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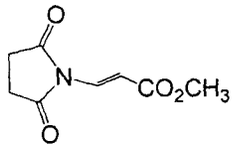
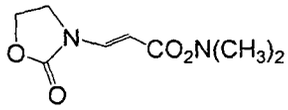
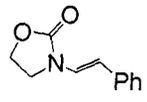


1h

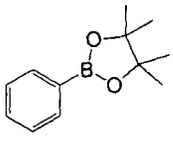


1i



1j

5. The method of claim 1, wherein Ar-M is an aryl pinacol boronic ester selected from the group consisting of



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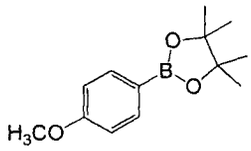

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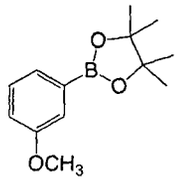

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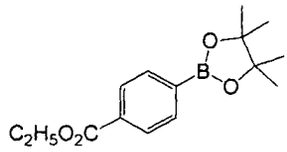

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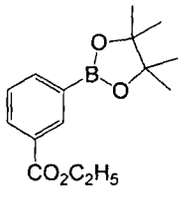

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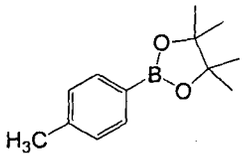

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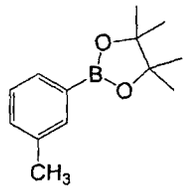

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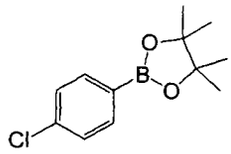
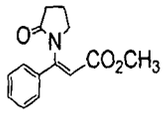
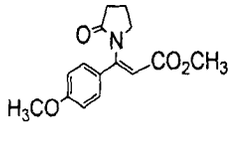


2h

6. The method of claim 1, wherein the compound of Formula I is selected from the group consisting of



3aa



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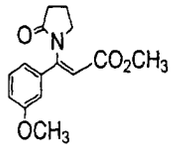
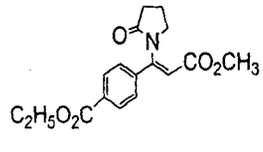


3ac



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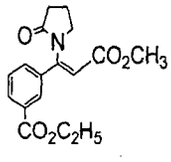

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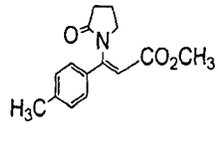

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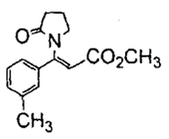

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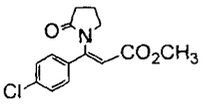

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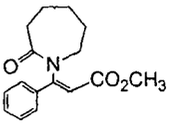

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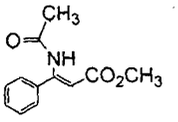

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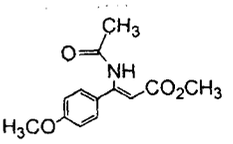

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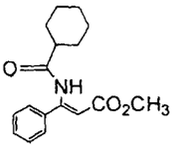

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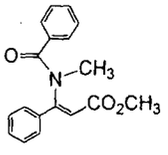

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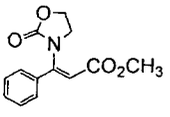

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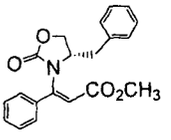

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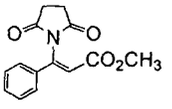

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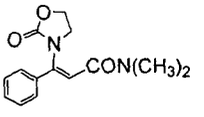

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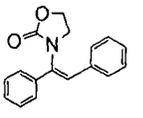

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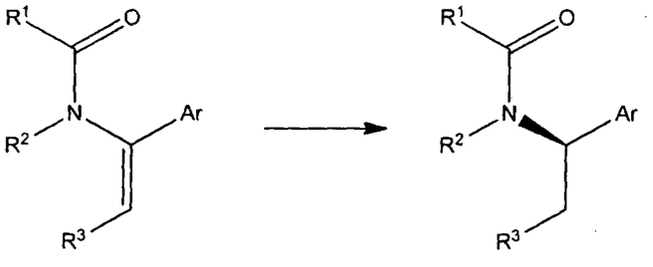
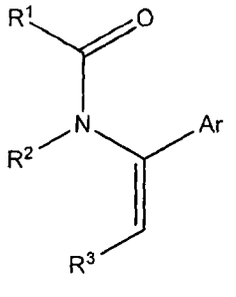
7. The method of claim 1, further comprising the step of asymmetrically hydrogenating the compound of Formula I to produce a β-amino acid derivative compound of Formula IV:



(I) (IV),

the method comprising the step exposing the compound of Formula I to asymmetric hydrogenation conditions employing the catalyst generated from bis(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate ($[Rh(cod)_2]BF_4$) and (R,R)-1,2-Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2′,1′-e)phosphepino]-benzene ((R)-BINAPHANE) in the presence of hydrogen to produce the compound of Formula IV.

8. A compound of Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl, or

R^1 and R^2 are each independently selected from CH_2, C=O and oxygen, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

R^4 is selected H, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted (C_1-C_6)alkyl, substituted or unsubstituted (C_3-C_7)cycloalkyl, and substituted or unsubstituted aryl, or

R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring; and

Ar is substituted or unsubstituted aryl.

9. The compound of claim 8, wherein:

R^1 and R^2, or the 5-, 6- or 7-membered ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

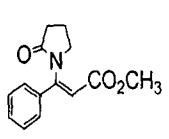
R^3 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy

R^4 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

R^5 and R^6, or the 5-, 6- or 7-membered heterocyclic ring, or the 5-membered heteroaryl ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

Ar is optionally substituted with halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or $CO_2(C_1-C_6)$alkyl.

10. The compound of claim 8, wherein the compound of Formula I is selected from the group consisting of



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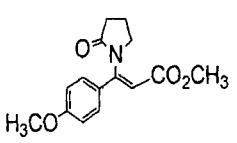

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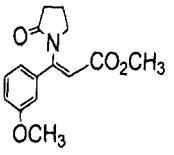

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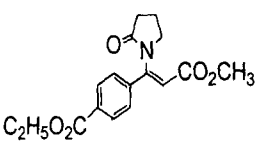

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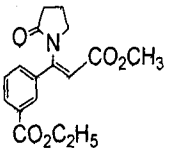

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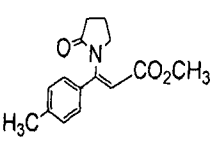

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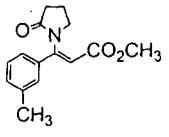

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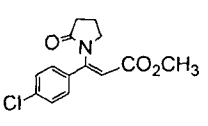

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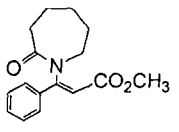

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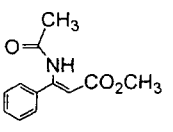

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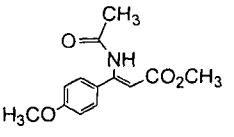

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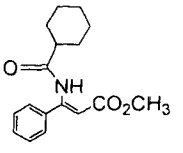

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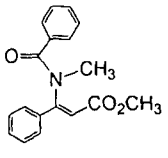

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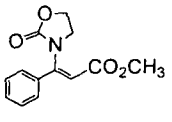

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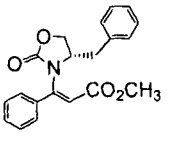

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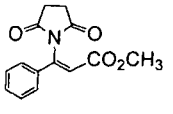

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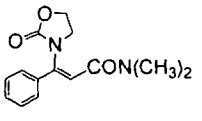

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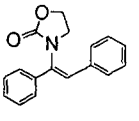
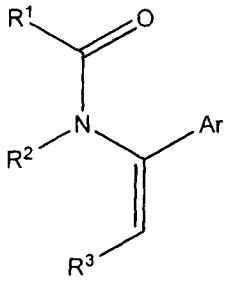


3ja

11. A compound of Formula I:



(I),

wherein:

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^1 and R^2 are each independently selected from CH_2, C=O and oxygen, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

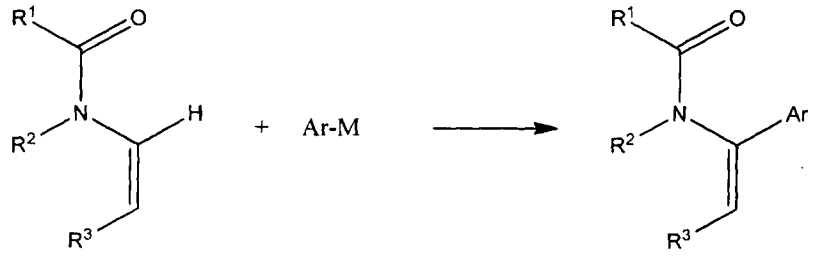
R^4 is selected H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl;

R^5 and R^6 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring;

Ar is substituted or unsubstituted aryl,

wherein the compound of Formula I is prepared by a method comprising the steps of reacting a compound of Formula II with a compound of Formula III:



(II) (III) (I),

wherein the reaction occurs in the presence of:

about 1 mol % to about 20 mol % $Pd(OAc)_2$;

about 1 equivalent to about 3 equivalents of Ar-M, wherein Ar-M is an arylboron derivative selected from phenyl potassium trifluoroborate, substituted or unsubstituted phenylboronic acid, and substituted or unsubstituted pinacol phenylboronate;

optionally, about 5 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'- tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, $(p\text{-}CF_3C_6H_4)_3P$, $(p\text{-}CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos);

optionally, about 1 equivalent to about 10 equivalents of an additive fluoride source selected from silver fluoride (AgF), copper fluoride (CuF_2), cesium fluoride (CsF), and potassium bifluoride (KHF_2);

about 0.1 equivalent to about 10 equivalents of an oxidant selected from copper(II) acetate ($Cu(OAc)_2$), silver oxide (Ag_2O), silver fluoride (AgF), benzoquinone (BQ), potassium persulfate ($K_2S_2O_8$), potassium ferricyanide ($K_3Fe(CN)_6$) and combinations thereof, either in the presence of absence of from about 1 atm oxygen to about 10 atm oxygen;

about 1 equivalent to about 10 equivalents of a base selected from sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof; and

a solvent selected from acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof,

to provide the compound of Formula I.

12. The compound of claim 11, wherein:

R^1 and R^2, or the 5-, 6- or 7-membered ring they form, are each optionally independently substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

R^3 is optionally substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy

R^4 is optionally substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy;

R^5 and R^6, or the 5-, 6- or 7-membered heterocyclic ring, or the 5-membered heteroaryl ring they form, are each optionally independently substituted with halogen, $(C_1\text{-}C_6)$alkyl, or $(C_1\text{-}C_6)$alkoxy; and

Ar is optionally substituted with halogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy or $CO_2(C_1\text{-}C_6)$alkyl.

13. The compound of claim 11, wherein the reaction occurs in the presence of:

about 10 mol % $Pd(OAc)_2$;

about 3 equivalents of Ar-M, wherein Ar-M is selected from phenyl potassium trifluoroborate, phenylboronic acid, ortho-, meta- or para-methyl phenylboronic acid, ortho-, meta- or para-methoxy phenylboronic acid, pinacol phenylboronate, pinacol

ortho-, meta- or para-methyl phenylboronate, and pinacol phenylboronate ortho-, meta- or para-methoxy phenylboronate;

optionally, about 15 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and 1,1'-bis(diphenylphosphino)-ferrocene (DPPF);

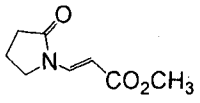
optionally, about 5 equivalent of an additive fluoride source of potassium bifluoride (KHF_2);

about 20 mol % of an oxidant selected from copper (II) acetate ($Cu(OAc)_2$) in conjunction with about 1 atm of oxygen;

about 5 equivalents of a base selected potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), and cesium carbonate (Cs_2CO_3); and

a solvent of about 20 % acetic acid (AcOH) in tert-butyl alcohol (tert-BuOH).

14. The compound of claim 11, wherein the compound of Formula II is a β-amidoacrylate selected from the group consisting of



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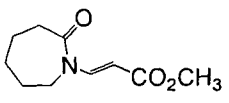

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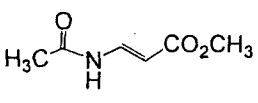

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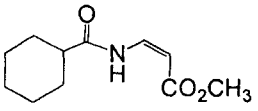

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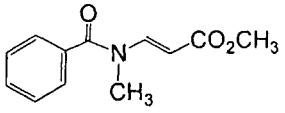

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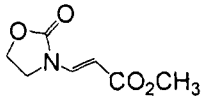

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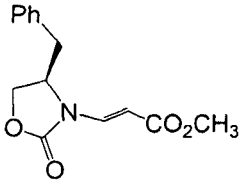

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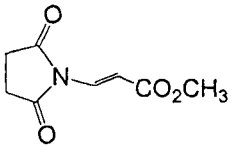

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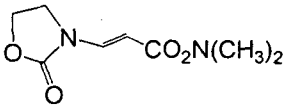

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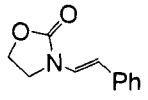

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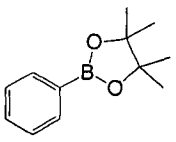
15. The compound of claim 11, wherein Ar-M is an aryl pinacol boronic ester selected from the group consisting of



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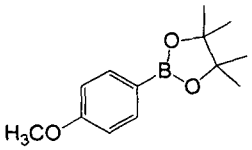

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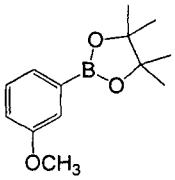

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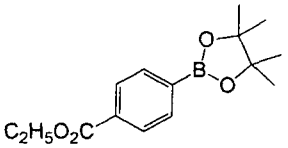

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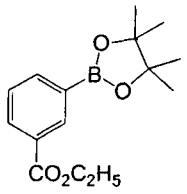

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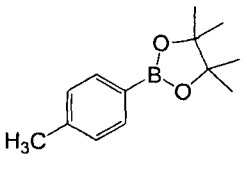

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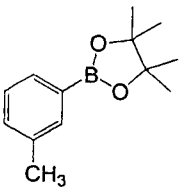

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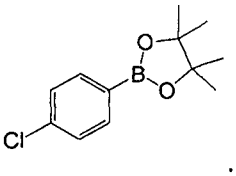

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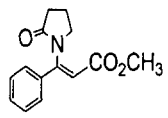
16. The compound of claim 11, wherein the compound of Formula I is selected from the group consisting of



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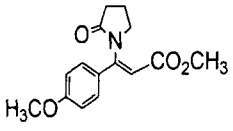

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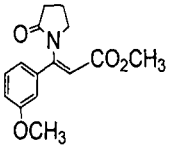

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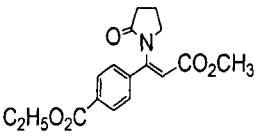

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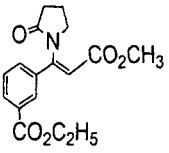

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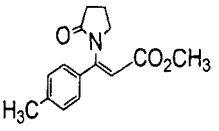

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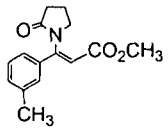

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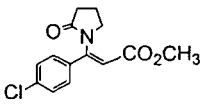

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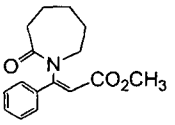

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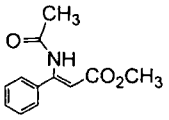

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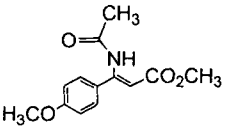

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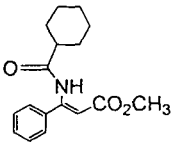

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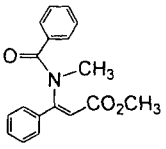

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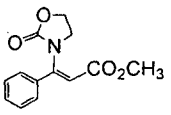

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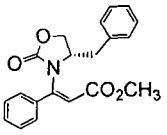

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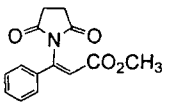

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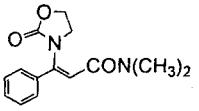

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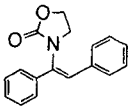

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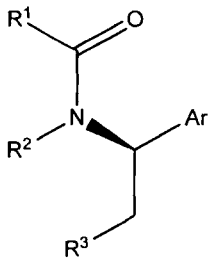
17. A compound of Formula IV:



(IV),

wherein:

R^1 and R^2 are each independently selected from hydrogen, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^1 and R^2 are each independently selected from CH_2, C=O and oxygen, and together form a substituted or unsubstituted 5-, 6- or 7-membered ring;

R^3 is selected from CO_2R^4, $CONR^5R^6$ and substituted or unsubstituted aryl;

R^4 is selected H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl;

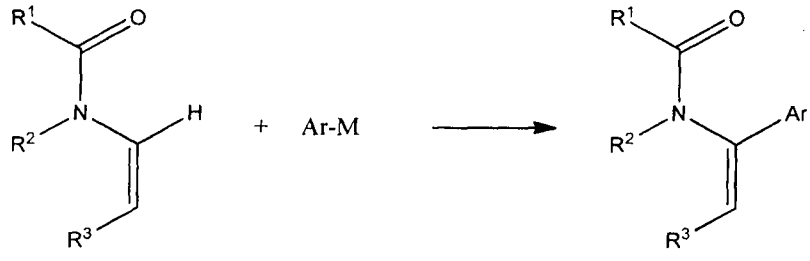
R^5 and R^6 are each independently selected from H, substituted or unsubstituted $(C_1\text{-}C_6)$alkyl, substituted or unsubstituted $(C_3\text{-}C_7)$cycloalkyl, and substituted or unsubstituted aryl, or

R^5 and R^6 together from a substituted or unsubstituted 5-, 6- or 7-membered heterocyclic ring, or R^5 and R^6 together form a substituted or unsubstituted 5-membered heteroaryl ring;

Ar is substituted or unsubstituted aryl,

wherein the compound of Formula IV is prepared by a method comprising the steps of

i) reacting a compound of Formula II with a compound of Formula III:



(II) (III) (I),

wherein the reaction occurs in the presence of:

about 1 mol % to about 20 mol % $Pd(OAc)_2$;

about 1 equivalent to about 3 equivalents of Ar-M, wherein Ar-M is an arylboron derivative selected from phenyl potassium trifluoroborate, substituted or unsubstituted phenylboronic acid, and substituted or unsubstituted pinacol phenylboronate;

optionally, about 5 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), 1,1'-

bis(diphenylphosphino)ferrocene (DPPF), N,N,N',N'- tetramethylethylenediamine (TMEDA), 2,6-lutidine, 2,2'-bipyridyl (Bipy), 1,10-phenanthroline (phen), triphenylphosphine (Ph_3P), o-tol_3P, (p-$CF_3C_6H_4)_3P$, (p-$CH_3C_6H_4)_3P$, phenylphosphite ($(PhO)_3P$), bis(diphenylphosphino)methane (DPPM), bis(diphenylphosphino)ethane (DPPE), bis(diphenylphosphino)propane (DPPP), 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl (tol-BINAP), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos);

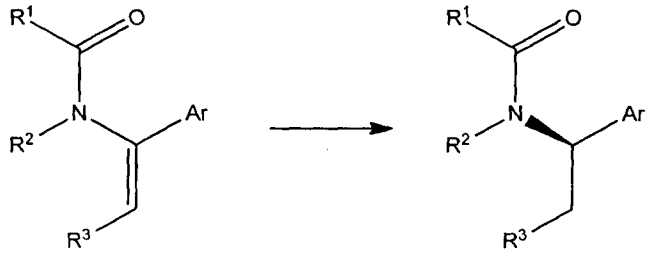
optionally, about 1 equivalent to about 10 equivalents of an additive fluoride source selected from silver fluoride (AgF), copper fluoride (CuF_2), cesium fluoride (CsF), and potassium bifluoride (KHF_2);

about 0.1 equivalent to about 10 equivalents of an oxidant selected from copper(II) acetate ($Cu(OAc)_2$), silver oxide (Ag_2O), silver fluoride (AgF), benzoquinone (BQ), potassium persulfate ($K_2S_2O_8$), potassium ferricyanide ($K_3Fe(CN)_6$) and combinations thereof, either in the presence of absence of from about 1 atm oxygen to about 10 atm oxygen;

about 1 equivalent to about 10 equivalents of a base selected from sodium carbonate (Na_2CO_3), potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and combinations thereof; and

a solvent selected from acetic acid (AcOH), acetonitrile (CH_3CN), N,N-dimethyl formamide (DMF), tert-butyl alcohol (tert-BuOH), 1,4-dioxane, and combinations thereof, and

ii) asymmetrically hydrogenating the compound of Formula I to produce a β-amino acid derivative compound of Formula IV:



(I) (IV),

by a method comprising the step of exposing the compound of Formula I to asymmetric hydrogenation conditions employing the catalyst generated from bis(cycloocta-1,5-diene)rhodium(I) tetrafluoroborate ($[Rh(cod)_2]BF_4$) and (R,R)-1,2-

Bis[(R)-4,5-dihydro-3H-binaphtho(1,2-c:2',1'-e)phosphepino]-benzene ((R)-BINAPHANE) in the presence of hydrogen to produce the compound of Formula IV.

10. The compound of claim 9, wherein:

R^1 and R^2, or the 5-, 6- or 7-membered ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

R^3 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy

R^4 is optionally substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy;

R^5 and R^6, or the 5-, 6- or 7-membered heterocyclic ring, or the 5-membered heteroaryl ring they form, are each optionally independently substituted with halogen, (C_1-C_6)alkyl, or (C_1-C_6)alkoxy; and

Ar is optionally substituted with halogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy or $CO_2(C_1-C_6)$alkyl.

18. The compound of claim 17, wherein the reaction in step i) occurs in the presence of:

about 10 mol % $Pd(OAc)_2$;

about 3 equivalents of Ar-M, wherein Ar-M is selected from phenyl potassium trifluoroborate, phenylboronic acid, ortho-, meta- or para-methyl phenylboronic acid, ortho-, meta- or para-methoxy phenylboronic acid, pinacol phenylboronate, pinacol ortho-, meta- or para-methyl phenylboronate, and pinacol phenylboronate ortho-, meta- or para-methoxy phenylboronate;

optionally, about 15 mol% to about 30 mol% of a ligand selected from 2,9-dimethyl-1,10-phenanthroline (DMPHEN), 2-(dicyclohexylphosphino)-biphenyl ($bpPCy_2$), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), and 1,1'-bis(diphenylphosphino)-ferrocene (DPPF);

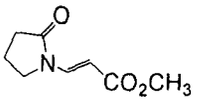
optionally, about 5 equivalent of an additive fluoride source of potassium bifluoride (KHF_2);

about 20 mol % of an oxidant selected from copper (II) acetate ($Cu(OAc)_2$) in conjunction with about 1 atm of oxygen;

about 5 equivalents of a base selected potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), and cesium carbonate (Cs_2CO_3); and

a solvent of about 20 % acetic acid (AcOH) in tert-butyl alcohol (tert-BuOH).

19. The compound of claim 17, wherein the compound of Formula II is a β-amidoacrylate selected from the group consisting of



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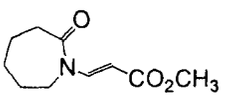

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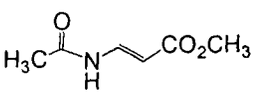

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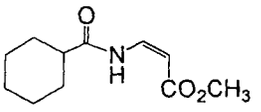

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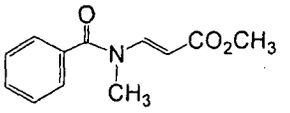

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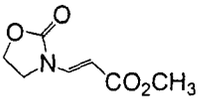

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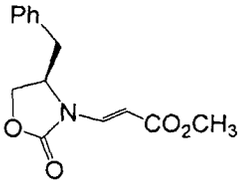

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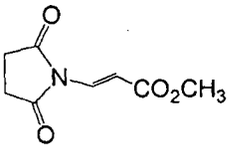

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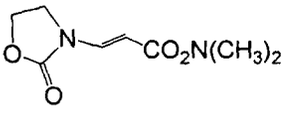

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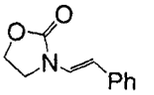

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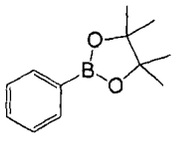
20. The compound of claim 17, wherein Ar-M is an aryl pinacol boronic ester selected from the group consisting of



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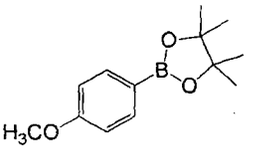

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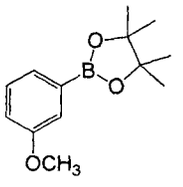

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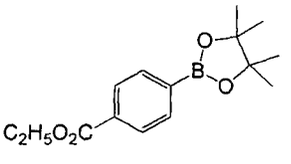

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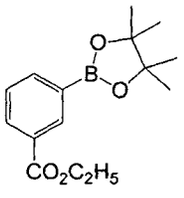

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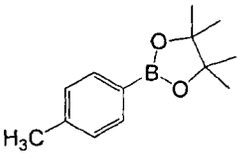

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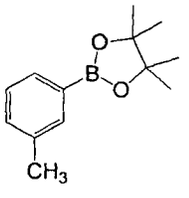

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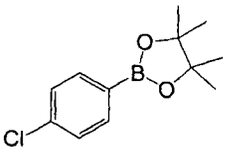

2h

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2012/000209

A. CLASSIFICATION OF SUBJECT MATTER

C07C 231/12 (2006.01) ***C07D 263/22 (2006.01)*** ***C07D 207/404 (2006.01)*** ***C07C 233/47 (2006.01)*** ***C07C 233/63 (2006.01)*** ***C07C 233/87 (2006.01)*** ***C07D 207/27 (2006.01)***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: Databases (File Registry and File CAPlus) – Search based on Formula I and Formula IV

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2012	23 October 2012

Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au Facsimile No.: +61 2 6283 7999	Grace Wong Hui AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. 0262832915

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. PCT/SG2012/000209
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/011414 A1 (DSM IP ASSETS B.V.) 05 February 2004 See abstract; E-3, Z-3, E-12, Z-12, E-13, Z-13, E-14, Z-14, E-15, Z-15, E-16, Z-16, E-18, Z-18, E-19, Z-19 and example V	8-16 and 10a
X	WO 2002/040491 A1 (THE PENN STATE RESEARCH FOUNDATION) 23 May 2002 See abstract; page 51; E/Z mixture on page 52	8-9, 10a, 11-13 and 15
X	Lubell et al., "Enantioselective synthesis of β-amino acids based on BINAP-ruthenium(II) catalyzed hydrogenation", Tetrahedron: Asymmetry, 1991, 2(7), 543-554 See abstract; compound 4c on page 545; compounds 5 and 10 on page 545, (R)-10 in line 13 on page 546 and (R)-5 on page 547	8-20 and 10a
X	US 2004/0229846 A1 (ZHANG et al.) 18 November 2004 See abstract; entries 5 and 6 in table 1 on page 11; enamides of entries 1-10, 15-16 in paragraph [0180]	8-9, 10a, 11-13 and 15
X	Enthaler et al., "Iridium-catalyzed hydrogenation of β-dehydroamino acid derivatives using monodentate phosphoramidites", European Journal of Organic Chemistry, 2008, (19), 3352-3362 See abstract; E-6, Z-6 on page 3353, entries 7-12 in table 5, entries 6-10 in table 6 and entries 7-11 in table 7	8-16 and 10a
X	Hu et al., "Practical Rh(I)-catalyzed asymmetric hydrogenation of β-(acylamino)acrylates using a new unsymmetrical hybrid ferrocenylphosphine-phosphoramidite ligand: Crucial influence of an N-H proton in the ligand", Organic Letters, 2005, 7(3), 419-422 See abstract; compounds (Z)-3a to (Z)-3i in Table 2; compounds (R)-5a to (R)-5i in Table 2; compounds 3e and (R)-5e	8-20 and 10a
X	You et al., "Preparation and asymmetric hydrogenation of β-aryl-substituted β-acylaminoacrylates", Angewandte Chemie, International Edition, 2003, 42(8), 913-916 See abstract; compounds in Table 2	8-16 and 10a
X	CAS Registry RN [306767-88-4], STN Entry Date 5 December 2000 See Registry compound	17-18 and 20
X	CAS Registry RNs [224635-09-0] and [224634-94-0], STN Entry Date 11 June 1999 See Registry compounds	17-18 and 20
X	CAS Registry RN [117020-31-2], STN Entry Date 22 October 1988 See Registry compound	17-18 and 20
A	Werner et al., "A highly selective and general palladium catalyst for the oxidative heck reaction of electronically nonbiased olefins", J. Am. Chem. Soc., 2010, 132, 13981-13983 See abstract; Table 3	1-20 and 10a
A	Zhou et al., "Direct arylation of cyclic enamides via Pd(II)-catalyzed C-H activation", Chemical Communications, 2009, 3472-3474 See abstract; Table 1, entry 5	1-20 and 10a
X P,X	Liu et al., "Stereoselective Synthesis of Highly Substituted Enamides by an Oxidative Heck Reaction", Angewandte Chemie International Edition, 28 June 2011, 50(32), 7333-7336 See title and tables 1 and 2; equation 2 and compound 4 in column 2 on page 7335 See whole document	17-20 1-16 and 10a

INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation).	DOCUMENTS CONSIDERED TO BE RELEVANT	**PCT/SG2012/000209**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. PCT/SG2012/000209

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
WO 2004/011414 A1	05 Feb 2004	AU 2003256149 A1	16 Feb 2004
		WO 2004011414 A1	05 Feb 2004
WO 2002/040491 A1	23 May 2002	AU 1671902 A	27 May 2002
		CA 2427579 A1	23 May 2002
		CN 1610688 A	27 Apr 2005
		EP 1341797 A1	10 Sep 2003
		JP 2004513950 A	13 May 2004
		JP 4167899 B2	22 Oct 2008
		US 2002128501 A1	12 Sep 2002
		US 6653485 B2	25 Nov 2003
		US 2004068126 A1	08 Apr 2004
		US 6855657 B2	15 Feb 2005
		WO 0240491 A1	23 May 2002
US 2004/0229846 A1	18 Nov 2004	AU 2002363788 A1	26 May 2003
		CA 2466449 A1	22 May 2003
		CN 1608074 A	20 Apr 2005
		CN 1608074 B	07 Sep 2011
		CN 101565435 A	28 Oct 2009
		EP 1451133 A2	01 Sep 2004
		JP 2005509012 A	07 Apr 2005
		JP 4488739 B2	23 Jun 2010
		US 2003144137 A1	31 Jul 2003
		US 7105702 B2	12 Sep 2006
		US 2005119495 A1	02 Jun 2005
		US 7153809 B2	26 Dec 2006
		US 2004229846 A1	18 Nov 2004
		US 7169953 B2	30 Jan 2007
		WO 03042135 A2	22 May 2003
		WO 2005117907 A2	15 Dec 2005

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. PCT/SG2012/000209

This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.