

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
25 January 2007 (25.01.2007)

PCT

(10) International Publication Number
WO 2007/011910 A2

(51) International Patent Classification:
C07C 211/02 (2006.01)

(74) Agent: ROBIDOUX, Andrea, L.C.; Choate, Hall & Stewart LLP, Two International Place, Boston, MA 02110 (US).

(21) International Application Number:

PCT/US2006/027778

(22) International Filing Date: 19 July 2006 (19.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/700,870 19 July 2005 (19.07.2005) US
60/778,000 1 March 2006 (01.03.2006) US

(71) Applicant (for all designated States except US):
TRUSTEES OF BOSTON UNIVERSITY [US/US];
One Sherborn Street, Boston, MA 02215 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): SCHAUS, Scott, Edward [US/US]; 43 St. Germain Street, Apt. 3, Boston, MA 02115 (US). LOU, Sha [CN/US]; 1160 Commonwealth Avenue, Apt. 11, Allston, MA 02134 (US). TING, Amal [US/US]; 38 Knowles Street, Newton, MA 02459 (US). BODE, Christine [US/US]; 38 Price Street, Cambridge, MA 02139 (US). TAOKA, Brandon, M. [US/US]; 12 Gardner Street, Apt. 3C, Allston, MA 02134 (US). DAI, Peng [CN/US]; 74 Raymond Street, Allston, MA 02134 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CHIRAL AMINE-CATALYZED ASYMMETRIC ADDITION OF CARBON-CENTERED NUCLEOPHILES TO IMINES

(57) Abstract: The present invention relates to an asymmetric synthesis useful for preparing compounds useful for the treatment of cardiovascular diseases and for studying the role of motor proteins in cell cycle progression.



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CHIRAL AMINE-CATALYZED ASYMMETRIC ADDITION OF CARBON-CENTERED NUCLEOPHILES TO IMINES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present invention claims priority to United States provisional patent application serial number 60/700,870, filed July 19, 2005, and United States provisional patent application serial number 60/778,000, filed March 1, 2006, the entirety of each of which is hereby incorporated herein by reference.

FIELD OF THE INVENTION

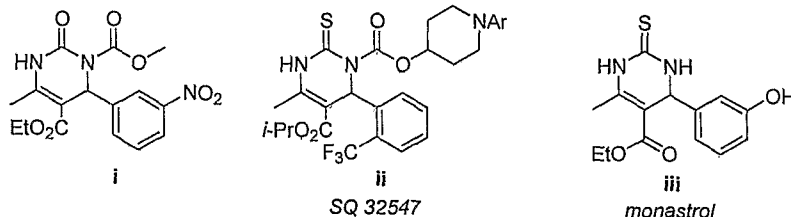
[0002] The present invention relates to an asymmetric synthesis useful for preparing compounds useful for the treatment of cardiovascular diseases and for studying the role of motor proteins in cell cycle progression.

GOVERNMENT SUPPORT

[0003] This invention was made with Government Support under Contract No. GM67041 awarded by the National Institutes of Health and Contract No. CHE-0349206 awarded by the National Science Foundation. The Government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0004] Substituted 4-aryl-dihydropyrimidones are interesting targets for library synthesis. Representative members of this structural class include compounds **i** and SQ32547 (**ii**), calcium channel blockers useful for the treatment of various cardiovascular diseases, and monastrol **iii**, a kinesin inhibitor and valuable tool for studying the role of motor proteins in cell cycle progression.



[0005] Although dihydropyrimidones are useful biological and pharmacological research tools, there are few procedures for preparing compounds of this structural class in enantioenriched form. Preparation of 1,3-unsubstituted dihydropyrimidones of this type in

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racemic form is accomplished using Biginelli reaction conditions by refluxing urea, aryl aldehydes, and the corresponding β -keto ester under acid catalysis in benzene. *See* Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones by Aluminum Hydrogensulfate. Khodaei, M. M. *et al. Pol. J. Chem.* **2004**, 78, 385; and One-pot Biginelli Condensation Reaction in an Ionic Liquid. Madje, B. R. *et al. Ind. J. Heterocyclic Chem.* **2004**, 14, 87. Then, typically, dihydropyrimidones are obtained in enantioenriched form by resolution processes. *See* Enantioseparation of Racemic 4-aryl-3,4-dihydro-2(1H)-pyrimidones on Chiral Stationary Phases Based on 3,5-Dimethylanilides of N-(4-Alkylamino-3,5-dinitro)benzoyl L-Alpha-amino Acids. Kontrec, D. *et al. Chirality* **2003**, 15, 550; and Chiral Separation of Pharmacologically Active Dihydropyrimidinones with Carboxymethyl-beta-cyclodextrin. Lecnik, O. *et al. Electrophoresis* **2001**, 22, 3198. To date, an enantioselective Biginelli reaction has yet to be identified that yields the corresponding products in high optical purity. Accordingly, there remains an unmet need to synthesize 4-aryl-dihydropyrimidones in an enantioselective manner.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] **Figure 1** depicts the X-ray crystal structure of (*R*)-1-[(*S*)-(3-Fluoro-phenyl)-methoxycarbonylamino-methyl]-2-oxo-cyclopentanecarboxylic acid methyl ester.

[0007] **Figure 2** depicts the X-ray crystal structure of [(*S*)-(*S*)-(1-Acetyl-2-oxo-cyclopentyl)-(3-fluoro-phenyl)-methyl]-carbamic acid methyl ester.

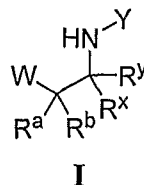
[0008] **Figure 3** depicts the X-ray crystal structure of [(*E*)-(*S*)-1-((*S*)-1-Acetyl-2-oxo-cyclopentyl)-3-phenyl-allyl]-carbamic acid methyl ester.

DETAILED DESCRIPTION OF THE INVENTION

1. General Description of Compounds of the Invention:

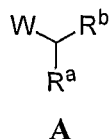
[0009] As described herein, the present invention provides asymmetric C-C bond-forming reactions catalyzed by chiral amine bases. In certain embodiments the C-C bond-forming reaction is a Mannich reaction. In other embodiments the C-C bond-forming reaction is an aza-Henry reaction.

[0010] In certain embodiments, the present invention provides a method for preparing a compound of formula I:



wherein said method comprises the step of:

reacting a compound of formula A:



wherein:

W is C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, NO₂, CN, or P(O)(OR)₂;

each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

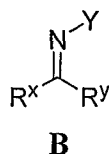
two occurrences of R are optionally taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R' is independently hydrogen or R;

R^a is R', halo, N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂; and

R^b is R', halo, C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, NO₂, CN, or P(O)(OR)₂,

with a compound of formula B:



wherein:

Y is R, C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, P(O)(OR)₂, N(R')C(O)R', N(R')C(O)OR, N(R')C(O)NR'₂, N(R')S(O)₂R, or N(S(O)₂R)₂;

each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4

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heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R' is independently hydrogen or R; and

R^x and R^y are each independently R';

in the presence of a chiral amine base and optionally in a suitable medium.

2. *Compounds and Definitions:*

[0011] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001.

[0012] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle", "cycloaliphatic", "cycloalkyl", or "cycloalkenyl"). For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, or (cycloalkyl)alkenyl. Unless otherwise specified, in various embodiments, aliphatic groups have 1–20, 1–15, 1–12, 1–10, 1–8, 1–6, 1–4, or 1–3 carbon atoms.

[0013] The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, refer to a saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 members, wherein the aliphatic ring system is optionally substituted. Cycloaliphatic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl,

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cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl. In some embodiments, the cycloalkyl has 3–6 carbons. The terms “cycloaliphatic”, “carbocycle”, “carbocyclyl”, “carbocyclo”, or “carbocyclic” also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings, such as decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

[0014] The term “alkoxy”, or “thioalkyl”, as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen (“alkoxy”) or sulfur (“thioalkyl”) atom.

[0015] The terms “haloaliphatic”, “haloalkyl”, “haloalkenyl” and “haloalkoxy” refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, substituted with one or more halogen atoms. As used herein, the term “halogen” or “halo” means F, Cl, Br, or I. Unless otherwise indicated, the terms “alkyl”, “alkenyl”, and “alkoxy” include haloalkyl, haloalkenyl, and haloalkoxy groups, including, in particular, those with 1–5 fluorine atoms. By way of example, the terms “C₁₋₃ aliphatic” and “C₁₋₃ alkyl” include within their scope trifluoromethyl and pentafluoroethyl groups.

[0016] The term “heteroatom” means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0017] The terms “aryl” and “ar-”, used alone or as part of a larger moiety, e.g., “aralkyl”, “aralkoxy”, or “aryloxyalkyl”, refer to a C₆₋₁₄ aromatic moiety comprising one to three aromatic rings, which are optionally substituted. Preferably, the aryl group is a C₆₋₁₀ aryl group. Aryl groups include, without limitation, phenyl, naphthyl, and anthracenyl. The term “aryl”, as used herein, also includes groups in which an aromatic ring is fused to one or more heteroaryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the aromatic ring. Nonlimiting examples of such fused ring systems include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, fluorenyl, indanyl, phenanthridinyl, tetrahydronaphthyl, indolinyl, phenoxazinyl, benzodioxanyl, and benzodioxolyl. An aryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term

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“aryl” may be used interchangeably with the terms “aryl group”, “aryl ring”, and “aromatic ring”.

[0018] An “aralkyl” or “arylalkyl” group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C₆₋₁₀ aryl(C₁₋₆)alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0019] The terms “heteroaryl” and “heteroar-”, used alone or as part of a larger moiety, e.g., “heteroaralkyl”, or “heteroaralkoxy”, refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to four heteroatoms. The term “heteroatom” refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizynyl, purinyl, naphthyridinyl, and pteridinyl. The terms “heteroaryl” and “heteroar-”, as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizynyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term “heteroaryl” may be used interchangeably with the terms “heteroaryl ring”, “heteroaryl group”, or “heteroaromatic”, any of which terms include rings that are optionally substituted. The term “heteroaralkyl” refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0020] As used herein, the terms “heterocycle”, “heterocyclyl”, “heterocyclic radical”, and “heterocyclic ring” are used interchangeably and refer to a stable 5- to 7-membered monocyclic or 7–10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle,

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the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0021] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0022] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0023] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein *n* is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0024] An alkylene chain also can be optionally replaced by a functional group. An alkylene chain is "replaced" by a functional group when an internal methylene unit is replaced with the functional group. Examples of suitable "interrupting functional groups" are described in the specification and claims herein.

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[0025] As described herein, compounds of the invention may be optionally substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the phrase “optionally substituted” is used interchangeably with the phrase “substituted or unsubstituted.” In general, the term “substituted”, whether preceded by the term “optionally” or not, means that one or more hydrogens of the designated moiety are replaced. Unless otherwise indicated, an optionally substituted group may have a substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. The phrase “one or more substituents”, as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds.

[0026] An aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be “optionally substituted”. In addition to the substituents defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group also include and are generally selected from halogen; $-R^\circ$; $-OR^\circ$; $-SR^\circ$; phenyl (Ph) optionally substituted with R° ; $-OPh$ optionally substituted with R° ; $-(CH_2)_{1-2}Ph$, optionally substituted with R° ; $-CH=CHPh$, optionally substituted with R° ; $-NO_2$; $-CN$; $-N(R^\circ)_2$; $-N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(O)OR^\circ$; $-C(O)R^\circ$; $-C(S)R^\circ$; $-C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-OC(O)NR^\circ_2$; $-OC(O)R^\circ$; $-C(O)N(OR^\circ)R^\circ$; $-C(NOR^\circ)R^\circ$; $-S(O)_2R^\circ$; $-S(O)_2OR^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-(CH_2)_{0-2}N(R^\circ)C(O)R^\circ$; wherein each independent occurrence of R° is selected from hydrogen, optionally substituted C_{1-6} aliphatic, an unsubstituted 5–6-membered heteroaryl or heterocyclic ring, phenyl, $-OPh$, or $-CH_2Ph$, or, notwithstanding the definition above, two independent occurrences of R° on the same substituent or different substituents, taken together with their intervening atom(s), form an optionally substituted 3–12-membered saturated, partially unsaturated, or fully unsaturated

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monocyclic or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0027] Suitable substituents on the aliphatic group of R° include and are generally selected from halogen, $R^\bullet$, halo $R^\bullet$, OH, OR $^\bullet$, O(halo $R^\bullet$), CN, C(O)OH, C(O)OR $^\bullet$, NH $_2$, NHR $^\bullet$, NR $^\bullet_2$, or NO $_2$, wherein $R^\bullet$ is unsubstituted C $_{1-4}$ aliphatic.

[0028] An aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be “optionally substituted”. Unless otherwise defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR * , =NNR $^{*}_2$, =NNHC(O)R * , =NNHC(O)OR $^\square$, =NNHS(O) $_2$ R $^\square$, or =NR * , where each R * is independently selected from hydrogen or an optionally substituted C $_{1-6}$ aliphatic group and each R $^\square$ is independently an optionally substituted C $_{1-6}$ aliphatic group.

[0029] Suitable substituents on the aliphatic groups of R * and on R $^\square$ include and are generally selected from halogen, $R^\bullet$, halo $R^\bullet$, OH, OR $^\bullet$, O(halo $R^\bullet$), CN, C(O)OH, C(O)OR $^\bullet$, NH $_2$, NHR $^\bullet$, NR $^\bullet_2$, or NO $_2$, wherein $R^\bullet$ is unsubstituted C $_{1-4}$ aliphatic.

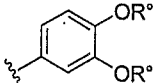
[0030] In addition to the substituents defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring also include and are generally selected from –R † , –NR †_2 , –C(O)R † , –C(O)OR † , –C(O)C(O)R † , –C(O)C(H) $_2$ C(O)R † , –S(O) $_2$ R † , –S(O) $_2$ NR †_2 , –C(S)NR †_2 , –C(NH)NR †_2 , or –N(R †)S(O) $_2$ R † ; wherein R † is hydrogen, an optionally substituted C $_{1-6}$ aliphatic, optionally substituted phenyl, optionally substituted –OPh, optionally substituted –CH $_2$ Ph, optionally substituted –(CH $_2$) $_{1-2}$ Ph; optionally substituted –CH=CHPh; or an unsubstituted 5–6-membered heteroaryl or heterocyclic ring having one to four heteroatoms independently selected from oxygen, nitrogen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R † , on the same substituent or different substituents, taken together with their intervening atom(s) form an optionally substituted 3–12-membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

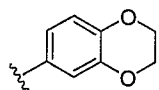
[0031] Suitable substituents on the aliphatic group of R $^\circ$ include and are generally selected from halogen, $R^\bullet$, halo $R^\bullet$, OH, OR $^\bullet$, O(halo $R^\bullet$), CN, C(O)OH, C(O)OR $^\bullet$, NH $_2$, NHR $^\bullet$, NR $^\bullet_2$, or NO $_2$, wherein $R^\bullet$ is unsubstituted C $_{1-4}$ aliphatic.

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[0032] As detailed above, in some embodiments, two independent occurrences of R° (or $R^\dagger$ or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) to form an optionally substituted 3–12-membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] Exemplary rings that are formed when two independent occurrences of R° (or $R^\dagger$, or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) include, but are not limited to the following: a) two independent occurrences of R° (or $R^\dagger$, or any other variable similarly defined in the specification or claims herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, NR°_2 , where both occurrences of R° are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R° (or $R^\dagger$, or any other variable similarly defined in the specification or claims herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with two

occurrences of OR° , these two occurrences of R° are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:



. It will be appreciated that a variety of other rings (e.g., spiro and bridged rings) can be formed when two independent occurrences of R° (or $R^\dagger$, or any other variable similarly defined in the specification and claims herein) are taken together with their intervening atom(s) and that the examples detailed above are not intended to be limiting.

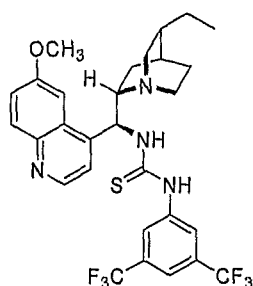
[0034] Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0035] It will be appreciated by one of ordinary skill in the art that suitable substituents are those do not allow for the existence of acidic protons that would make it unfavorable for the reaction to proceed as intended.

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3. *Description of Exemplary Embodiments:*

[0036] As defined above, reactions of the present invention employ a chiral amine base in the preparation of formula I. Such amine bases include, but are not limited to, cinchonine, cinchonidine, quinine, quinidine, the dihydro derivatives of the preceding amine bases, and the amine base depicted below (immediately following this paragraph), as well as diastereomers and demethoxy-analogs thereof. In certain embodiments, the amine base is cinchonine or cinchonidine. In other embodiments, the amine base is quinine or quinidine. In still other embodiments, the amine base is that depicted below (the structure that immediately follows).



[0037] In certain embodiments, a compound of formula I prepared according to the present invention is enantiomerically enriched. As used herein, the term “enantiomerically enriched” denotes that one enantiomer makes up at least 75% of the preparation. In certain embodiments, the term denotes that one enantiomer makes up at least 80% of the preparation. In other embodiments, the term denotes that at least 90% of the preparation is one of the enantiomers. In other embodiments, the term denotes that at least 95% of the preparation is one of the enantiomers. In still other embodiments, the term denotes that at least 97.5% of the preparation is one of the enantiomers.

[0038] In other embodiments, a compound of formula I prepared according to the present invention is diastereomerically enriched. As used herein, the term “diastereomerically enriched” denotes that the ratio of one pair of enantiomers to its diastereomeric pair of enantiomers is other than 1:1. In certain embodiments, the ratio is within the range extending from 1:1 to about 2:1. In other embodiments, the ratio is within the range from about 2:1 to about 5:1. In still other embodiments, the ratio is within the range from about 5:1 to about 20:1. In certain embodiments the ratio is at least 2:1. In other embodiments, the ratio is at least 5:1. In still other embodiments, the ratio is at least 20:1.

[0039] In certain embodiments, the chiral amine base used in the method for preparing compounds of formula I is employed in substoichiometric amounts. As used herein, the term “substoichiometric amounts” denotes that the amine base is used in less than 1 mole

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equivalent relative to the compound of formula A. In certain embodiments the amine base is employed in less than 0.5 mole equivalents. In other embodiments the amine base is employed in less than 0.25 mole equivalents. In other embodiments, the amine base is employed in less than 0.1 mole equivalents. In still other embodiments, the amine base is employed in less than 0.05 mole equivalents. In other embodiments, the quantity of amine base employed is between about 0.05 and about 0.25 mole equivalents. In still other embodiments, the quantity of amine base employed is between about 0.005 and about 0.1 mole equivalents.

[0040] As used herein, a suitable medium for the preparation of compounds of formula I refers to a solvent, or a mixture of two or more solvents, which induces conditions which are favorable for the reaction to proceed as intended. Suitable solvents include, but are not limited to, polar aprotic solvents and halogenated hydrocarbon solvents. Examples of polar aprotic solvents include, but are not limited to, DMF, DMSO, THF, glyme, diglyme, MTBE, and acetonitrile. Examples of halogenated hydrocarbon solvents include, but are not limited to, CH₂Cl₂, CHCl₃, and CCl₄.

[0041] In certain embodiments the temperature employed in the preparation of compounds of formula I is between about -80° C and about 25° C. In other embodiments, the temperature employed is between about -40° C and about 25° C. In still other embodiments, the temperature employed is between about 0° C and about 25° C. In yet other embodiments, the temperature employed is between about 0° C and about 50° C. In other embodiments, the temperature employed is between about 0° C and about 100° C. In other embodiments, the temperature employed is above about -80° C. In still other embodiments, the temperature employed is above about -40° C. In yet other embodiments, the temperature employed is above about 0° C. In other embodiments, the temperature employed is below about 50° C. In other embodiments, the temperature employed is below about 100° C. In other embodiments, the temperature employed is below about 150° C.

[0042] As defined generally above, the W group of formulae A and I is C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, NO₂, CN, or P(O)(OR)₂. In certain embodiments, the W group of formulae A and I is C(O)R, C(O)OR, C(O)SR, C(S)OR, or C(O)NR'₂. In other embodiments, the W group of formulae A and I is S(O)₂R, S(O)₂NR'₂, or S(O)R. In still other embodiments, the W group of formulae A and I is NO₂, CN, or P(O)(OR)₂. In yet other embodiments, the W group of formulae A and I is C(O)R. In other embodiments, the W group of formulae A and I is NO₂. In other embodiments, the W group of formulae A and I is C(O)OR. In still other embodiments, the W group of

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formulae **A** and **I** is $\text{C(O)NR}'_2$. In yet other embodiments, the W group of formulae **A** and **I** is $\text{S(O)}_2\text{R}$. In other embodiments, the W group of formulae **A** and **I** is S(O)R . In still other embodiments, the W group of formulae **A** and **I** is CN . In yet other embodiments, the W group of formulae **A** and **I** is P(O)(OR)_2 . In other embodiments, the W group of formulae **A** and **I** is C(O)OR wherein R is optionally substituted C_{1-6} aliphatic. In other embodiments, the W group of formulae **A** and **I** is C(O)R wherein R is optionally substituted C_{1-6} aliphatic. In still other embodiments, the W group of formulae **A** and **I** is C(O)CH_3 . In still other embodiments, the W group of formulae **A** and **I** is C(O)OCH_3 .

[0043] As defined generally above, the R^a group of formulae **A** and **I** is R' , halo, $\text{N(R}')C(O)R}'$, $\text{N(R}')C(O)OR}$, or $\text{N(R}')C(O)NR}'_2$. In certain embodiments, the R^a group of formulae **A** and **I** is R' . In other embodiments, the R^a group of formulae **A** and **I** is halo. In still other embodiments, the R^a group of formulae **A** and **I** is $\text{N(R}')C(O)R}'$, $\text{N(R}')C(O)OR}$, or $\text{N(R}')C(O)NR}'_2$. In yet other embodiments, the R^a group of formulae **A** and **I** is hydrogen. In other embodiments, the R^a group of formulae **A** and **I** is optionally substituted C_{1-6} aliphatic. In still other embodiments, the R^a group of formulae **A** and **I** is optionally substituted C_{1-3} aliphatic. In still other embodiments, the R^a group of formulae **A** and **I** is methyl. In other embodiments, the R^a group of formulae **A** and **I** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^a group of formulae **A** and **I** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^a group of formulae **A** and **I** is optionally substituted phenyl. In still other embodiments, the R^a group of formulae **A** and **I** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^a group of formulae **A** and **I** is optionally substituted naphthyl. In yet other embodiments, the R^a group of formulae **A** and **I** is phenyl,

[0044] In certain embodiments, an R group on W and an R group on R^a of formulae **A** and **I** are taken together with their intervening atoms to form an optionally substituted 5–8-membered saturated or partially unsaturated monocyclic ring having 0–3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, an R group on W and an R group on R^a of formulae **A** and **I** are taken together with their intervening atoms to form an optionally substituted 5–6-membered saturated or partially unsaturated monocyclic ring having 0–1 heteroatoms independently selected from nitrogen, oxygen, or

sulfur. In certain embodiments, an R group on W and an R group on R^a of formulae A and I are taken together with their intervening atoms to form an optionally substituted 5–6-membered saturated or partially unsaturated monocyclic carbocycle. In certain embodiments, an R group on W and an R group on R^a of formulae A and I are taken together with their intervening atoms to form an optionally substituted cyclopentanone, γ -lactone, or γ -lactam.

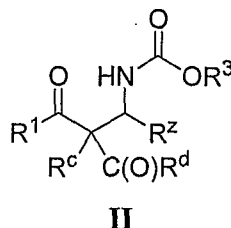
[0045] As defined generally above, the R^b group of formulae A and I is R', halo, C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, NO₂, CN, or P(O)(OR)₂. In certain embodiments, the R^b group of formulae A and I is R'. In other embodiments, the R^b group of formulae A and I is halo. In still other embodiments, the R^b group of formulae A and I is C(O)R, C(O)OR, C(O)SR, C(S)OR, or C(O)NR'₂. In yet other embodiments, the R^b group of formulae A and I is S(O)₂R, S(O)₂NR'₂, or S(O)R. In other embodiments, the R^b group of formulae A and I is NO₂, CN, or P(O)(OR)₂. In still other embodiments, the R^b group of formulae A and I is C(O)OR. In other embodiments, the R^b group of formulae A and I is optionally substituted C(O)OR, wherein the R group is C_{1–6} aliphatic. In still other embodiments, the R^b group of formulae A and I is C(O)OCH₂CHCH₂. In other embodiments, the R^b group of formulae A and I is optionally substituted C(O)OCH₃. In still other embodiments, the R^b group of formulae A and I is C(O)R. In other embodiments, the R^b group of formulae A and I is C(O)R, wherein the R group is optionally substituted C_{1–6} aliphatic. Such R^b groups of formulae A and I include C(O)CH₂CHCH₂ and C(O)CH₃.

[0046] As defined generally above, the Y group of formulae B and I is R, C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, P(O)(OR)₂, N(R')C(O)R', N(R')C(O)OR, N(R')C(O)NR'₂, N(R')S(O)₂R, or N(S(O)₂R)₂. In certain embodiments, the Y group of formulae B and I is R'. In other embodiments, the Y group of formulae B and I is C(O)R, C(O)OR, C(O)SR, C(S)OR, or C(O)NR'₂. In still other embodiments, the Y group of formulae B and I is S(O)₂R, S(O)₂NR'₂, or S(O)R. In yet other embodiments, the Y group of formulae B and I is P(O)(OR)₂. In certain embodiments, the Y group of formulae B and I is N(R')C(O)R', N(R')C(O)OR, N(R')C(O)NR'₂, N(R')S(O)₂R, or N(S(O)₂R)₂. In other embodiments, the Y group of formulae B and I is C(O)OR. In still other embodiments, the Y group of formulae B and I is C(O)OR where the R group is optionally substituted C_{1–6} aliphatic. Such Y groups of formulae B and I include C(O)OC(CH₃)₃, C(O)OCH₂CH₃, C(O)OCH₃, and C(O)OCH₂CHCH₂.

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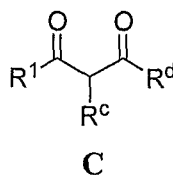
[0047] As defined generally above, the R^x and R^y groups of formulae **B** and **I** are each independently R' . In certain embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is hydrogen. In other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is optionally substituted C_{1-6} aliphatic. In still other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is optionally substituted C_{1-3} aliphatic. In still other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is optionally substituted CH_3 . In other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is optionally substituted phenyl. In still other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is optionally substituted naphthyl. In yet other embodiments, at least one of the R^x and R^y groups of formulae **B** and **I** is phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-bromophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3,4-(OCH_2O) C_6H_3 -, furan-2-yl, thien-2-yl, naphth-2-yl, $PhCH=CH$ -, $(2-C_4H_3O)CH=CH$ -, or $PhCH_2CH_2$ -.

[0048] In another embodiment, the present invention provides a method for preparing a compound of formula **II**:



wherein said method comprises the step of:

reacting a compound of formula **C**:



wherein:

R^1 is R, OR, SR, or NR'_2 ;

each R is independently an optionally substituted group selected from C_{1-6} aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

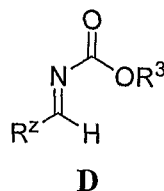
two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R' is independently hydrogen or R;

R^c is R' , halo, $N(R')C(O)R'$, $N(R')C(O)OR$, or $N(R')C(O)NR'_2$; and

R^d is R or OR;

with a compound of formula **D**:



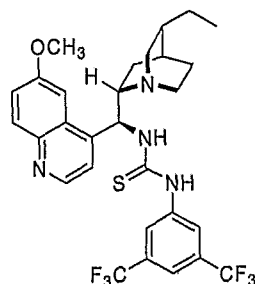
wherein:

R^Z is R' ; and

R^3 is R;

in the presence of a chiral amine base and optionally in a suitable medium.

[0049] As defined above, reactions of the present invention employ a chiral amine base in the preparation of formula **II**. Such amine bases include, but are not limited to, cinchonine, cinchonidine, quinine, quinidine, the dihydro derivatives of the preceding amine bases, and the amine base depicted below (immediately following this paragraph), as well as diastereomers and demethoxy-analogs thereof. In certain embodiments, the amine base is cinchonine or cinchonidine. In other embodiments, the amine base is quinine, or quinidine. In still other embodiments, the amine base is that depicted below (the structure that immediately follows).



[0050] In certain embodiments, a compound of formula **II** prepared according to the present invention is enantiomerically enriched. As used herein, the term “enantiomerically enriched” denotes that one enantiomer makes up at least 75% of the preparation. In certain embodiments, the term denotes that one enantiomer makes up at least 80% of the preparation. In other embodiments, the term denotes that at least 90% of the preparation is one of the enantiomers. In other embodiments, the term denotes that at least 95% of the preparation is one of the enantiomers. In still other embodiments, the term denotes that at least 97.5% of the preparation is one of the enantiomers.

[0051] In other embodiments, a compound of formula **II** prepared according to the present invention is diastereomerically enriched. As used herein, the term “diastereomerically enriched” denotes that the ratio of one pair of enantiomers to its diastereomeric pair of enantiomers is other than 1:1. In certain embodiments, the ratio is within the range extending from 1:1 to about 2:1. In other embodiments, the ratio is within the range from about 2:1 to about 5:1. In still other embodiments, the ratio is within the range from about 5:1 to about 20:1. In certain embodiments the ratio is at least 2:1. In other embodiments, the ratio is at least 5:1. In still other embodiments, the ratio is at least 20:1.

[0052] In certain embodiments, the chiral amine base used in the method for preparing compounds of formula **II** is employed in substoichiometric amounts. As used herein, the term “substoichiometric amounts” denotes that the amine base is used in less than 1 mole equivalent relative to the compound of formula **C**. In certain embodiments the amine base is employed in less than 0.5 mole equivalents. In certain embodiments the amine base is employed in less than 0.25 mole equivalents. In other embodiments, the amine base is employed in less than 0.1 mole equivalents. In still other embodiments, the amine base is employed in less than 0.05 mole equivalents. In other embodiments, the quantity of amine base employed is between about 0.05 and about 0.25 mole equivalents. In still other embodiments, the quantity of amine base employed is between about 0.005 and about 0.1 mole equivalents.

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[0053] As used herein, a suitable medium for the preparation of compounds of formula **II** refers to a solvent, or a mixture of two or more solvents, which induces conditions which are favorable for the reaction to proceed as intended. Suitable solvents include, but are not limited to, polar aprotic solvents and halogenated hydrocarbon solvents. Examples of polar aprotic solvents include, but are not limited to, DMF, DMSO, THF, glyme, diglyme, MTBE, and acetonitrile. Examples of halogenated hydrocarbon solvents include, but are not limited to, CH₂Cl₂, CHCl₃, and CCl₄.

[0054] In certain embodiments the temperature employed in the preparation of compounds of formula **II** is between about -80° C and about 25° C. In other embodiments, the temperature employed is between about -40° C and about 25° C. In still other embodiments, the temperature employed is between about 0° C and about 25° C. In yet other embodiments, the temperature employed is between about 0° C and about 50° C. In other embodiments, the temperature employed is between about 0° C and about 100° C. In other embodiments, the temperature employed is above about -80° C. In still other embodiments, the temperature employed is above about -40° C. In yet other embodiments, the temperature employed is above about 0° C. In other embodiments, the temperature employed is below about 50° C. In other embodiments, the temperature employed is below about 100° C. In other embodiments, the temperature employed is below about 150° C.

[0055] As defined generally above, the R¹ group of formulae **C** and **II** is R, OR, SR, or NR'₂. In certain embodiments, the R¹ group of formulae **C** and **II** is R. In other embodiments, the R¹ group of formulae **C** and **II** is OR, SR, or NR'₂. In still other embodiments, the R¹ group of formulae **C** and **II** is optionally substituted C₁₋₆ aliphatic. In still other embodiments, the R¹ group of formulae **C** and **II** is optionally substituted C₁₋₃ aliphatic. In still other embodiments, the R¹ group of formulae **C** and **II** is CH₃. In other embodiments, the R¹ group of formulae **C** and **II** is an optionally substituted 3-8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R¹ group of formulae **C** and **II** is an optionally substituted 5-6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R¹ group of formulae **C** and **II** is optionally substituted phenyl. In still other embodiments, the R¹ group of formulae **C** and **II** is an optionally substituted 8-10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or

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sulfur. In other embodiments, the R^1 group of formulae **C** and **II** is optionally substituted naphthyl.

[0056] As defined generally above, the R^c group of formulae **C** and **II** is R' , halo, $N(R')C(O)R'$, $N(R')C(O)OR$, or $N(R')C(O)NR'_2$. In certain embodiments, the R^c group of formulae **C** and **II** is R' . In other embodiments, the R^c group of formulae **C** and **II** is halo. In still other embodiments, the R^c group of formulae **C** and **II** is $N(R')C(O)R'$, $N(R')C(O)OR$, or $N(R')C(O)NR'_2$. In yet other embodiments, the R^c group of formulae **C** and **II** is hydrogen. In other embodiments, the R^c group of formulae **C** and **II** is optionally substituted C_{1-6} aliphatic. In still other embodiments, the R^c group of formulae **C** and **II** is optionally substituted C_{1-3} aliphatic. In still other embodiments, the R^c group of formulae **C** and **II** is CH_3 . In other embodiments, the R^c group of formulae **C** and **II** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^c group of formulae **C** and **II** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^c group of formulae **C** and **II** is optionally substituted phenyl. In still other embodiments, the R^c group of formulae **C** and **II** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^c group of formulae **C** and **II** is optionally substituted naphthyl.

[0057] In certain embodiments, an R group on R^1 and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted 5–8-membered saturated or partially unsaturated monocyclic ring having 0–3 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, an R group on R^1 and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted 5–6-membered saturated or partially unsaturated monocyclic ring having 0–1 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, an R group on R^1 and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted 5–6-membered saturated or partially unsaturated monocyclic carbocycle. In certain embodiments, an R group on R^1 and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted cyclopentanone. In other embodiments, an R group on R^1 and an R group on R^c of formulae **C** and **II** are taken

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together with their intervening atoms to form an optionally substituted γ -lactone. In yet other embodiments, an R group on R¹ and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted γ -lactam.

[0058] As defined generally above, the R^d group of formulae **C** and **II** is R or OR. In certain embodiments, the R^d group of formulae **C** and **II** is R. In other embodiments, the R^d group of formulae **C** and **II** is OR. In other embodiments, the R^d group of formulae **C** and **II** is optionally substituted C₁₋₆ aliphatic. In still other embodiments, the R^d group of formulae **C** and **II** is optionally substituted C₁₋₃ aliphatic. Such R^d groups of formulae **C** and **II** include CH₃, CH₂CHCH₃, C(CH₃)₃, and CH₂Ph. In other embodiments, the R^d group of formulae **C** and **II** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **C** and **II** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **C** and **II** is optionally substituted phenyl. In still other embodiments, the R^d group of formulae **C** and **II** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **C** and **II** is optionally substituted naphthyl. In other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is optionally substituted C₁₋₆ aliphatic. In still other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is optionally substituted C₁₋₃ aliphatic. Such R^d groups of formulae **C** and **II** include OCH₃, OCH₂CHCH₃, OC(CH₃)₃, and OCH₂Ph. In other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is optionally substituted phenyl. In still other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In

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other embodiments, the R^d group of formulae **C** and **II** is OR, wherein R is optionally substituted naphthyl.

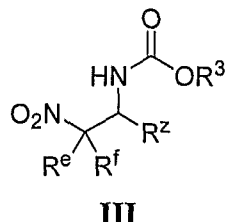
[0059] As defined generally above, the R^z group of formulae **D** and **II** is R' . In certain embodiments, the R^z group of formulae **D** and **II** is hydrogen. In other embodiments, the R^z group of formulae **D** and **II** is optionally substituted C_{1-6} aliphatic. In still other embodiments, the R^z group of formulae **D** and **II** is optionally substituted C_{1-3} aliphatic. In still other embodiments, the R^z group of formulae **D** and **II** is CH_3 . In other embodiments, the R^z group of formulae **D** and **II** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^z group of formulae **D** and **II** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^z group of formulae **D** and **II** is optionally substituted phenyl. In still other embodiments, the R^z group of formulae **D** and **II** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^z group of formulae **D** and **II** is optionally substituted naphthyl. In yet other embodiments, the R^z group of formulae **D** and **II** is phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-bromophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3,4-(OCH_2O) C_6H_3 -, furan-2-yl, thien-2-yl, naphth-2-yl, $PhCH=CH$ -, $(2-C_4H_3O)CH=CH$ -, or $PhCH_2CH_2$ -.

[0060] As defined generally above, the R^3 group of formula **II** is R. In certain embodiments, the R^3 group of formulae **D** and **II** is optionally substituted C_{1-6} aliphatic. In other embodiments, the R^3 group of formulae **D** and **II** is optionally substituted C_{1-3} aliphatic. Such R^3 group of formula **II** include CH_3 , CH_2CH_3 , CH_2CHCH_2 , and $C(CH_3)_3$. In other embodiments, the R^3 group of formulae **D** and **II** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^3 group of formulae **D** and **II** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^3 group of formulae **D** and **II** is optionally substituted phenyl. In still other embodiments, the R^3 group of formulae **D** and **II** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen,

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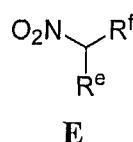
or sulfur. In other embodiments, the R^3 group of formulae **D** and **II** is optionally substituted naphthyl.

[0061] In another embodiment, the present invention provides a method for preparing a compound of formula **III**:



wherein said method comprises the step of:

reacting a compound of formula **E**:



wherein:

R^e is R' , halo, $N(R')C(O)R'$, $N(R')C(O)OR$, or $N(R')C(O)NR'_2$;

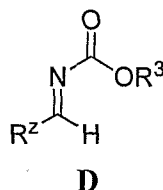
each R' is independently hydrogen or R ;

each R is independently an optionally substituted group selected from C_{1-6} aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

R^f is halo or R' ;

with a compound of formula **D**:



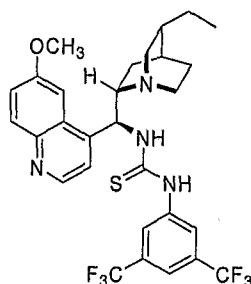
wherein:

R^z is R' ; and

R^3 is R;

in the presence of a chiral amine base and optionally in a suitable medium.

[0062] As defined above, reactions of the present invention employ a chiral amine base in the preparation of formula **III**. Such amine bases include, but are not limited to, cinchonine, cinchonidine, quinine, quinidine, the dihydro derivatives of the preceding amine bases, and the amine base depicted below (immediately following this paragraph), as well as diastereomers and demethoxy-analogs thereof. In certain embodiments, the amine base is cinchonine or cinchonidine. In other embodiments, the amine base is quinine, or quinidine. In still other embodiments, the amine base is that depicted below (the structure that immediately follows).



[0063] In certain embodiments, a compound of formula **III** prepared according to the present invention is enantiomerically enriched. As used herein, the term “enantiomerically enriched” denotes that one enantiomer makes up at least 75% of the preparation. In certain embodiments, the term denotes that one enantiomer makes up at least 80% of the preparation. In other embodiments, the term denotes that at least 90% of the preparation is one of the enantiomers. In other embodiments, the term denotes that at least 95% of the preparation is one of the enantiomers. In still other embodiments, the term denotes that at least 97.5% of the preparation is one of the enantiomers.

[0064] In other embodiments, a compound of formula **III** prepared according to the present invention is diastereomerically enriched. As used herein, the term “diastereomerically enriched” denotes that the ratio of one pair of enantiomers to its diastereomeric pair of enantiomers is other than 1:1. In certain embodiments, the ratio is within the range extending from 1:1 to about 2:1. In other embodiments, the ratio is within the range from about 2:1 to about 5:1. In still other embodiments, the ratio is within the range from about 5:1 to about 20:1. In certain embodiments the ratio is at least 2:1. In other embodiments, the ratio is at least 5:1. In still other embodiments, the ratio is at least 20:1.

[0065] In certain embodiments, the chiral amine base used in the method for preparing compounds of formula **III** is employed in substoichiometric amounts. As used herein, the

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term "substoichiometric amounts" denotes that the amine base is used in less than 1 mole equivalent relative to the compound of formula **E**. In certain embodiments the amine base is employed in less than 0.5 mole equivalents. In certain embodiments the amine base is employed in less than 0.25 mole equivalents. In other embodiments, the amine base is employed in less than 0.1 mole equivalents. In still other embodiments, the amine base is employed in less than 0.05 mole equivalents. In other embodiments, the quantity of amine base employed is between about 0.05 and about 0.25 mole equivalents. In still other embodiments, the quantity of amine base employed is between about 0.005 and about 0.1 mole equivalents.

[0066] As used herein, a suitable medium for the preparation of compounds of formula **III** refers to a solvent, or a mixture of two or more solvents, which induces conditions which are favorable for the reaction to proceed as intended. Suitable solvents include, but are not limited to, polar aprotic solvents and halogenated hydrocarbon solvents. Examples of polar aprotic solvents include, but are not limited to, DMF, DMSO, THF, glyme, diglyme, MTBE, and acetonitrile. Examples of halogenated hydrocarbon solvents include, but are not limited to, CH₂Cl₂, CHCl₃, and CCl₄.

[0067] In certain embodiments the temperature employed in the preparation of compounds of formula **III** is between about -80° C and about 25° C. In other embodiments, the temperature employed is between about -40° C and about 25° C. In still other embodiments, the temperature employed is between about 0° C and about 25° C. In yet other embodiments, the temperature employed is between about 0° C and about 50° C. In other embodiments, the temperature employed is between about 0° C and about 100° C. In other embodiments, the temperature employed is above about -80° C. In still other embodiments, the temperature employed is above about -40° C. In yet other embodiments, the temperature employed is above about 0° C. In other embodiments, the temperature employed is below about 50° C. In other embodiments, the temperature employed is below about 100° C. In other embodiments, the temperature employed is below about 150° C.

[0068] As defined generally above, the R^e group of formulae **E** and **III** is R', halo, N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂. In certain embodiments, the R^e group of formulae **E** and **III** is R'. In other embodiments, the R^e group of formulae **E** and **III** is halo. In still other embodiments, the R^e group of formulae **E** and **III** is N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂. In yet other embodiments, the R^e group of formulae **E** and **III** is hydrogen. In other embodiments, the R^e group of formulae **E** and **III** is optionally substituted C₁₋₆ aliphatic. In still other embodiments, the R^e group of formulae **E** and **III** is

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optionally substituted C₁₋₃ aliphatic. In still other embodiments, the R^e group of formulae **E** and **III** is CH₃. In other embodiments, the R^e group of formulae **E** and **III** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^e group of formulae **E** and **III** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^e group of formulae **E** and **III** is optionally substituted phenyl. In still other embodiments, the R^e group of formulae **E** and **III** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^e group of formulae **E** and **III** is optionally substituted naphthyl.

[0069] As defined generally above, the R^f group of formulae **E** and **III** is halo or R'. In certain embodiments, the R^f group of formulae **E** and **III** is R'. In other embodiments, the R^f group of formulae **E** and **III** is halo. In yet other embodiments, the R^f group of formulae **E** and **III** is hydrogen. In other embodiments, the R^f group of formulae **E** and **III** is optionally substituted C₁₋₆ aliphatic. In still other embodiments, the R^f group of formulae **E** and **III** is optionally substituted C₁₋₃ aliphatic. In still other embodiments, the R^f group of formulae **E** and **III** is optionally substituted CH₃. In other embodiments, the R^f group of formulae **E** and **III** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^f group of formulae **E** and **III** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^f group of formulae **E** and **III** is optionally substituted phenyl. In still other embodiments, the R^f group of formulae **E** and **III** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^f group of formulae **E** and **III** is optionally substituted naphthyl.

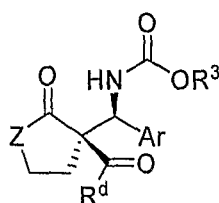
[0070] In certain embodiments, at least one of the R^e and R^f groups of formulae **E** and **III** is hydrogen. In one embodiment, both of the R^e and R^f groups of formulae **E** and **III** are hydrogen.

[0071] Embodiments of the R^z and R³ groups of formulae **D** and **III** are as described above for the R^z and R³ groups of formulae **D** and **II**.

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[0072] One of ordinary skill in the art will recognize that the imine represented by either of formulae **B** or **D** can be generated either in situ under the reaction conditions for addition to the imine, or alternatively, prior to addition to said imine, from a corresponding α -amidosulfone (see *infra*). Accordingly, embodiments of the present invention are envisioned to include the above-described addition reactions wherein the imine is derived from an α -amidosulfone.

[0073] In another embodiment, the present invention provides a method for preparing a compound of formula **IV**:

**IV**

wherein:

Z is -O-, -S-, -NR', or -C(R')₂;

each R' is independently hydrogen or R;

each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

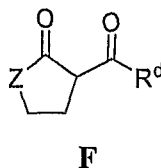
R³ is R;

R^d is R or OR; and

Ar is an optionally substituted group selected from 5-6 membered aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein said method comprises the step of:

reacting a compound of formula **F**:



wherein:

Z is -O-, -S-, -NR'-, or -C(R')₂;

each R' is independently hydrogen or R;

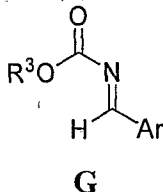
each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3-8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3-8-membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R³ is R; and

R^d is R or OR;

with a compound of formula G:



wherein:

Ar is an optionally substituted group selected from 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10-membered aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

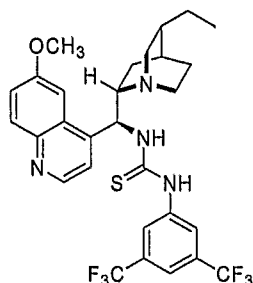
R³ is R,

in the presence of a chiral amine base and optionally in a suitable medium.

[0074] As defined above, reactions of the present invention employ a chiral amine base in the preparation of formula IV. Such amine bases include, but are not limited to, cinchonine, cinchonidine, quinine, quinidine, the dihydro derivatives of the preceding amine bases, and the amine base depicted below (immediately following this paragraph), as well as diastereomers and demethoxy-analogs thereof. In certain embodiments, the amine base is

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cinchonine or cinchonidine. In other embodiments, the amine base is quinine, or quinidine. In still other embodiments, the amine base is that depicted below (the structure that immediately follows).



[0075] In certain embodiments, a compound of formula **IV** prepared according to the present invention is enantiomerically enriched. As used herein, the term “enantiomerically enriched” denotes that one enantiomer makes up at least 75% of the preparation. In certain embodiments, the term denotes that one enantiomer makes up at least 80% of the preparation. In other embodiments, the term denotes that at least 90% of the preparation is one of the enantiomers. In other embodiments, the term denotes that at least 95% of the preparation is one of the enantiomers. In still other embodiments, the term denotes that at least 97.5% of the preparation is one of the enantiomers.

[0076] In other embodiments, a compound of formula **IV** prepared according to the present invention is diastereomerically enriched. As used herein, the term “diastereomerically enriched” denotes that the ratio of one pair of enantiomers to its diastereomeric pair of enantiomers is other than 1:1. In certain embodiments, the ratio is within the range extending from 1:1 to about 2:1. In other embodiments, the ratio is within the range from about 2:1 to about 5:1. In still other embodiments, the ratio is within the range from about 5:1 to about 20:1. In certain embodiments the ratio is at least 2:1. In other embodiments, the ratio is at least 5:1. In still other embodiments, the ratio is at least 20:1.

[0077] In certain embodiments, the chiral amine base used in the method for preparing compounds of formula **IV** is employed in substoichiometric amounts. As used herein, the term “substoichiometric amounts” denotes that the amine base is used in less than 1 mole equivalent relative to the compound of formula **F**. In certain embodiments the amine base is employed in less than 0.5 mole equivalents. In certain embodiments the amine base is employed in less than 0.25 mole equivalents. In other embodiments, the amine base is employed in less than 0.1 mole equivalents. In still other embodiments, the amine base is employed in less than 0.05 mole equivalents. In other embodiments, the quantity of amine base employed is between about 0.05 and about 0.25 mole equivalents. In still other

embodiments, the quantity of amine base employed is between about 0.005 and about 0.1 mole equivalents.

[0078] As used herein, a suitable medium for the preparation of compounds of formula **IV** refers to a solvent, or a mixture of two or more solvents, which induces conditions which are favorable for the reaction to proceed as intended. Suitable solvents include, but are not limited to, polar aprotic solvents and halogenated hydrocarbon solvents. Examples of polar aprotic solvents include, but are not limited to, DMF, DMSO, THF, glyme, diglyme, MTBE, and acetonitrile. Examples of halogenated hydrocarbon solvents include, but are not limited to, CH_2Cl_2 , CHCl_3 , and CCl_4 .

[0079] In certain embodiments the temperature employed in the preparation of compounds of formula **IV** is between about -80°C and about 25°C . In other embodiments, the temperature employed is between about -40°C and about 25°C . In still other embodiments, the temperature employed is between about 0°C and about 25°C . In yet other embodiments, the temperature employed is between about 0°C and about 50°C . In other embodiments, the temperature employed is between about 0°C and about 100°C . In other embodiments, the temperature employed is above about -80°C . In still other embodiments, the temperature employed is above about -40°C . In yet other embodiments, the temperature employed is above about 0°C . In other embodiments, the temperature employed is below about 50°C . In other embodiments, the temperature employed is below about 100°C . In other embodiments, the temperature employed is below about 150°C .

[0080] As defined generally above, the R^d group of formulae **F** and **IV** is R or OR. In certain embodiments, the R^d group of formulae **F** and **IV** is R. In other embodiments, the R^d group of formulae **F** and **IV** is OR. In other embodiments, the R^d group of formulae **F** and **IV** is optionally substituted C_{1-6} aliphatic. In still other embodiments, the R^d group of formulae **F** and **IV** is optionally substituted C_{1-3} aliphatic. Such R^d groups of formulae **F** and **IV** include CH_3 , CH_2CHCH_3 , $\text{C}(\text{CH}_3)_3$, and CH_2Ph . In other embodiments, the R^d group of formulae **F** and **IV** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **F** and **IV** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **F** and **IV** is optionally substituted phenyl. In still other embodiments, the R^d group of formulae **F** and **IV** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having

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0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **F** and **IV** is optionally substituted naphthyl. In other embodiments, the R^d group of OR, wherein R is optionally substituted C_{1-6} aliphatic. In still other embodiments, the R^d group of formulae **F** and **IV** is OR, wherein R is optionally substituted C_{1-3} aliphatic. Such R^d groups of formulae **F** and **IV** include OCH_3 , OCH_2CHCH_3 , $OC(CH_3)_3$, and OCH_2Ph . In other embodiments, the R^d group of formulae **F** and **IV** is OR, wherein R is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **F** and **IV** is OR, wherein R is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **F** and **IV** is OR, wherein R is optionally substituted phenyl. In still other embodiments, the R^d group of formulae **F** and **IV** is OR, wherein R is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^d group of formulae **F** and **IV** is OR, wherein R is optionally substituted naphthyl.

[0081] In certain embodiments, the Ar group of formulae **G** and **IV** is optionally substituted phenyl. In still other embodiments, the Ar group of formulae **G** and **IV** is an optionally substituted 8–10 membered aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the Ar group of formulae **G** and **IV** is optionally substituted naphthyl. In yet other embodiments, the Ar group of formulae **G** and **IV** is phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-bromophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3,4- $(OCH_2O)C_6H_3-$, furan-2-yl, thien-2-yl, naphth-2-yl, $PhCH=CH-$, $(2-C_4H_3O)CH=CH-$, or $PhCH_2CH_2-$.

[0082] As defined generally above, the R^3 group of formula **IV** is R. In certain embodiments, the R^3 group of formulae **F** and **IV** is optionally substituted C_{1-6} aliphatic. In other embodiments, the R^3 group of formulae **F** and **IV** is optionally substituted C_{1-3} aliphatic. Such R^3 group of formula **IV** include CH_3 , CH_2CH_3 , CH_2CHCH_2 , and $C(CH_3)_3$. In other embodiments, the R^3 group of formulae **F** and **IV** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^3 group of formulae **F** and **IV** is an optionally substituted 5–6-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently

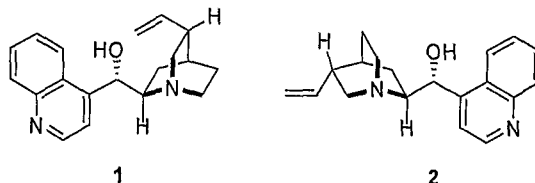
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selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^3 group of formulae **F** and **IV** is optionally substituted phenyl. In still other embodiments, the R^3 group of formulae **F** and **IV** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In other embodiments, the R^3 group of formulae **F** and **IV** is optionally substituted naphthyl.

4. General Methods of Providing the Compounds:

Introduction

[0083] Highly functionalized amine-containing building blocks in enantioenriched form are valuable starting materials for asymmetric synthesis.¹ The asymmetric direct Mannich reaction² is an attractive approach towards the construction of these building blocks.³ In particular, the direct addition of β -keto esters to imines affords multifunctional secondary amines.⁴ Based on our interest in the synthetic utility of β -keto esters,⁵ we proposed a chiral base mediated direct addition of β -keto esters to acyl imines.⁶ The cinchona alkaloids are effective organic chiral bases capable of promoting a range of nucleophilic reactions in an asymmetric manner,⁷ including alcoholysis of anhydrides,⁸ cyanation of carbonyl-containing compounds,⁹ conjugate additions to ynones,¹⁰ chalcones,¹¹ nitro-olefins¹² and vinyl sulfones.¹³ Herein we report the enantioselective addition of β -keto esters and other 1,3-dicarbonyl compounds to acyl aryl imines catalyzed by the cinchona alkaloids cinchonine (**1**) and cinchonidine (**2**), as well as additional chiral amines.



Results and Discussion

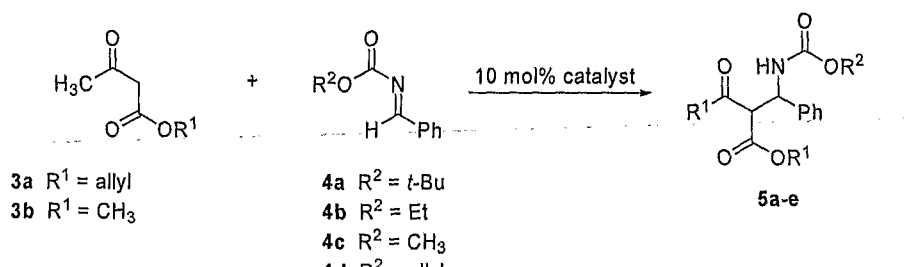
[0084] We initially evaluated the use of cinchona alkaloids as the catalyst in the asymmetric Mannich reaction of allyl acetoacetate **3a** with acyl imines (Table 1). The reaction of **3a** with *tert*-butyl benzylidene carbamate **4a** catalyzed by cinchonine (**1**) in CH_2Cl_2 at -35°C afforded the corresponding β -amino ester **5a** in 85% isolated yield of a 3:1 mixture of diastereomers (entry 1, Table 1). For purposes of analysis, the mixture of diastereomers was subjected to decarboxylation using $\text{Pd}(0)$ and methyl acetoacetate to yield the corresponding ketone in 87% and 80% ee. The quinine-catalyzed reaction of **3a** with **4a**

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afforded the product in 1:1 dr and 60% ee. Higher enantioselectivities were obtained in the reactions of **3a** with ethyl benzyldiene carbamate **4b** and **3a** with methyl benzyldiene carbamate **4c** (86% and 92% ee respectively, entries 3 and 4). Using the pseudoenantiomeric cinchonidine **2** as the catalyst in the reaction of **3a** with **4c** afforded the product in similar ee and dr but with the opposite sense of enantioselectivity (entry 5).

[0085] The cinchonine and cinchonidine-promoted asymmetric Mannich reaction of β -keto esters with acyl imines was also found to be effective with methyl acetoacetate **3b** as the nucleophile. These reactions were highly diastereoselective; the addition of **3b** to **4c** afforded the product **5d** in 20:1 dr and in 94% ee (entry 8). The enantiomeric excess of the product derived from **3b** was determined by selective conversion to the *Z*-enamine with benzyl amine using $\text{HC}(\text{OCH}_3)_3$ and cat. $\text{Yb}(\text{OTf})_3$. The asymmetric Mannich reaction was similarly diastereo- and enantioselective using cinchonine as the catalyst (entry 9). Lastly, the reaction of **3b** with allyl benzyldienecarbamate **4d** afforded the product in 90% ee.

Table 1. Asymmetric Mannich Reactions of β -Keto Esters^a

 3a R¹ = allyl 3b R¹ = CH₃ 4a R² = <i>t</i>-Bu 4b R² = Et 4c R² = CH₃ 4d R² = allyl 5a-e						
entry	catalyst	ester	imine	yield (%) ^b	dr ^c	% ee ^d
1	1	3a	4a	5a (85)	3:1	80
2	quinine	3a	4a	5a (86)	1:1	60
3	1	3a	4b	5b (91)	2:1	86
4	1	3a	4c	5c (99)	3:1	92
5	2	3a	4c	5c (96)	2:1	90
6	quinine	3a	4c	5c (90)	1:1	60
7	quinidine	3a	4c	5c (95)	1:1	65
8	1	3b	4c	5d (99)	20:1 ^e	94
9	2	3b	4c	5d (95)	20:1	90
10	quinine	3b	4c	5d (97)	4:1	60
11	quinidine	3b	4c	5d (98)	5:1	65

12 1 3b 4d 5e (91) 2:1 90

^a Reactions were carried out using 0.5 mmol ester, 0.5 mmol imine, and 0.05 mmol catalyst in CH₂Cl₂ (0.5 M) at -35 °C for 16 h under Ar, followed by flash chromatography on silica gel. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d Enantiomeric excess of diastereomeric mixture determined by chiral HPLC analysis: see Examples section, *infra*. ^e The major isomer is (1*R*, 2*S*).

[0086] The reaction conditions that proved optimal for β-keto ester **3a**, benzylidene carbamate **4c**, and cinchonine as the catalyst (Table 1, entry 4) were found to be general for a variety of aryl methyl carbamate imines (Table 2). Most aryl imines readily formed the Mannich products with **3a** in good isolated yields (81 – 99%) and good enantioselectivities (80 – 96% ee, Table 2, entries 1 - 10).

Table 2. Asymmetric Mannich Reactions of β-Keto Esters ^a

entry	Ar	% yield ^b	dr ^c	yield (%) ^d	% ee ^e
1	Ph (4a)	99	3:1	7a (80)	92
2	4-Cl-C ₆ H ₄ (6a)	93	1:1	7b (80)	83
3	4-F-C ₆ H ₄ (6b)	98	1:1	7c (97)	93
4	3-F-C ₆ H ₄ (6c)	98	1:1	7d (84)	91
5	3-CH ₃ -C ₆ H ₄ (6d)	96	1:1	7e (81)	96
6	3-CF ₃ -C ₆ H ₄ (6e)	99	1:1	7f (83)	90
7	3,4-(OCH ₂ O)C ₆ H ₃ (6f)	95	1:1	7g (81)	80
8	2-C ₄ H ₉ O (6g)	81	1:1	7h (96)	93
9	2-C ₄ H ₉ S (6h)	84	1:1	7i (82)	92
10	2-naphthyl (6i)	96	5:1	7j (83)	95

^a Reactions were carried out using 0.5 mmol ester, 0.5 mmol imine, and 0.05 mmol cinchonine (**1**) in CH₂Cl₂ (0.5 M) at -35 °C for 16 h under Ar, followed by flash chromatography on silica gel. ^b Isolated yield. ^c Determined by ¹H NMR analysis. ^d Enantiomeric excess of diastereomeric mixture determined by chiral HPLC analysis: see Examples section, *infra*. ^e The major isomer is (1*R*, 2*S*).

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[0087] The asymmetric Mannich reaction was also found to be effective with cyclic nucleophiles (Table 3). This transformation provides a catalytic route towards cyclic β -amino esters that contain α -quaternary carbon centers. As indicated by Table 3, these reactions proceeded cleanly with nearly quantitative yields and high diastereo- and enantioselectivity. It is notable that both electron-rich and electron-poor aromatic acyl imines provide excellent results.

Table 3. Asymmetric Mannich Reactions Employing Cyclic Nucleophiles

8a X = CH₂, Y = OCH₃

8b X = CH₂, Y = OCH₂CH₃

8c X = CH₂, Y = CH₃

8d X = O, Y = CH₃

9a-e R⁴ = CH₃

9f, g R⁴ = allyl

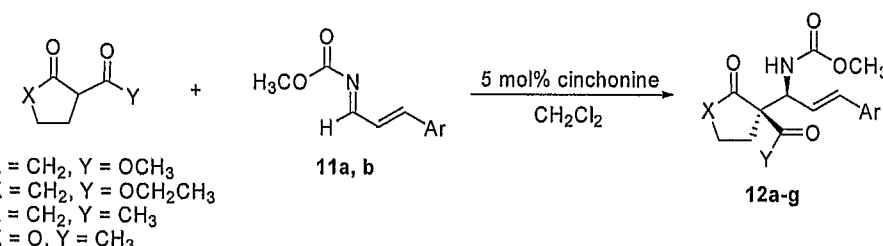
Entry	Ar	nucleophile	yield (%) ^b	de (%) ^c	ee (%) ^c
1 ^d	Ph (9a)	8a	10a (98)	98	90
2 ^d	Ph (9a)	8b	10b (96)	96	93
3	Ph(9a)	8c	10c (98)	98	93
4	Ph(9f)	8a	10d (98)	98	90
5	Ph(9f)	8b	10e (98)	99	90
6	Ph(9f)	8c	10f (98)	99	91
7	3-CH ₃ -C ₆ H ₄ (9b)	8a	10g (98)	93	96
8	3-CH ₃ -C ₆ H ₄ (9b)	8b	10h (98)	98	92
9	3-CH ₃ -C ₆ H ₄ (9b)	8c	10i (98)	94	94
10 ^e	3-CH ₃ -C ₆ H ₄ (9b)	8d	10j (88)	38	91
11	3-CH ₃ -C ₆ H ₄ (9g)	8a	10k (96)	97	92
12	3-CH ₃ -C ₆ H ₄ (9g)	8b	10l (98)	98	99
13	3-CH ₃ -C ₆ H ₄ (9g)	8c	10m (92)	92	98
14	3-CH ₃ -C ₆ H ₄ (9g)	8d	10n (78)	38	99
15 ^e	2-C ₄ H ₃ O (9c)	8a	10o (98)	99	99
16 ^e	2-C ₄ H ₃ O (9c)	8b	10p (98)	99	99
17 ^e	2-C ₄ H ₃ O (9c)	8c	10q (98)	99	99
18 ^f	3-F-C ₆ H ₄ (9d)	8a	10r (98)	99	90
19 ^g	3-F-C ₆ H ₄ (9d)	8b	10s (98)	99	92
20 ^e	3-F-C ₆ H ₄ (9d)	8c	10t (98)	99	93

^a Mannich reactions were carried out using 0.5 mmol nucleophile, 0.5 mmol acyl imine in CH₂Cl₂ (0.5 M) for 2-6 h, at -55 °C under N₂, followed by flash

chromatography on silica gel. ^b Isolated yield of Mannich reaction product. ^c Determined by chiral HPLC analysis: see Examples section, *infra*, for details. ^d Reactions were run at $-40\text{ }^{\circ}\text{C}$. ^e Reactions were run at $-78\text{ }^{\circ}\text{C}$. ^f Reactions were run at $-85\text{ }^{\circ}\text{C}$. ^g Reactions were run at $-90\text{ }^{\circ}\text{C}$.

[0088] Aryl-propenyl acyl imines are also effective as electrophiles in the asymmetric Mannich reaction employing cyclic nucleophiles (Table 4). By employing 5 mol% of cinchonine in CH_2Cl_2 the desired addition products were obtained in near-quantitative yields and high diastereo- and enantioselectivity.

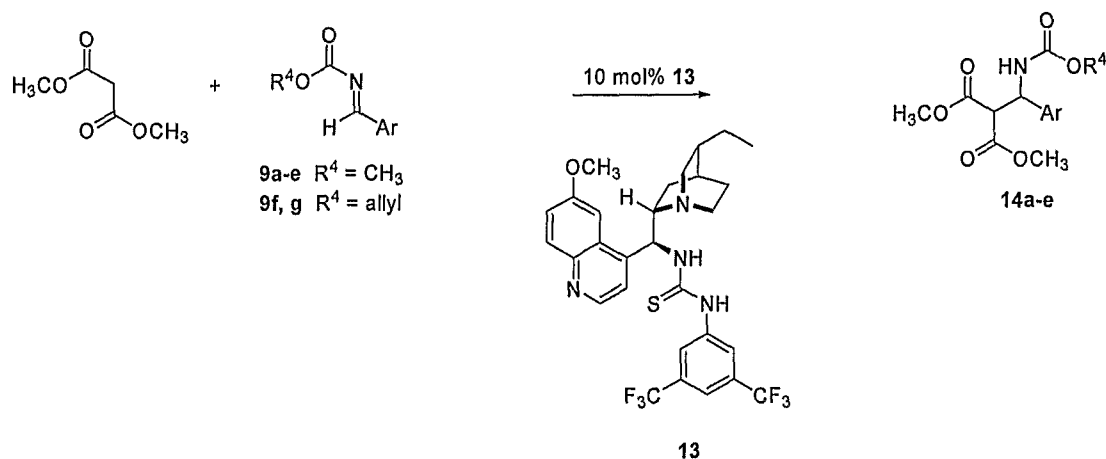
Table 4. Asymmetric Mannich Reactions Employing Aryl-Propenyl Acyl Imines

 ^{8a} X = CH_2, Y = OCH_3 ^{8b} X = CH_2, Y = OCH_2CH_3 ^{8c} X = CH_2, Y = CH_3 ^{8d} X = O, Y = CH_3 11a, b 5 mol% cinchonine CH_2Cl_2 12a-g					
entry	Ar	nucleophile	yield (%) ^b	de (%) ^c	ee (%) ^c
1	Ph (11a)	8a	12a (98)	90	99
2	Ph (11a)	8b	12b (98)	94	98
3	Ph (11a)	8c	12c (98)	95	99
4	Ph (11a)	8d	12d (88)	38	98
5	2- $\text{C}_4\text{H}_3\text{O}$ (11b)	8a	12e (98)	99	99
6 ^d	2- $\text{C}_4\text{H}_3\text{O}$ (11b)	8b	12f (98)	98	93
7	2- $\text{C}_4\text{H}_3\text{O}$ (11b)	8c	12g (98)	94	98

^a Mannich reactions were carried out using 0.5 mmol nucleophile, 0.5 mmol acyl imines in CH_2Cl_2 (0.5 M) for 2-3 h, at $-78\text{ }^{\circ}\text{C}$ under N_2 , followed by flash chromatography on silica gel. ^b Isolated yield of Mannich reaction product. ^c Determined by chiral HPLC analysis: see Examples, *infra*, for details. ^d Reaction was run at $-85\text{ }^{\circ}\text{C}$.

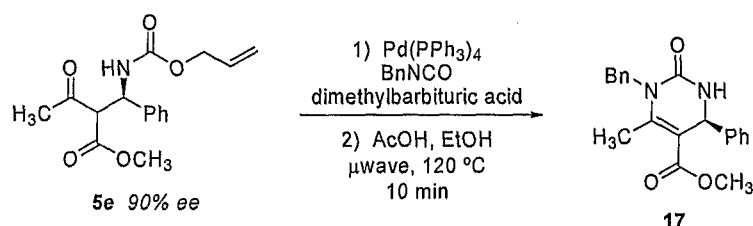
[0089] Excellent yields and enantioselectivities were also obtained in the reaction of dimethylmalonate with various aryl acyl imines when catalyzed by chiral amine 13 (Table 5).

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Table 5. Asymmetric Mannich Reactions Employing Dimethylmalonate

entry	Ar	yield (%) ^b	ee (%) ^c
1	Ph (9a)	14a (98)	95
2	Ph (9f)	14b (95)	93
3	3-F-C ₆ H ₄ (9d)	14c (98)	90
4	3-CH ₃ -C ₆ H ₄ (9b)	14d (97)	86
5	<i>E</i> -PHCH=CH (9e)	14e (95)	90

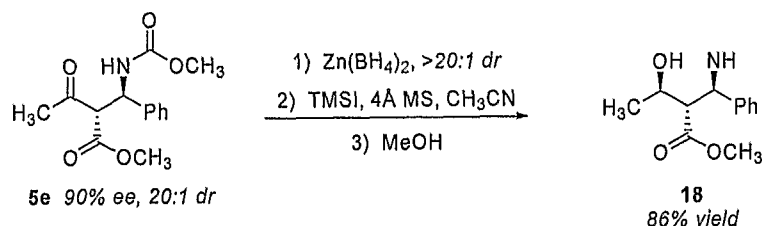
^a Mannich reactions were carried out using 1 mmol dimethyl malonate, 1 mmol acyl imine in CH₂Cl₂ (0.5 M) for 24 h, at -35 °C, followed by flash chromatography on silica gel. ^b Isolated yield. ^c Determined by chiral HPLC analysis.

Scheme 1. Synthesis of Enantioenriched Dihydropyrimidone

[0090] The asymmetric Mannich reaction provided ready access to highly functionalized building blocks, the synthetic utility of which merited exploration. We first considered **5e** as starting material for the asymmetric synthesis of dihydropyrimidones (Scheme 1). Although dihydropyrimidones are useful biological and pharmacological research tools,¹⁴ there are few procedures for their construction in enantioenriched form.^{14a,15} Preparation of the racemate is most commonly accomplished using the Biginelli reaction¹⁶ and single enantiomers are obtained by resolution processes.¹⁷ Treatment of **5e** with catalytic Pd(PPh₃)₄ and dimethyl barbituric acid as the allyl scavenger in the presence of benzyl isocyanate afforded the corresponding unsymmetrical urea in 85% isolated yield. Ring closure to the pyrimidone was

promoted by AcOH in EtOH under microwave conditions to afford the 5-benzyl pyrimidone **17** in 95% yield and 90% ee, thus demonstrating enantioselective access to Biginelli-type products.

Scheme 2. Synthesis of β -Amino Alcohols



[0091] The diastereomerically enriched Mannich product **5d** was easily converted to the corresponding β -amino alcohol using a reduction/deprotection sequence (Scheme 2). Reduction of **5d** using $\text{Zn}(\text{BH}_4)_2$ at -78°C ¹⁸ afforded the amino alcohol in 95% yield and >20:1 dr. The methyl carbamate **5** was deprotected *via* a two-step process using TMSI in CH_3CN followed by treatment with MeOH¹⁹ to yield amino alcohol **18** (86% over three steps).

[0092] We also report herein the enantioselective addition of nitroalkanes to acyl aryl imines catalyzed by chiral amines.^{20–27} The asymmetric aza-Henry reaction can be run with as little as 1 mol% of quinidine or quinine in the presence or absence of solvent (e.g., it can be run in neat nitro-alkane). Table 6 depicts the results of asymmetric aza-Henry reactions that employ chiral amine catalyst **13** and afford excellent yields (80–98%) and enantioselectivities (90–98% ee). ,

Table 6. Asymmetric aza-Henry Reactions^a

entry	Ar	Z	yield (%) ^b	ee (%) ^c
1	Ph (9a)	H	19a (98)	95
2	Ph (9f)	H	19b (95)	92
3	Ph (9f)	CH_3	19c (96)	95 (9:1 dr)
4	3-F- C_6H_4 (9d)	H	19d (98)	98
5	3-F- C_6H_4 (9d)	CH_3	19e (98)	91 (20:1 dr)
6 ^d	3- CH_3 - C_6H_4 (9b)	H	19f (98)	91

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7	3-CH ₃ -C ₆ H ₄ (9b)	CH ₃	19g (98)	97 (9:1 dr)
8	<i>E</i> -PHCH=CH (9e)	H	19h (80)	90
9	<i>E</i> -PHCH=CH (9e)	CH ₃	19i (80)	90 (11:1 dr)

^a aza-Henry reactions were carried out using 8 mmol nitro-alkane, 1 mmol acyl imine in CH₂Cl₂ (0.5 M) for 24 h, at -55 °C, followed by flash chromatography on silica gel. ^b Isolated yield. ^c Determined by chiral HPLC analysis.

[0093] Herein, we describe a diastereo- and enantioselective direct Mannich reaction of β-keto esters and other 1,3-dicarbonyl compounds with acyl aryl imines and a diastereo- and enantioselective direct aza-Henry reaction of nitroalkanes with acyl aryl imines catalyzed by chiral alkaloids. We have used the products from the reaction in the synthesis of enantioenriched dihydropyrimidones and β-amino-alcohols.

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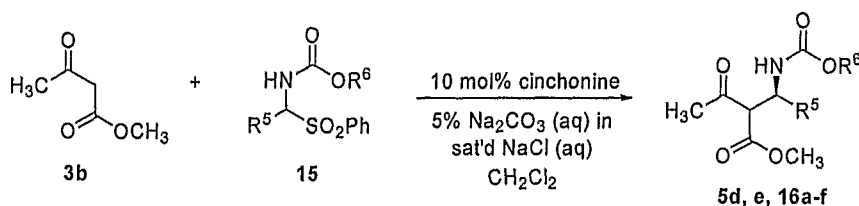
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[0094] In other embodiments, addition reactions in accordance with the present invention are preformed using α -amido sulphones as precursors to acyl imines, which are formed therefrom under the reaction conditions (Table 7). The use of α -amido sulfones as precursors to imines is well-documented in the literature and provides advantages in the areas of stability and handling when compared to the corresponding imines. In certain embodiments, these reactions employ a biphasic mixture comprising a basic brine phase and a CH_2Cl_2 phase. Of particular note, this procedure affords excellent results for aliphatic imine-derived Mannich products (entries 7 and 8, Table 7).

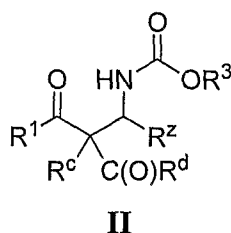
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Table 7. Asymmetric Mannich Reactions Employing α -Amido Sulfones

entry	R^5	R^6	yield (%) ^b	ee (%) ^c
1	Ph (15a)	CH_3	5d (99)	96
2	Ph (15b)	allyl	5e (95)	91
3	4-Br- C_6H_4 (15c)	CH_3	16a (93)	90
4	4-Br- C_6H_4 (15d)	allyl	16b (90)	90
5	2- $\text{C}_4\text{H}_3\text{O}$ (15e)	CH_3	16c (90)	92
6 ^d	2- $\text{C}_4\text{H}_3\text{O}$ (15f)	allyl	16d (88)	90
7	PhCH_2CH_2 (15g)	CH_3	16e (85)	90
8	PhCH_2CH_2 (15h)	allyl	16f (72)	90

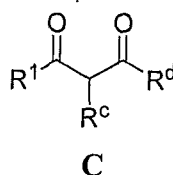
^a Mannich reactions were carried out using 1 mmol methyl acetoacetate, 0.5 mmol acyl imines in CH_2Cl_2 (0.5 M) for 16 h, at -15°C , followed by flash chromatography on silica gel. ^b Isolated yield. ^c Determined by chiral HPLC analysis.

[0095] Accordingly, another embodiment of the present invention provides a method for preparing a compound of formula **II**:



wherein said method comprises the step of:

reacting a compound of formula **C**:



wherein:

R^1 is R, OR, SR, or NR'_2 ;

each R is independently an optionally substituted group selected from C_{1-6} aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally

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substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

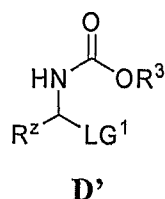
two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R' is independently hydrogen or R;

R^c is R', halo, N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂; and

R^d is R or OR;

with a compound of formula **D'**:



wherein:

LG¹ is a suitable leaving group;

R^z is R'; and

R³ is R;

in the presence of a chiral amine base and optionally in a suitable medium.

[0096] Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 5th Ed., pp. 351-357, John Wiley and Sons, N.Y. Such leaving groups include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulphonyloxy, optionally substituted arylsulphonyloxy, and diazonium moieties. Examples of suitable leaving groups include chloro, iodo, bromo, fluoro, methanesulphonyloxy (mesyloxy), tosyloxy, triflyloxy, nitro-phenylsulphonyloxy (nosyloxy), and bromo-phenylsulphonyloxy (brosyloxy). In certain embodiments, LG¹ is of the formula Ar-SO₂-, wherein Ar is an optionally substituted phenyl ring. Suitable substituents on Ar include halogen and nitro.

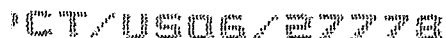
[0097] Embodiments, subclasses, and examples described herein above for compounds of formula **II**, **C**, and **D** apply singly and in combination to compounds of formula **II**, **C**, and **D'** as defined directly above.

[0098] α -Amido sulfones^[6] are bench-stable precursors to *N*-acylimines that have proven useful in a wide range of enantioselective reactions including aza-Henry reactions,^[7] imine alkylations,^[8] and aldehyde-imine cross-coupling reactions.^[9] Under basic conditions, α -amido sulfones are readily converted to the corresponding acyl imine.^[10] This approach

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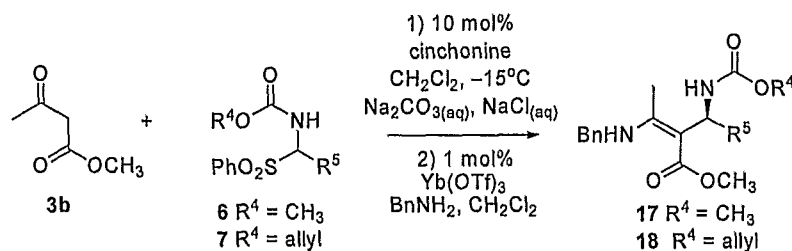
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5		4c	15	
6	2	4c	90	90 ^[e]
7	quinine	4c	81	68 ^[e]
8	quinidine	4c	62	72
9	hydroquinidine	4c	75	71

[a] Reactions were run with amido sulfone **4** (0.5 mmol), ester **3b** (1.5 mmol), and catalyst (0.05 mmol) in CH₂Cl₂ (5 mL) and Na₂CO₃ in brine (5 mL) at 15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yield of Isolated product. [c] Determined by chiral HPLC analysis. [d] Reaction was run without water using 10 mol% Na₂CO₃. [e] Opposite sense of enantioselectivity.

[00100] The optimal reaction conditions for the reaction of **3b** with **4c** proved general for a variety of *N*-methyl carbamate sulfones (Table 9). Nonsubstituted alkyl amido sulfone cleanly underwent the Mannich reaction to afford the desired Mannich product in greater than 85% isolated yields (Table 9 entries 1, 2). Subsequent condensation with benzyl amine gave *Z*- enamines in high yields (> 71%) and high ee (90%). α -Substituted (entry 3) alkyl amido sulfones reacted with **3b** under the general conditions, albeit at a slower rate, to give the Mannich adduct in comparable yields and enantioselectivity. The substrates bearing benzyl-protected alcohol (entry 4) were also tolerated under optimized conditions. Aromatic *N*-methyl carbamate sulfones proved to be more reactive than aliphatic derivatives. The addition of **3b** to phenyl amido sulfone (entry 5) took only 15 hours to generate the Mannich product in quantitative yield and excellent ee (96%). Electron withdrawing (entries 68) and electron donating (entries 9 & 10) substitution on the aromatic ring did not affect the reaction rate or enantioselectivity. Heteroaromatic amido sulfones (entries 11 & 12) were also tolerated under these conditions. The reaction rate and enantioselectivities were sensitive to the type of amido sulphone employed in the reaction. For reactions that were found to be slow or result in lower enantioselectivities we hypothesized that using *p*-chloro-phenyl sulfones in the reaction would more readily eliminate to form the acyl imine. *N*-Allyl carbamate *p*-chloro-phenyl sulfones were used in the Mannich reaction in order to achieve a higher reaction rate and higher enantioselectivity for aliphatic derivatives (entries 13 & 14) although aromatic and heteroaromatic *N*-allyl carbamate phenyl sulfones worked just as well as *N*-methyl carbamate sulfones to afford Mannich adducts with high yield and high enantioselectivity (entries 15 – 20).

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Table 9. Asymmetric Mannich reactions of β -keto ester **3b** ^[a]

entry	R^4	R^5	%yield ^[b]	yield(%) ^[c]	%ee ^[d]
1	CH_3	PhCH_2CH_2	85	17a (84)	90
2	CH_3	PhCH_2	87	17b (71)	90
3	CH_3	$(\text{CH}_3)_2\text{CH}$	84	17c (73)	93
4	CH_3	BnOCH_2	92	17d (78)	95
5	CH_3	Ph	99	17e (95)	97
6	CH_3	4-Br- C_6H_4	93	17f (83)	90
7	CH_3	3-F- C_6H_4	98	17g (82)	95
8	CH_3	3-CF ₃ - C_6H_4	96	17h (84)	91
9	CH_3	4-CH ₃ - C_6H_4	92	17i (96)	90
10	CH_3	3-CH ₃ O- C_6H_4	93	17j (86)	91
11	CH_3	2- $\text{C}_4\text{H}_3\text{O}$	90	17k (84)	92
12	CH_3	2- $\text{C}_4\text{H}_3\text{S}$	92	17l (88)	91
13 ^[e]	allyl	PhCH_2CH_2	91	18a (81)	90
14 ^[e]	allyl	BnOCH_2	90	18b (76)	90
15	allyl	Ph	95	18c (81)	91
16	allyl	4-Br- C_6H_4	90	18d (80)	90
17	allyl	3-F- C_6H_4	88	18e (83)	90
18	allyl	3-CF ₃ - C_6H_4	91	18f (82)	91
19	allyl	4-CH ₃ - C_6H_4	94	18g (84)	90
20	allyl	2- $\text{C}_4\text{H}_3\text{O}$	88	18h (81)	90

[a] Reactions were run with amido sulfones (0.5 mmol), ester **3b** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at 15°C for 48 h, followed by flash chromatography on silica gel. [b] Yield of isolated Mannich reaction product. [c] Yields of isolated enamine **17** and **18**. [d] Determined by chiral HPLC analysis. [e] *p*-Cl-Ph sulfones were used in the Mannich reactions.

[00101] The general reaction conditions proved to be highly effective in the Mannich reaction using 2,4-pentanedione **3c** as nucleophile (Table 10). Aliphatic and aromatic amido sulfones were examined in the reaction with **3c** to afford the Mannich product with a similar level of selectivity. Cinchonidine was also successfully used to promote the Mannich reaction of **3c** with a variety of α -amido sulfones. In all cases the reaction proceeded cleanly with greater than 85% yields and excellent ee (> 90%).

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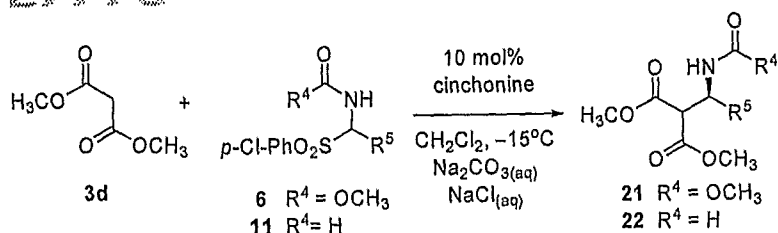
[00102] Dimethyl malonate **3d** proved to be less reactive under standard conditions than β -keto ester **3c** and diketone **3c**. When aliphatic phenyl sulfone **4c** was used, the reaction afforded the Mannich adduct in less than 50% yield. *p*-Chloro-phenyl sulfones were successfully utilized to increase the reaction rate (Table 11). Treatment of α -benzyloxy aliphatic amido sulfones with **3d** afforded the desired product in greater than 82% yield and 95% ee (entry 1). Aromatic derivatives were as effective as aliphatic derivatives (entries 2 & 3). However, the α -substituted substrate was less reactive, probably because of steric hindrance (entry 4). Low yields of the desired Mannich product were the result of an undesired reaction pathway to form the ene-amide (entry 5).

Table 10. Asymmetric Mannich reactions of diketone **3c** ^[a]

entry	R ⁵	yield (%) ^[b]	%ee ^[c]
1	PhCH ₂ CH ₂	26a (88)	90
2	Ph	26b (91)	93
3	4-Br-C ₆ H ₄	26c (90)	91
4	3-CF ₃ -C ₆ H ₄	26d (87)	92
5	2-C ₄ H ₃ O	26e (88)	91
6	2-C ₄ H ₃ S	26f (86)	93

[a] Reactions were run with amido sulfones (4.0 mmol), diketone **3c** (12.0 mmol), and catalyst (0.40 mmol) in CH₂CH₂ (5 mL) and aqueous Na₂CO₃ in brine (5 mL) at -15 °C for 48 h, followed by flash chromatography on silica gel. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 11. Asymmetric Mannich reactions of methyl malonate **3d** ^[a]



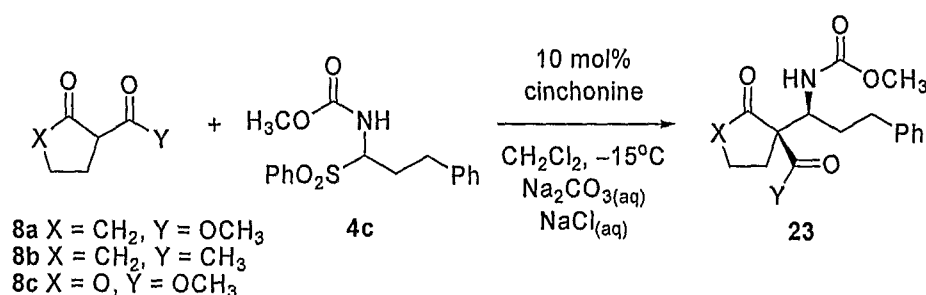
entry	R^4	R^5	yield (%) ^[b]	% ee ^[c]
1	OCH_3	BnOCH_2	21a (82)	95
2	OCH_3	Ph	21b (83)	90
3	OCH_3	4-Br- C_6H_4	21c (91)	90
4	OCH_3	$(\text{CH}_3)_2\text{CH}$	21d (58)	90
5	OCH_3	2,4,5-F- $\text{C}_6\text{H}_4\text{CH}_2$	21e (56)	70
6	H	$(\text{CH}_3)_2\text{CH}$	22a (72)	91
7	H	2,4,5-F- $\text{C}_6\text{H}_4\text{CH}_2$	22b (73)	95
8	H	Ph	22c (95)	98

[a] Reactions were run with amido sulfones (0.5 mmol), ester **3c** (1.5 mmol), and catalyst (0.05 mmol) in CH_2Cl_2 (5 mL) and aqueous Na_2CO_3 in brine (5 mL) at 15°C for 48 h, followed by flash chromatography on silica gel. [b] Yields of Isolated products. [c] Determined by chiral HPLC analysis.

[00103] α -Formido sulfones were successfully used as a solution for those two problematic substrates. In both cases, the yields were higher than 70% and ee are higher than 90% (entries 6 & 7). When phenyl formido sulfone was used in the Mannich reaction, quantitative yield and 98% ee were observed (entry 8).

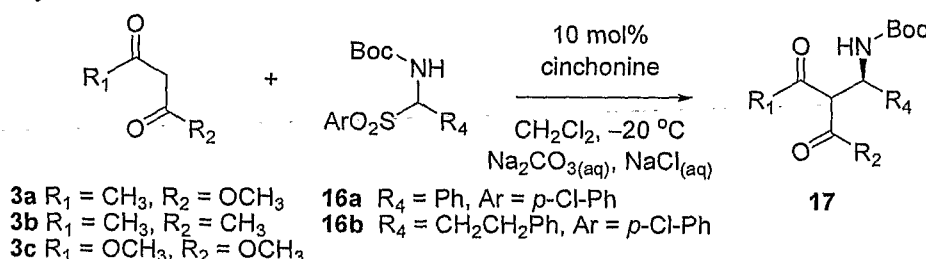
[00104] We have also expanded the scope of this reaction to include cyclic α -substituted β -keto ester **8a**, β -diketones **8b**, and β -keto lactone **8c** (Table 12). Treatment of α -amido sulfone with these dicarbonyls catalyzed by 10 mol % cinchonine **1** under biphasic conditions afforded the corresponding products in high yield (84-95%), high diastereoselectivity (98% de), and high enantioselectivity (90-97% ee) (Table 12, entries 1 – 3). The reaction provides a catalytic route towards the construction of cyclic β -amino esters with α -quaternary carbon centers as a supplement to our recent study.^[11b, 12]

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Table 12. Asymmetric Mannich reactions of dicarbonyls **8**^[a]

entry	dicarbonyls	yield (%) ^[b]	% de ^[c]	% ee ^[d]
1	8a	23a (91)	98	90
2	8b	23b (95)	98	97
3	8c	23c (84)	98	99

[a] Reactions were run with amido sulfones (0.5 mmol), dicarbonyls (1.5 mmol), and catalyst (0.05 mmol) in CH₂Cl₂ (5 mL) and aqueous Na₂CO₃ in brine (5 mL) at 15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yields of isolated products. [c] Determined by H-NMR. [d] Determined by chiral HPLC analysis.

Table 13. Asymmetric Mannich reactions of *N*-Boc sulfones **24**^[a]

entry	dicarbonyls	α -amido sulfones	yield (%) ^[b]	% ee ^[c]
1	3b	24a	25a (93)	95
2	3c	24a	25b (97)	95
3 ^[d]	3d	24a	25c (81)	90
4	3b	24b	25d (84)	90
5	3c	24b	25e (90)	92

[a] Reactions were run with amido sulfones (0.5 mmol), dicarbonyls (1.5 mmol), and catalyst (0.05 mmol) in CH₂Cl₂ (5 mL) and aqueous Na₂CO₃ in brine (5 mL) at 15 °C for 48 h, followed by flash chromatography on silica gel. [b] Yields of Isolated products. [c] Determined by chiral HPLC analysis. [d] Reaction was run in acetonitrile (2.5 mL), CH₂Cl₂ (2.5 mL) and aqueous Na₂CO₃ in brine at 30 °C (2.5 mL).

[00105] Finally, we employed the *N*-Boc α -amido sulfones **24a** and **24b** in the Mannich reaction (Table 13). The reactions of methyl acetoacetate **3b** and 2,4-pentanedione **3c** to **24a** or **24b** afforded the desired product in high yield and high ee. Reactions involving dimethyl

malonate **3d** as the nucleophile required lower temperatures in order to achieve good enantioselectivities. Acetonitrile was added in order to run the reaction at $-30\text{ }^{\circ}\text{C}$ without freezing the aqueous layer. We were able to isolate the malonate adduct **25c** in 81% yield and 90% ee.

[00106] Herein, we describe a general enantioselective Mannich reaction of β -dicarbonyls and α -amido sulphones as acyl imine precursors. The reactions are run under biphasic conditions requiring 10 mol% of the cinchona alkaloid catalyst and aqueous Na_2CO_3 . Reaction products are obtained in good yields, high enantioselectivities, and in diastereoselectivities that range from 1:1 to >99:1.

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EXAMPLES

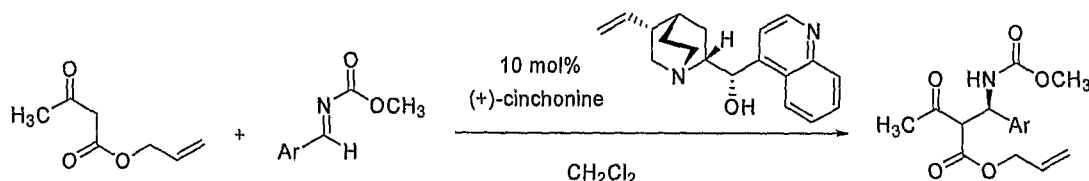
[00107] Compounds of the present invention were prepared in accordance with the general schemes depicted herein.

[00108] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

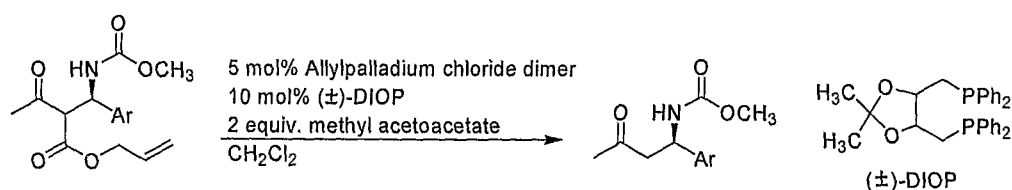
[00109] **General Information.** All ^1H NMR, and ^{13}C NMR spectra were recorded using Varian Unity Plus 400 (93.94 kG, ^1H 400 MHz) or Varian Gemini 300 (70.5 kG, ^{13}C 75 MHz) spectrometers at ambient temperature in CDCl_3 . Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant, and integration. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR ESP spectrophotometer. High-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory on a Finnegan MAT-90 spectrometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm, and were reported as $[\alpha]_D$ (concentration in grams/100 mL solvent). Analytical thin layer chromatography was performed using EMD 0.25 mm silica gel 60-F plates. Flash column chromatography was performed on Sorbent Technologies 60 Å silica gel. Chiral HPLC analysis was performed using an Agilent 1100 series HPLC with a diode array detector and using a Chiralcel[®]OD (Chiral Technologies Inc., 24cm×4.6mm I.D.), Chiralcel[®]OD-H (Chiral Technologies Inc., 15cm×4.6mm I.D.), Chiralpak[®]AD-H (Chiral Technologies Inc., 15cm×4.6mm I.D.), or a (*R,R*)-Whelk-O 1 (Regis[®] Technologies Inc., 25cm× 4.6mm I.D.) column. Hydrogenation was performed on H-Cube system supported by

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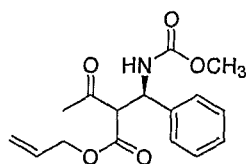
Thales Nanotechnology, Inc. All reactions were performed under nitrogen atmosphere, in oven dried glassware with magnetic stirring, unless otherwise noted. Reaction solvents were obtained from a dry solvent system (alumina) and used without further drying. All acyl imines were prepared according to the published procedure.¹ (+)-Cinchonine, quinine, quinidine and other reagents were used as supplied by Sigma-Aldrich, Alfa Aesar, Lancaster, or Acros unless otherwise noted.



[00110] General asymmetric mannich reaction procedure of allyl acetoacetate to acyl imines. In an oven dried 17×110 mm round bottom reaction vessel, (+)-cinchonine (15 mg, 0.05 mmol) was dissolved in 1.00 mL CH₂Cl₂. The solution was cooled down to -35 °C. The imine (0.50 mmol) and allyl acetoacetate (0.070 mL, 0.50 mmol) were added successively. The solution was stirred at -35 °C for 16 h. The reaction mixture was then passed through a plug of silica gel and eluted with 5 mL of ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (elution with 15%-30% ethyl acetate in hexanes) to afford the products shown.

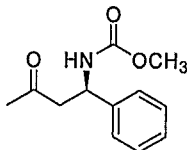


[00111] General Pd⁰ promoted decarboxylation procedure. An oven dried 17×110 mm round bottom reaction vessel was charged with allyl palladium chloride dimer (3.6 mg, 0.010 mmol) and (±)-2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((±)DIOP)² (10 mg, 0.020 mmol). The Pd catalyst and ligand were dissolved in CH₂Cl₂ (0.5 mL) and stirred at room temperature for 10 minutes. Methyl acetoacetate (0.045 mL, 0.40 mmol) and isolated product (0.20 mmol) were added successively. The reaction solution was stirred at room temperature for 3 h and subjected directly to flash chromatography over silica gel (elution with 30%-50% ethyl acetate in hexanes) to afford the products shown.

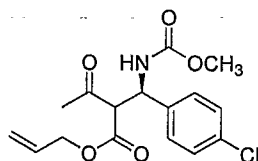


[00112] 2-((*R*)-Methoxycarbonylamino-phenyl-methyl)-3-oxo-butyric acid allyl ester.

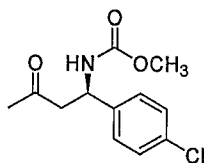
Yield: 151 mg, 99%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers reported): δ 7.33-7.22 (m, 10H), 6.30 (br, 1H), 5.92 (br, 1H), 5.81-5.67 (m, 2H), 5.56 (br, 1H), 5.45 (t, $J = 8.0$ Hz, 1H), 5.28-5.11 (m, 4H), 4.55 (d, $J = 5.6$ Hz, 2H), 4.52 (m, 2H), 4.05 (m, 2H), 3.62 (s, 3H), 3.58 (s, 3H), 2.30 (s, 3H), 2.13 (s, 3H). **HRMS:** calc'd for $(\text{M})^+$ $\text{C}_{14}\text{H}_{21}\text{O}_2$: 305.1263; found: 305.1257.



[00113] (*R*)-(3-Oxo-1-phenyl-butyl)-carbamic acid methyl ester. Yield: 35 mg, 80%. **ee:** 92%. **HPLC** analysis, t_r minor: 14.6 min, t_r major: 21.3 min, [(*R*, *R*)-Whelk-O 1 column, Hexanes:IPA 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.31-7.19 (m, 5H), 5.65 (br, 1H), 5.10 (dd, $J = 13, 6.0$ Hz, 1H), 3.61 (s, 3H), 3.06-3.00 (dd, $J = 16, 5.0$ Hz, 1H), 2.91-2.86 (dd, $J = 16, 11$ Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 208.2, 156.2, 141.2, 128.7, 127.5, 126.2, 52.2, 51.5, 49.0, 30.6. **IR** (thin film, cm^{-1}): 3328, 3030, 2952, 1712, 1700, 1538, 1455, 1360, 1258, 1057, 700. **HRMS:** calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{12}\text{H}_{15}\text{NO}_3$: 222.1085; found: 222.1154. $[\alpha]_D^{23} = +33.7^\circ$ ($c = 1.0$, CHCl_3).



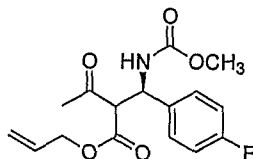
[00114] 2-[(*R*)-(4-Chloro-phenyl)-methoxycarbonylamino-methyl]-3-oxo-butyric acid allyl ester. Yield: 158 mg, 93%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers reported): δ 7.25 (m, 8H), 6.33 (br, 1H), 6.03 (br, 1H), 5.72 (m, 2H), 5.50 (br, 1H), 5.40 (t, 1H), 5.21 (m, 4H), 4.57 (dd, $J = 6.0, 1.2$ Hz, 2H), 4.53 (t, $J = 6.0$ Hz, 2H), 4.02 (br, 1H), 3.95 (br, 1H), 3.65 (s, 3H), 3.63 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H).



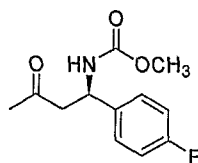
[00115] (*R*)-[1-(4-Chloro-phenyl)-3-oxo-butyl]-carbamic acid methyl ester. Yield: 41 mg, 80%. **ee:** 83%. **HPLC** analysis, t_r minor: 14.0 min, t_r major: 23.2 min, [(*R*,*R*)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.25 (d, $J = 9.0$ Hz, 2H), 7.20 (d, $J = 8.5$ Hz, 2H), 5.71 (br, 1H), 5.03 (dd, $J = 14, 6.0$ Hz, 1H), 3.61 (s, 3H), 3.04-2.99 (dd, $J = 17, 6.0$ Hz, 1H), 2.90-2.84 (dd, $J = 17, 6.0$ Hz, 1H), 2.06 (s, 3H). ^{13}C

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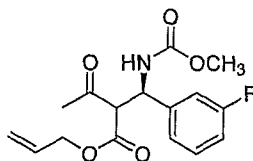
NMR (75.0 MHz, CDCl₃): δ 206.3, 156.2, 139.8, 128.7, 127.6, 52.2, 50.8, 48.6, 30.6. **IR** (thin film, cm⁻¹): 3328, 2962, 1715, 1695, 1544, 1404, 1347, 1260, 1090, 1060, 1015, 800. **HRMS**: calc'd for (M)⁺ C₁₂H₁₄ClNO₃: 255.0662; found: 255.0684. $[\alpha]^{23}_{\text{D}} = +21.1^{\circ}$ (c = 1.0, CHCl₃).



[00116] 2-[(R)-(4-Fluoro-phenyl)-methoxycarbonylamino-methyl]-3-oxo-butyl ester. Yield: 158 mg, 98%. **¹H NMR** (400 MHz, CDCl₃, both diastereomers reported): δ 7.26 (m, 4H), 6.99 (m, 4H), 6.34 (d, *J* = 8.0 Hz, 1H), 6.04 (d, *J* = 8.4 Hz, 1H), 5.75 (m, 2H), 5.51 (br, 2H), 5.41 (t, *J* = 7.2 Hz, 1H), 5.20 (m, 4H), 4.55 (d, *J* = 5.2 Hz, 2H), 4.51 (m, 2H), 4.01 (d, *J* = 5.6 Hz, 1H), 3.96 (br, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 2.30 (s, 3H), 2.14 (s, 3H).



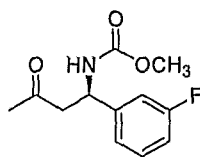
[00117] (R)-[1-(4-Fluoro-phenyl)-3-oxo-butyl]-carbamic acid methyl ester. Yield: 46 mg, 97%. **ee:** 93%. **HPLC** analysis, *t_r* minor: 14.3 min, *t_r* major: 20.8 min, [(*R,R*)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. **¹H NMR** (400 MHz, CDCl₃): δ 7.23 (dd, *J* = 7.0, 2.0 Hz, 2H), 6.97 (dd, *J* = 9.0, 2.0 Hz, 2H), 5.67 (br, 1H), 5.05 (dd, *J* = 14, 6.0 Hz, 1H), 3.61 (s, 3H), 3.05-2.99 (dd, *J* = 17, 6.0 Hz, 1H), 2.90-2.84 (dd, *J* = 15, 6.0 Hz, 1H), 2.06 (s, 3H). **¹³C NMR** (75.0 MHz, CDCl₃): δ 206.5, 156.2, 137.1, 128.0, 127.8, 115.6, 115.3, 52.2, 50.9, 48.8, 30.6. **IR** (thin film, cm⁻¹): 3326, 1713, 1698, 1542, 1274, 1160, 1058, 822. **HRMS**: calc'd for (M+H)⁺ C₁₂H₁₄FNO₃: 240.0991; found: 240.1036. $[\alpha]^{23}_{\text{D}} = +29.5^{\circ}$ (c = 0.6, CHCl₃).



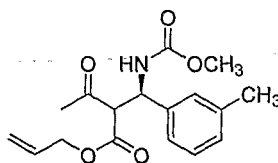
2-[(R)-(3-Fluoro-phenyl)-methoxycarbonylamino-methyl]-3-oxo-butyl ester. Yield: 158 mg, 98%. **¹H NMR** (400 MHz, CDCl₃, both diastereomers reported): δ 7.27 (t, *J* = 8 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.93 (t, *J* = 8.8 Hz, 1H), 6.12

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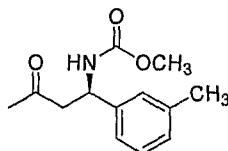
(d, $J = 7.2$ Hz, 1H), 5.80 (m, 1H), 5.44 (t, 1H), 5.26 (d, $J = 16.8$ Hz, 1H), 5.23 (d, $J = 10$ Hz, 1H), 4.58 (d, $J = 5.6$ Hz, 2H), 4.04 (d, $J = 4.8$ Hz, 1H), 3.64 (s, 3H), 2.14 (s, 3H).



[00118] **(R)- [1-(3-Fluorophenyl)-3-oxo-butyl]-carbamic acid methyl ester.** Yield: 40 mg, 84%. ee: 91%. HPLC analysis, t_r minor: 12.9 min, t_r major: 17.7 min, [(R,R)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.26 (m, 1H), 7.05 (d, $J = 8.0$ Hz, 1H), 6.98 (d, $J = 9.6$ Hz), 6.92 (t, $J = 8.4$ Hz), 5.74 (br, 1H), 5.09 (dd, $J = 14, 6.0$ Hz), 3.64 (s, 3H), 3.06-3.03 (dd, $J = 17, 6.0$ Hz, 1H), 2.93-2.87 (dd, $J = 17, 6$ Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 206.2, 155.8, 143.4, 129.8, 121.4, 114.0, 112.9, 51.8, 50.4, 48.0, 30.3. IR (thin film, cm^{-1}): 3326, 1717, 1697, 1592, 1538, 1451, 1363, 1258, 1058, 695. HRMS: calc'd for $(\text{M})^+$ $\text{C}_{12}\text{H}_{14}\text{FNO}_3$: 239.0958; found: 239.0940. $[\alpha]_D^{23} = +18.4^\circ$ ($c = 0.9$, CHCl_3).



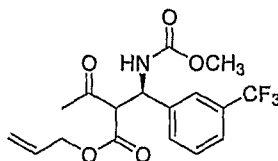
[00119] **2-((R)-Methoxycarbonylamino-m-tolyl-methyl)-3-oxo-butyric acid allyl ester.** Yield: 153 mg, 96%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers reported): δ 7.18 (m, 2H), 7.05 (m, 6H), 6.35 (d, $J = 8.8$ Hz, 1H), 6.21 (d, $J = 8.8$ Hz, 1H), 5.74 (m, 2H), 5.53 (m, 1H), 5.41 (t, $J = 7.2$ Hz, 1H), 5.18 (m, 4H), 4.55 (d, $J = 5.2$ Hz, 2H), 4.53 (d, $J = 6.4$ Hz, 2H), 4.03 (d, $J = 7.2$ Hz, 1H), 4.00 (d, $J = 4.0$ Hz, 1H), 3.64 (s, 3H), 3.62 (s, 3H), 2.30 (s, 3H), 2.29 (s, 6H), 2.13 (s, 1H).



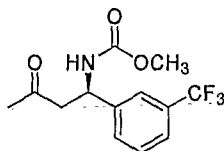
[00120] **(R)- (3-Oxo-1-m-tolyl-butyl)-carbamic acid methyl ester.** Yield: 38 mg, 81%. ee: 96%. HPLC analysis, t_r minor: 13.0 min, t_r major: 22.6 min, [(R,R)-Whelk-O 1 column, Hexanes: IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.19 (t, $J = 18$ Hz, 1H), 7.05 (m, 3H), 5.57 (br, 1H), 5.08 (dd, $J = 14, 6.0$ Hz, 1H), 3.63 (s, 3H), 3.04-3.00 (dd, $J = 15$,

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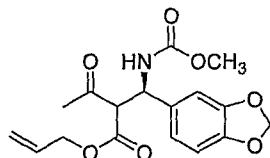
4.0 Hz, 1H), 2.92-2.86 (dd, $J = 16, 7.0$ Hz), 2.31 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 206.2, 156.0, 138.4, 128.6, 128.3, 126.9, 123.1, 52.2, 51.4, 49.0, 30.6, 21.5. IR (thin film, cm^{-1}): 3326, 2954, 1720, 1700, 1533, 1362, 1262, 1193, 1159, 1060, 787, 704. HRMS: calc'd for $(\text{M})^+$ $\text{C}_{13}\text{H}_{17}\text{NO}_3$: 235.1208; found: 235.1208. $[\alpha]^{23}_{\text{D}} = +25.7^\circ$ ($c = 0.75$, CHCl_3).



[00121] 2-[(*R*)-Methoxycarbonylamino-(3-trifluoromethyl-phenyl)-methyl]-3-oxo-butyric acid allyl ester. Yield: 188 mg, 99%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers were reported): δ 7.52 (m, 6H), 7.45 (m, 2H), 6.48 (d, $J = 8.8$ Hz, 1H), 6.27 (d, $J = 9.2$ Hz, 1H), 5.74 (m, 2H), 5.62 (dd, $J = 9.2, 4$ Hz, 1H), 5.51 (br, 1H), 5.26-5.12 (m, 4H), 4.56 (d, $J = 4.8$ Hz, 2H), 4.52 (d, $J = 6$ Hz, 2H), 4.09 (d, $J = 6$ Hz, 1H), 4.02 (d, $J = 4.4$ Hz, 1H), 3.66 (s, 3H), 3.63 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H).



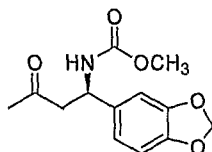
[00122] (*R*)-[3-Oxo-1-(3-trifluoromethyl-phenyl)-butyl]-carbamic acid methyl ester. Yield: 46 mg, 83%; ee: 90%. HPLC analysis, t_{r} minor: 9.2 min, t_{r} major: 12.6 min, [(*R,R*)-Whelk-O 1, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.48 (m, 4H), 5.78 (br, 1H), 5.15 (m, 1H), 3.64 (s, 1H), 3.10-3.06 (dd, $J = 14, 5.2$ Hz, 1H), 2.97-2.91 (dd, $J = 14, 5.2$ Hz, 1H), 2.09 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 206.4, 156.1, 142.4, 129.8, 129.1, 124.3, 122.9, 52.3, 51.0, 49.9, 48.5, 30.7. IR (thin film, cm^{-1}): 3340, 1715, 1695, 1540, 1328, 1270, 1165, 1106, 1061. HRMS: calc'd for $(\text{M})^+$ $\text{C}_{13}\text{H}_{14}\text{F}_3\text{NO}_3$: 289.0926; found: 289.0953. $[\alpha]^{23}_{\text{D}} = +15.0^\circ$ ($c = 1.0$, CHCl_3).



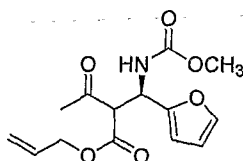
[00123] 2-((*R*)-Benzo[1,3]dioxol-5-yl-methoxycarbonylamino-methyl)-3-oxo-butyric acid allyl ester. Yield: 166 mg, 95%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers

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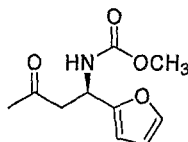
reported): δ 6.76 (m, 2H), 6.72 (m, 4H), 6.29 (d, $J = 7.6$ Hz, 1H), 5.92 (s, 2H), 5.91 (s, 2H), 5.77 (m, 2H), 5.43 (br, 1H), 5.33 (t, $J = 8.0$ Hz, 1H), 5.27-5.17 (m, 4H), 4.55 (m, 4H), 3.99 (d, $J = 6.0$ Hz, 1H), 3.93 (br, 1H), 3.63 (s, 3H), 3.61 (s, 3H), 2.28 (s, 3H), 2.15 (s, 3H).



[00124] **(R)- (1-Benzo[1,3]dioxol-5-yl-3-oxo-butyl)-carbamic acid methyl ester.** Yield: 43 mg, 81%. ee: 80%. HPLC analysis, t_r minor: 27.1 min, t_r major: 44.3 min[(R,R)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 6.75 (s, 1H), 6.71 (d, $J = 1.0$ Hz, 2H), 5.90 (s, 2H) 5.54 (br, 1H), 4.98 (dd, $J = 14$, 6.0 Hz, 1H), 3.61 (s, 3H), 3.02-2.96 (dd, $J = 16.5$, 6.0 Hz, 1H), 2.87-2.81 (dd, $J = 17$, 6.0 Hz, 1H), 2.07 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 209.6, 156.3, 119.5, 108.3, 106.9, 101.1, 52.2, 51.2, 48.9, 30.6. IR (thin film, cm^{-1}): 3332, 2923, 1714, 1697, 1504, 1490, 1444, 1358, 1242, 1038, 930. HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{13}\text{H}_{15}\text{NO}_5$: 265.0950; found: 265.0955. $[\alpha]_D^{23} = +13.0^\circ$ (c = 0.8, CHCl_3).



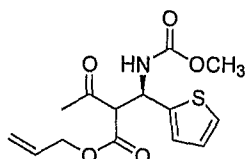
[00125] **2-((R)-Furan-2-yl-methoxycarbonylamino-methyl)-3-oxo-butyric acid allyl ester.** Yield: 120 mg, 81%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers reported): δ 7.28 (d, $J = 6.8$ Hz, 2H), 6.28 (m, 2H), 6.20 (m, 2H), 6.09 (d, $J = 9.6$ Hz, 1H), 5.91 (d, $J = 8.8$ Hz, 1H), 5.84 (m, 2H), 5.60 (dd, $J = 10$, 4.4 Hz, 1H), 5.53 (dd, $J = 8.4$, 6 Hz, 1H), 5.24 (m, 4H), 4.60 (d, $J = 6.4$ Hz, 4H), 4.18 (d, $J = 5.6$ Hz, 1H), 4.13 (d, $J = 4.0$ Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 2.30 (s, 3H), 2.23 (s, 3H).



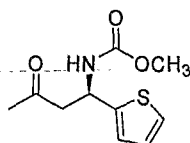
[00126] **(R)-1-(1-Furan-2-yl-3-oxo-butyl)-carbamic acid methyl ester.** Yield: 40 mg, 96%; ee: 93%. HPLC analysis, t_r minor: 29.0 min, t_r minor: 30.5 min, [(R,R)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.28 (d, $J = 2.0$

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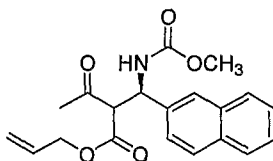
Hz, 1H), 6.27 (dd, $J = 3.1, 2.0$ Hz, 1H), 6.16 (d, $J = 3.4$ Hz, 1H), 5.58 (br, 1H), 5.17 (dd, $J = 14, 6.0$ Hz, 1H), 3.64 (s, 3H), 3.09-3.05 (dd, $J = 16, 5.0$ Hz, 1H), 2.94-2.88 (dd, $J = 17, 6.0$ Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 206.5, 153.5, 141.8, 110.5, 106.2, 52.2, 46.1, 45.6, 30.3. IR (thin film, cm^{-1}): 3324, 2950, 1708, 1693, 1290, 1257, 1237, 1047, 1014, 926, 737. HRMS: calc'd for $(\text{M})^+ \text{C}_{10}\text{H}_{13}\text{NO}_4$: 211.0845; found: 211.0816. $[\alpha]_D^{23} = +49.1^\circ$ ($c = 0.44$, CHCl_3).



[00127] **2-((*R*)-Methoxycarbonylamino-thiophen-2-yl-methyl)-3-oxo-butyl allyl ester.** Yield: 130 mg, 84%. ^1H NMR (400 MHz, CDCl_3 , both diastereomers reported): δ 7.19 (m, 2H), 6.90 (m, 4H), 6.29 (d, $J = 8.8$ Hz, 1H), 6.08 (d, $J = 4.0$ Hz, 1H), 5.78 (m, 3H), 5.71 (m, 1H), 5.30-5.19 (m, 4H), 4.60 (m, 4H), 4.13 (m, 1H), 4.09 (d, 7.2 Hz, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 2.32 (s, 3H), 2.22 (s, 3H).



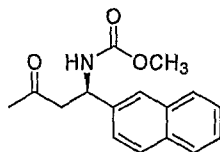
[00128] **(*R*)-(1-Oxo-1-thiophen-2-yl-butyl)-carbamic acid methyl ester.** Yield: 37 mg, 82%. ee: 92%. HPLC analysis, t_r minor: 31.9 min, t_r minor: 37.0 min, [(*R,R*)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.16 (t, $J = 3.2$ Hz, 1H), 6.90 (d, $J = 2.8$ Hz, 2H), 5.70 (br, 1H), 5.36 (dd, $J = 14, 6.0$ Hz, 1H), 3.65 (s, 3H), 3.15-3.09 (dd, $J = 17, 5.0$ Hz, 1H), 3.01-2.95 (dd, $J = 17, 6.0$ Hz, 1H), 2.14 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 206.6, 156.2, 126.9, 126.1, 124.5, 52.2, 48.8, 47.4, 30.5. IR (thin film, cm^{-1}): 3328, 2952, 1715, 1697, 1540, 1350, 1269, 1160, 1060. HRMS: calc'd for $(\text{M})^+ \text{C}_{10}\text{H}_{13}\text{NO}_3\text{S}$: 227.0620; found: 227.0616. $[\alpha]_D^{23} = +19.3^\circ$ ($c = 0.6$, CHCl_3).



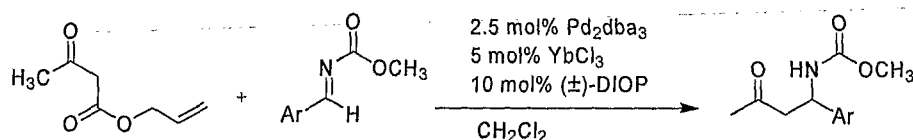
[00129] **2-((*R*)-Methoxycarbonylamino-naphthalen-2-yl-methyl)-3-oxo-butyl allyl ester.** Yield: 160 mg, 96%. ^1H NMR (400 MHz, CDCl_3 , major diastereomer

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reported): δ 7.83 (m, 3H), 7.77 (s, 1H), 7.49 (m, 2H), 4.41 (d, J = 8.4 Hz, 1H), 6.22 (d, J = 8.8 Hz, 1H), 5.82 (m, 1H), 5.67 (m, 1H), 5.23 (m, 2H), 4.60 (d, J = 4.8 Hz, 2H), 4.20 (d, J = 5.6 Hz, 1H), 3.67 (s, 3H), 2.16 (s, 3H).



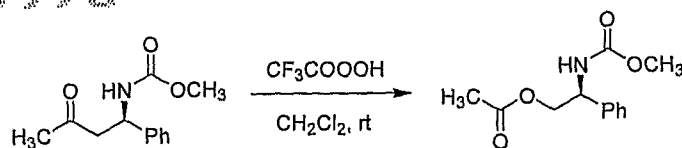
[00130] **(*R*)-(1-Naphthalen-2-yl-3-oxo-butyl)-carbamic acid methyl ester.** Yield: 46 mg, 83%. ee: 95%. HPLC analysis, t_r minor: 18.3 min, t_r minor: 21.1 min, Chiralcel[®]OD Column, Hexanes : IPA = 90 : 10, 1.5 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 7.79 (m, 3H), 7.72 (s, 1H), 7.44 (m, 2H), 7.39 (d, J = 8.8 Hz, 1H), 5.77 (br, 1H), 5.27 (dd, J = 14, 6.0 Hz, 1H), 3.64 (s, 3H), 3.14-3.11 (dd, J = 17, 5.0 Hz, 1H), 3.02-2.95 (dd, J = 17, 6.0 Hz, 1H), 2.07 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 207.1, 156.4, 138.6, 133.2, 132.7, 128.6, 128.0, 127.6, 126.4, 126.1, 125.0, 124.4, 52.5, 51.5, 48.8, 30.7. IR (thin film, cm⁻¹): 3336, 2953, 1712, 1706, 1533, 1362, 1249, 1057, 744. HRMS: calc'd for (M+H)⁺ C₁₆H₁₇NO₃: 272.1242; found: 272.1261. $[\alpha]_D^{23}$ = + 40.7° (c = 1.1, CHCl₃).



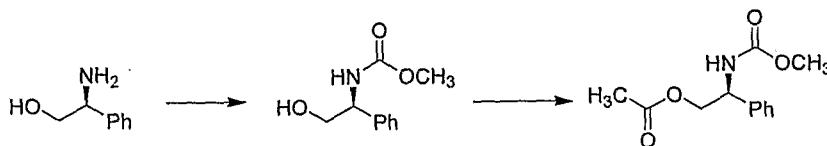
[00131] **Preparation of racemic β -amino ketones.** An oven dried 17×110 mm round bottom reaction vessel was charged with YbCl₃ (7.0 mg, 0.025 mmol). The metal salt was flamed dried under high vacuum and purged with nitrogen. The vessel was cooled to room temperature. Pd₂(dba)₃ (11.4 mg, 0.0125 mmol) and (±)DIOP² (25 mg, 0.050 mmol) were added. The solids were taken up in 1.0 mL CH₂Cl₂. The solution was stirred at room temperature for 30 min. Imine (**6**, 0.50 mmol) and allyl acetoacetate (1.25 mmol) were added successively. The solution was stirred at room temperature for 24 h. The reaction mixture was concentrated under reduced pressure and subjected directly to flash chromatography over silica gel (elution with 30%-50% ethyl acetate in hexanes) to give the β -amino ketones shown

[00132] The absolute configuration of (+)-3-Oxo-1-phenyl-butyl)-carbamic acid methyl ester was determined to be *R* isomer by comparing the optical rotation and chiral HPLC with the authentic sample.

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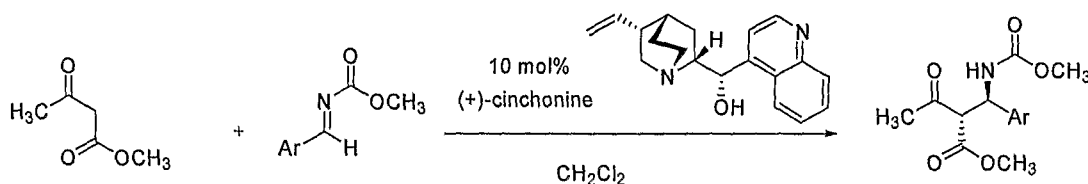
[00133] (R)-Acetic acid 2-methoxycarbonylamino-2-phenyl-ethyl ester. To a suspension of sodium percarbonate (636 mg, 4.0 mmol) in CH_2Cl_2 was added trifluoroacetic anhydride (924 mg, 4.4 mmol) over 3 min. The mixture was stirred at room temperature for 15 min. The solution became slightly cloudy and was transferred via syringe to the solution of (R)-(3-Oxo-1-phenyl-butyl)-carbamic acid methyl ester (86 mg, 0.37 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred overnight until the starting material was not detectable by TLC. The reaction was quenched by the addition of saturated $\text{Na}_2\text{S}_2\text{O}_3$ solution (5 mL). The organic layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was further purified by flash chromatography on silica gel (elution with 30% ethyl acetate in hexanes) to give the product 50 mg (58% yield). **Yield:** 50 mg, 58%. **ee:** 86%. **HPLC** analysis, t_r minor: 15.1 min, t_r major: 20.6 min, [(R,R)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 7.33-7.22 (m, 5H), 5.43 (br, 1H), 4.97 (br, 1H), 4.30 (dd, $J = 11, 6.0$ Hz, 1H), 4.24-4.20 (dd, $J = 11, 6.0$ Hz, 1H), 3.63 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 170.9, 156.2, 138.5, 128.7, 127.9, 126.4, 66.3, 54.3, 52.2, 20.7. **IR** (thin film, cm^{-1}): 3328, 3030, 2952, 1712, 1700, 1538, 1455, 1360, 1258, 1057, 700. **HRMS:** calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{12}\text{H}_{15}\text{NO}_4$: 238.1035; found: 238.1076. $[\alpha]_D^{23} = +37.5$ ($c = 1.1$, CHCl_3).



[00134] (R)-Acetic acid 2-methoxycarbonylamino-2-phenyl-ethyl ester. To a solution of (R)-2-amino-2-phenylethanol (137 mg, 1.0 mmol) in 2 mL CH_2Cl_2 was added a solution of methyl chloroformate (0.070 mL, 0.80 mmol) in 1 mL CH_2Cl_2 . The reaction was stirred at room temperature for 2 h and was quenched by the addition of saturated NaHCO_3 aqueous solution (5 mL). The organic layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (elution with 40% ethyl acetate in hexanes) to give the (2-Hydroxy-1-phenyl-ethyl)-carbamic acid methyl ester (135 mg, 70% yield). The product (60 mg, 0.30 mmol) was treated with acetic anhydride (0.036

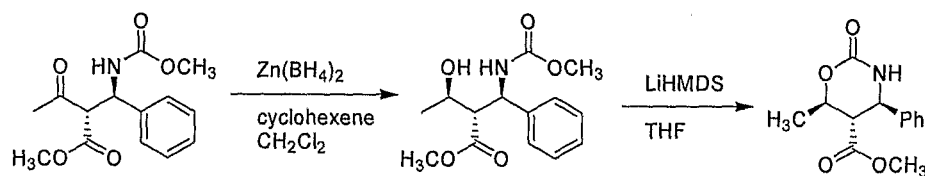
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mL, 0.36 mmol) and stirred in 2 mL pyridine until the alcohol was not detectable by TLC. The reaction solution was subjected directly to flash chromatography on silica gel (elution with 30% ethyl acetate in hexanes) to give the product (52 mg, 71% yield). **HPLC** analysis, t_r : 19.5 min, [(*R,R*)-Whelk-O 1 column, Hexanes:IPA, 85:15, 1.5 mL/min]. **^1H NMR** (400 MHz, CDCl_3): δ 7.33-7.22 (m, 5H), 5.43 (br, 1H), 4.97 (br, 1H), 4.30 (dd, $J = 11, 6.0$ Hz, 1H), 4.24-4.20 (dd, $J = 11, 6.0$ Hz, 1H), 3.63 (s, 3H), 2.01 (s, 3H). **^{13}C NMR** (75.0 MHz, CDCl_3): δ 170.9, 156.2, 138.5, 128.7, 127.9, 126.4, 66.3, 54.3, 52.2, 20.7. **IR** (thin film, cm^{-1}): 3328, 3030, 2952, 1712, 1700, 1538, 1455, 1360, 1258, 1057, 700. **HRMS**: calc'd for $(\text{M}+\text{H})^+ \text{C}_{12}\text{H}_{15}\text{NO}_4$: 238.1035; found: 238.1076. $[\alpha]_D^{23} = +40.6$ ($c = 1.0$, CHCl_3).



[00135] General asymmetric Mannich reaction procedure of methyl acetoacetate to acyl imines. In an oven dried 25 mL round bottom flask, (+)-cinchonine (15mg, 0.050 mmol) was dissolved in 1.0 mL CH_2Cl_2 . The solution was cooled down to -35°C . The imine (0.50 mmol) and methyl acetoacetate (0.060 mL, 0.50 mmol) were added successively. The reaction mixture was stirred at -35°C for 16 h. The solution was then passed through a plug of silica gel and eluted with 5 mL ethyl acetate. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (elution with 15-30% ethyl acetate in hexanes) to give the products shown.

[00136] The *anti* diastereoselectivity was determined by ^1H -NMR analogy of 6-methyl-2-oxo-4-phenyl-[1,3]oxazinane-5-carboxylic acid methyl ester with known compounds³.

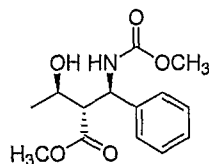


[00137] (4*R*, 5*S*, 6*R*)-6-Methyl-2-oxo-4-phenyl-[1,3]oxazinane-5-carboxylic acid methyl ester. The compound shown at left above (558mg, 2.0 mmol) was dissolved in 12 mL CH_2Cl_2 and cooled to -78°C . Cyclohexene (0.812 mL, 12 mmol) was added. Then a solution of $\text{Zn}(\text{BH}_4)_2$ in ether⁴ (16 mL, 0.15 M, 2.4 mmol) was added in dropwise. The solution was stirred at -78°C for 30 min. The reaction mixture was warmed up to -45°C and

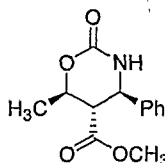
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stirred for 1h, warmed up to -15 °C and stirred for 1 h. The reaction was quenched by the addition of saturated ammonium chloride solution (8 mL). The mixture was transferred to 80 mL saturated NH₄Cl solution and extracted with CH₂Cl₂ (3×80 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (elution with 40% ethyl acetate in hexanes) to give the major diastereomer, (2*S*, 3*R*)-3-Hydroxy-2-((*R*)-methoxycarbonylamino-phenyl-methyl)-butyric acid methyl ester (510 mg), minor diastereomer (15 mg). (95%yield, dr = 34 : 1)

[00138] A 5 mL round bottom flask was charged with hexamethyldisilazane (0.316mL, 1.5 mmol) and cooled to 0 °C. *n*-BuLi (0.94 mL, 1.6 M) was added. The solution was diluted with an additional 0.9 mL THF. The 3-Hydroxy-2-(methoxycarbonylamino-phenyl-methyl)-butyric acid methyl ester (422 mg, 1.5 mmol) was dissolved in 2 mL THF and cooled to -20 °C. LiHMDS solution was added to the methyl ester THF solution dropwise. The reaction mixture was stirred at -20 °C for 5 minutes and was quenched with 4 M HCl (20 mL). The organic layer was extracted with CH₂Cl₂ (3×30 mL). The collected organic layers were combined and dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography over silica gel (elution with 10-20% ethyl acetate in hexanes) to give the 6-Methyl-2-oxo-4-phenyl-[1,3]oxazinane-5-carboxylic acid methyl ester (346 mg, 82% yield).



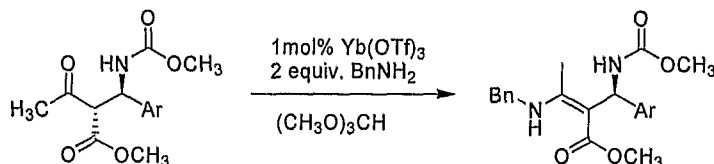
[00139] (2*S*, 3*R*)-3-Hydroxy-2-((*R*)-methoxycarbonylamino-phenyl-methyl)-butyric acid methyl ester. Yield: 510 mg, 91%. ¹H NMR (400 MHz, CDCl₃): δ 7.33-7.21(m, 5H), 5.78 (d, *J* = 8.4 Hz, 1H), 5.21 (t, *J* = 8 Hz, 1H), 4.11 (br, 1H), 3.62 (s, 3H), 3.51 (s, 3H), 2.91 (t, *J* = 7.2 Hz, 1H), 2.20 (br, 1H), 1.20 (d, *J* = 6 Hz, 3H). HRMS: calc'd for (M+H)⁺ C₁₄H₁₉NO₅: 282.1297 ; found: 282.1341.



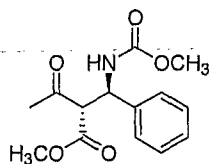
[00140] (4*R*, 5*S*, 6*R*)-6-Methyl-2-oxo-4-phenyl-[1,3]oxazinane-5-carboxylic acid methyl ester. Yield: 346 mg, 82%. ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.34 (m, 2H),

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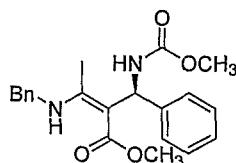
7.31-7.23 (m, 3H), 5.15 (s, 1H), 4.78 (d, $J = 10.4$ Hz, 1H), 4.60 (m, 1H), 3.55 (s, 3H), 2.68 (t, $J = 10.4$ Hz, 1H), 1.37 (d, $J = 6$ Hz, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 169.8, 153.2, 138.1, 128.9, 126.3, 74.2, 58.0, 53.7, 52.1, 19.0. HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{13}\text{H}_{15}\text{NO}_4$: 250.1035; found: 250.1099.



[00141] **General procedure for the preparation of (Z)-enamines.** An oven dried 17×110 mm round bottom reaction vessel was charged with $\text{Yb}(\text{OTf})_3$ (2.0 mg, 0.003 mmol). This metal salt was flamed dried under high vacuum and purged with nitrogen. The vessel was cooled to room temperature and the product shown at left above (0.30 mmol) was added. Trimethyl orthoformate (1 mL) and benzyl amine (0.070 mL, 0.60 mmol) were added successively. The solution was stirred for 4.0 h. The reaction mixture was subjected directly to the flash chromatography over silica gel (elution with 15-20% ethyl acetate in hexanes) to give the enamines shown. The (Z) configuration of the enamines were determined by ^1H -NMR analogy of reported compounds.⁵



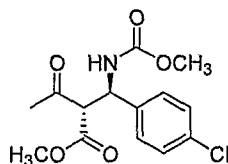
[00142] **(S) - 2-((R)-Methoxycarbonylamino-phenyl-methyl)-3-oxo-butyric acid methyl ester.** Yield: 139 mg, 99%. ^1H NMR (400 MHz, CDCl_3 , major diastereomer reported): δ 7.28 (m, 5H), 6.08 (br, 1H), 5.45 (m, 1H), 4.07 (d, $J = 4.0$ Hz, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 2.12 (s, 3H). HRMS: calc'd for $(\text{M})^+$ $\text{C}_{14}\text{H}_{17}\text{NO}_5$: 279.1107; found: 279.1084.



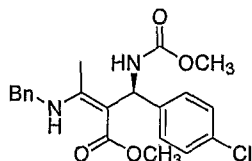
[00143] **(Z)-3-Benzylamino-2-((S)-methoxycarbonylamino-phenyl-methyl)-but-2-enoic acid methyl ester.** Yield: 105 mg, 95%. ee: 94%. HPLC analysis, t_r major: 12.8 min, t_r minor: 16.2 min, Chiralcel[®] OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ^1H NMR (400 MHz, CDCl_3): δ 9.90 (br, 1H), 7.36-7.15 (m, 10H), 5.95 (s, 2H), 4.48 (d, $J = 6.0$ Hz, 2H), 3.70 (s, 3H), 3.43 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 170.1, 161.6, 157.0, 143.3, 138.3, 128.8, 127.9, 127.4, 126.8, 126.1, 125.4, 94.3, 52.2, 52.0, 50.1, 47.4,

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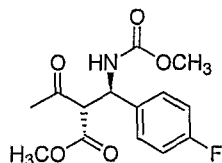
15.4. IR (thin film, cm^{-1}): 3447, 3395, 2950, 1719, 1649, 1594, 1453, 1247, 1191, 1090. HRMS: calc'd for $(M)^+$ $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$: 368.1736; found: 368.1725. $[\alpha]^{23}_{\text{D}} = -52.4^\circ$ ($c = 1.0$, CHCl_3).



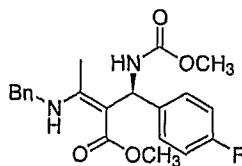
[00144] (S)-2-[(R)-(4-Chloro-phenyl)-methoxycarbonylamino-methyl]-3-oxo-butyric acid methyl ester. Yield: 126 mg, 81%. ^1H NMR (400 MHz, CDCl_3 , major diastereomer reported): δ 7.33-7.19 (m, 4H), 6.17 (d, $J = 9.6$ Hz, 1H), 5.38 (t, $J = 6.6$ Hz, 1H), 4.00 (d, $J = 5.6$ Hz, 1H), 3.66 (s, 3H), 3.61 (s, 3H), 2.13 (s, 3H). HRMS: calc'd for $(M)^+$ $\text{C}_{14}\text{H}_{16}\text{ClNO}_5$: 313.0717; found: 313.0715.



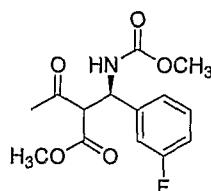
[00145] (Z)-3-Benzylamino-2-[(S)-(4-chloro-phenyl)-methoxycarbonylamino-methyl]-but-2-enoic acid methyl ester. Yield: 100 mg, 83%. ee: 81%. HPLC analysis, t_{r} major: 12.4 min, t_{r} minor: 16.4 min, Chiralcel[®] OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ^1H NMR (400 MHz, CDCl_3): δ 9.88 (br, 1H), 7.33 (m, 3H), 7.26 (m, 3H), 7.20 (m, 2H), 7.14 (m, 2H), 5.88 (s, 2H), 4.48 (d, $J = 7.0$ Hz, 2H), 3.69 (s, 3H), 3.42 (s, 3H), 2.18 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 169.9, 161.8, 156.9, 142.0, 138.1, 131.8, 128.9, 128.0, 127.5, 126.9, 126.8, 93.9, 52.2, 51.9, 50.2, 47.5, 15.5. IR (thin film, cm^{-1}): 3446, 3388, 2950, 1719, 1650, 1594, 1490, 1453, 1247, 1190, 1091, 1012. HRMS: calc'd for $(M)^+$ $\text{C}_{21}\text{H}_{23}\text{ClN}_2\text{O}_4$: 402.1346; found: 402.1344. $[\alpha]^{23}_{\text{D}} = -87.1^\circ$ ($c = 0.66$, CHCl_3).



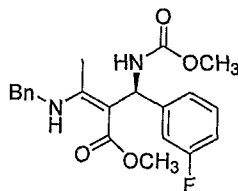
[00146] (S)-2-[(R)-(4-Fluoro-phenyl)-methoxycarbonylamino-methyl]-3-oxo-butyric acid methyl ester. Yield: 129 mg, 87%. ^1H NMR (400 MHz, CDCl_3 , major diastereomer reported): δ 7.24 (m, 2H), 6.95 (m, 2H), 6.12 (d, $J = 9.1$ Hz, 1H), 5.40 (t, $J = 6.6$ Hz, 1H), 3.65 (s, 3H), 3.61 (s, 3H), 2.13 (s, 3H). HRMS: calc'd for $(M)^+$ $\text{C}_{14}\text{H}_{16}\text{FNO}_5$: 297.1013; found: 297.0998.



[00147] **(Z)-3-Benzylamino-2-[(S)-(4-fluoro-phenyl)-methoxycarbonylamino-methyl]-but-2-enoic acid methyl ester.** Yield: 95 mg, 82%. ee: 91%. HPLC analysis, t_r major: 11.2 min, t_r minor: 14.5 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 9.89 (br, 1H), 7.32 (m, 2H), 7.26 (m, 3H), 7.18 (t, J = 6.0 Hz, 2H), 6.92 (t, J = 6.0 Hz, 2H), 5.91 (s, 2H), 4.47 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H), 3.44 (s, 3H), 2.18 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 169.9, 161.6, 156.9, 138.9, 138.1, 128.8, 127.4, 127.0, 126.9, 126.7, 114.7, 114.4, 94.0, 52.0, 51.7, 50.1, 47.3, 15.4. IR (thin film, cm⁻¹): 3448, 3390, 2950, 1719, 1650, 1593, 1495, 1454, 1248, 1220, 1190, 1089, 1027. HRMS: calc'd for (M+H)⁺ C₂₁H₂₃FN₂O₄: 386.1642; found: 386.1654. $[\alpha]_D^{23}$ = - 85.5 ° (c = 1.0, CHCl₃).



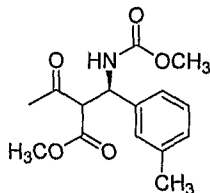
[00148] **2-[(R)-(3-Fluoro-phenyl)-methoxycarbonylamino-methyl]-3-oxo-but-2-enoic acid methyl ester.** Yield: 148 mg, 99%. ¹H NMR (400 MHz, CDCl₃, both diastereomers reported): δ 7.18 (m, 2H), 7.00 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 10 Hz, 2H), 6.85 (m, 2H), 6.41 (d, J = 9.2 Hz, 1H), 6.32 (d, J = 8.8 Hz, 1H), 5.48 (m, 1H), 5.37 (t, J = 7.6 Hz, 1H), 3.99 (m, 2H), 3.567 (s, 3H), 3.560 (s, 3H), 3.554 (s, 3H), 3.534 (s, 3H), 2.20 (s, 3H), 2.09 (s, 3H). HRMS: calc'd for (M)⁺ C₁₄H₁₆FN₂O₅: 297.1013; found: 297.1012.



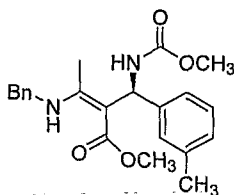
[00149] **(Z)-3-Benzylamino-2-[(S)-(3-fluoro-phenyl)-methoxycarbonylamino-methyl]-but-2-enoic acid methyl ester.** Yield: 95 mg, 82%. ee: 92%. HPLC analysis, t_r major: 12.3 min, t_r minor: 16.1 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 9.89 (br, 1H), 7.34 (m, 2H), 7.27 (m, 3H), 7.19 (t, J = 6.0 Hz, 1H), 7.00 (d, J = 8 Hz, 1H), 6.94 (d, J = 10 Hz, 1H), 6.84 (t, J = 8.8 Hz, 1H), 5.91 (s, 2H), 4.50 (d, J = 6.0 Hz, 2H), 3.70 (s, 3H), 3.43 (s, 3H), 2.19 (s, 3H). ¹³C NMR (75.0 MHz,

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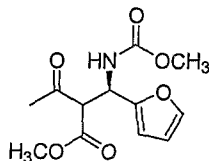
CDCl₃): δ 169.4, 161.3, 156.5, 146.1, 137.7, 128.9, 128.4, 127.0, 126.4, 120.6, 112.4, 93.6, 51.7, 49.7, 46.9, 14.9. IR (thin film, cm⁻¹): 3446, 3390, 2951, 1720, 1650, 1591, 1499, 1453, 1253, 1193, 1090. HRMS: calc'd for (M)⁺ C₂₁H₂₃FN₂O₄: 386.1642; found: 386.1649. $[\alpha]_D^{23} = -72.3^\circ$ (c = 1.0, CHCl₃).



[00150] 2-((R)-Methoxycarbonylamino-m-tolyl-methyl)-3-oxo-butyric acid methyl ester. Yield: 129 mg, 88%. ¹H NMR (400 MHz, CDCl₃, both diastereomers reported): δ 7.17 (m, 2H), 7.06 (m, 6H), 6.31 (br, 1H), 6.01 (br, 1H), 5.49 (m, 1H), 5.40 (t, *J* = 7.2 Hz, 1H), 4.02 (d, *J* = 6.4 Hz, 1H), 3.97 (br, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.63 (s, 3H), 3.63 (s, 3H), 2.317 (s, 3H), 2.310 (s, 3H), 2.296 (s, 3H), 2.12 (s, 3H). HRMS: calc'd for (M)⁺ C₁₅H₁₉NO₅: 293.1263; found: 293.1287.



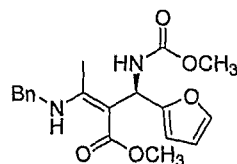
[00151] (Z)-3-Benzylamino-2-((S)-methoxycarbonylamino-m-tolyl-methyl)-but-2-enoic acid methyl ester. Yield: 110 mg, 96%. ee: 90%. HPLC analysis, *t_r* major: 14.5 min, *t_r* minor: 18.0 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 9.91 (br, 1H), 7.35 (m, 2H), 7.27 (m, 3H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.05 (s, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8 Hz, 1H), 5.93 (dd, *J* = 14.4, 10 Hz, 2H), 4.49 (d, *J* = 5.6 Hz, 2H), 3.71(s, 3H), 3.45(s, 3H), 2.31(s, 3H), 2.19(s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 170.1, 161.6, 156.9, 143.1, 138.8, 137.4, 128.8, 127.8, 127.4, 126.9, 126.8, 126.2, 122.5, 94.3, 52.1, 50.1, 47.3, 21.5, 15.4. IR (thin film, cm⁻¹): 3451, 3390, 2949, 1719, 1651, 1593, 1497, 1454, 1251, 1192, 1090, 1028. HRMS: calc'd for (M)⁺ C₂₂H₂₆N₂O₄: 382.1893; found: 382.1899. $[\alpha]_D^{23} = -15.5^\circ$ (c = 1.0, CHCl₃).



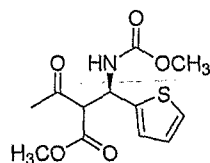
[00152] 2-((R)-Furan-2-yl-methoxycarbonylamino-methyl)-3-oxo-butyric acid methyl ester. Yield: 111 mg, 83%. ¹H NMR (400 MHz, CDCl₃, major diastereomers reported):

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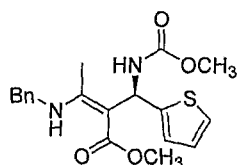
δ 7.30 (m, 1H), 6.28 (dd, $J = 3.2, 1.6$ Hz, 1H), 6.19 (d, $J = 6.4$ Hz, 1H), 6.09 (d, $J = 9.2$ Hz, 1H), 5.59 (dd, $J = 9.6, 4.0$ Hz, 1H), 4.11 (d, $J = 4.0$ Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.29 (s, 3H).



[00153] (Z)-3-Benzylamino-2-((S)-furan-2-yl-methoxycarbonylamino-methyl)-but-2-enoic acid methyl ester. Yield: 90 mg, 84%. ee: 90%. HPLC analysis, t_r major: 14.2 min, t_r minor: 18.8 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 9.89 (br, 1H), 7.32 (m, 2H), 7.25 (m, 4H), 6.23 (dd, $J = 3.6, 2.0$ Hz, 1H), 5.98 (d, $J = 3.2$ Hz, 1H), 5.92 (t, $J = 10$ Hz, 2H), 4.45 (d, $J = 6$ Hz, 2H), 3.67(s, 3H), 3.55(s, 3H), 2.18 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 169.7, 161.4, 156.2, 155.4, 140.6, 137.7, 128.4, 127.0, 126.4, 109.8, 104.2, 91.7, 51.6, 49.8, 47.7, 46.9, 14.8. IR (thin film, cm⁻¹): 3447, 3390, 2950, 1720, 1650, 1595, 1498, 1454, 1260, 1192, 1090, 1008. HRMS: calc'd for (M)⁺ C₁₉H₂₂N₂O₅: 358.1529; found: 358.1541. $[\alpha]_D^{23} = -28.6^\circ$ (c = 1.0, CHCl₃).



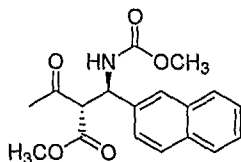
[00154] 2-((R)-Methoxycarbonylamino-thiophen-2-yl-methyl)-3-oxo-but-2-enoic acid methyl ester. Yield: 122 mg, 86%. ¹H NMR (400 MHz, CDCl₃, both diastereomers reported): δ 7.23 (t, $J = 4.8$ Hz, 1H), 7.14 (m, 2H), 6.94 (t, $J = 3.6$ Hz, 1H), 6.88 (m, 2H), 6.28 (d, $J = 8.0$ Hz, 1H), 6.13 (d, $J = 8.0$ Hz, 1H), 5.74 (m, 1H), 5.67 (t, $J = 8.0$ Hz, 1H), 4.11 (m, 2H), 3.67(s, 3H), 3.65(s, 3H), 3.63(s, 3H), 3.61(s, 3H), 2.27(s, 3H), 2.19 (s, 3H). HRMS: calc'd for (M)⁺ C₁₂H₁₅NO₅S: 285.0671; found: 285.0662.



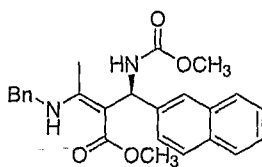
[00155] (Z)-3-Benzylamino-2-((S)-methoxycarbonylamino-thiophen-2-yl-methyl)-but-2-enoic acid methyl ester. Yield: 99 mg, 88%. ee: 93%. HPLC analysis, t_r major: 11.9 min, t_r minor: 15.1 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 9.89 (br, 1H), 7.31 (m, 2H), 7.22 (m, 3H), 7.06 (d, $J = 4.8$ Hz,

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1H), 6.85 (t, $J = 4.8$ Hz, 1H), 6.73 (d, $J = 3.2$ Hz, 1H), 6.05 (m, 2H), 4.45 (d, $J = 6.4$ Hz, 2H), 3.66 (s, 3H), 3.51 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 170.1, 161.6, 156.6, 149.3, 138.2, 128.8, 127.5, 126.7, 123.5, 122.7, 94.5, 52.1, 50.3, 49.8, 47.3, 15.2. IR (thin film, cm^{-1}): 3450, 3317, 2951, 1717, 1652, 1594, 1497, 1455, 1254, 1080. HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_3\text{S}$: 375.1334; found: 375.1419. $[\alpha]_D^{23} = -26.0^\circ$ ($c = 1.0$, CHCl_3).

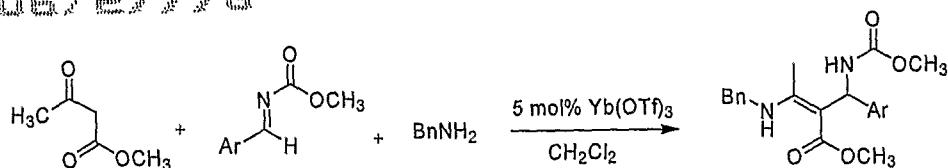


[00156] **(S)-2-((R)-Methoxycarbonylamino-naphthalen-2-yl-methyl)-3-oxo-butyl acid methyl ester.** Yield: 156 mg, 95%. ^1H NMR (400 MHz, CDCl_3 , major diastereomer reported): δ 7.78 (m, 4H), 7.37 (m, 3H), 6.20 (br, 1H), 5.62 (br, 1H), 4.14 (br, 1H), 3.69 (s, 3H), 3.65 (s, 1H), 2.12 (s, 1H). HRMS: calc'd for $(\text{M})^+$ $\text{C}_{18}\text{H}_{19}\text{NO}_5$: 329.1263; found: 329.1240.

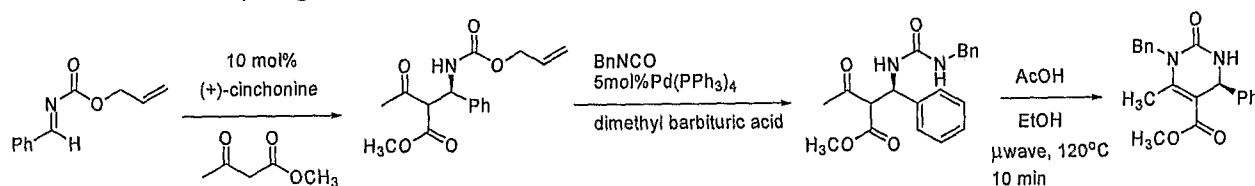


[00157] **(Z)-3-Benzylamino-2-((S)-methoxycarbonylamino-naphthalen-2-yl-methyl)-but-2-enoic acid methyl ester.** Yield: 120 mg, 96%. ee: 94%. HPLC analysis, t_r major: 22.0 min, t_r minor: 29.7 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ^1H NMR (400 MHz, CDCl_3): δ 9.97 (br, 1H), 7.77 (m, 4H), 7.66 (s, 1H), 7.45-7.35 (m, 5H), 7.30 (m, 2H), 6.07 (dd, $J = 20, 10$ Hz, 2H), 4.53 (d, $J = 6.0$ Hz, 2H), 3.75 (s, 3H), 3.41 (s, 3H), 2.25 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 170.2, 161.8, 157.0, 140.8, 138.3, 133.2, 132.2, 128.9, 127.8, 127.6, 127.5, 127.4, 126.8, 125.8, 125.3, 124.5, 123.7, 94.2, 52.4, 52.1, 50.2, 47.4, 15.5. IR (thin film, cm^{-1}): 3446, 3395, 2949, 1717, 1651, 1593, 1497, 1455, 1239, 1089. HRMS: calc'd for $(\text{M})^+$ $\text{C}_{25}\text{H}_{26}\text{N}_2\text{O}_4$: 418.1893; found: 418.1891. $[\alpha]_D^{23} = -77.9^\circ$ ($c = 0.68$, CHCl_3).

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[00158] Preparation of racemic (*Z*)- enamines. An oven dried 17×110 mm round bottom reaction vessel was charged with Yb(OTf)₃ (7 mg, 0.025 mmol). The metal salt was flamed dried under high vacuum, purged with nitrogen and dissolved in CH₂Cl₂ (1.0 mL). Imine (0.50 mmol) and methyl acetoacetate (0.50 mmol) were added in successively. The solution was stirred at room temperature for overnight. The benzyl amine (1.50 mmol) was added and the reaction was stirred at room temperature for an additional 15 hours. The reaction mixture was subjected directly to the flash chromatography over silica gel (elution with 15-20% ethyl acetate in hexanes) to give the products shown.



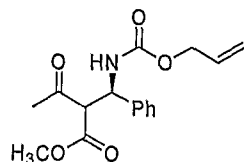
[00159] 2-((*R*)-Allyloxycarbonylamino-phenyl-methyl)-3-oxo-butyl acid methyl ester. In an oven dried 100 mL round bottom flask, (+)-cinchonine (294mg, 1.0 mmol) was dissolved in 40 mL CH₂Cl₂. The solution was cooled to -35 °C. Benzylidene-carbamic acid allyl ester (1.89g, 10 mmol) and the solution of methyl acetoacetate (1.08 mL, 10 mmol) in CH₂Cl₂ (10 mL) were added successively. The solution was stirred at -35 °C for 15 h. The reaction mixture was then passed through a plug of silica gel and eluted with ethyl acetate (150 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (elution with 15-30% ethyl acetate in hexanes) to give the allyl carbamate intermediate shown (2.95g, 97% yield).

[00160] An oven dried 100 mL round bottom flask was charged with Pd(PPh₃)₄ (115 mg, 0.10 mmol) and 1,3-dimethylbarbituric acid (780 mg, 5.0 mmol). A solution of 2-((allyloxycarbonylamino-phenyl-methyl)-3-oxo-butyl acid methyl ester (1.52 g, 5.0 mmol) in 20 mL CH₂Cl₂ and benzyl isocyanate (680 μL, 5.0 mmol) were added successfully. The solution was stirred at room temperature for 30 min. The reaction mixture was then passed through a plug of silica gel and eluted with ethyl acetate (100 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography

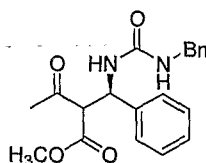
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over silica gel (elution with 30-70% ethyl acetate in hexanes) to give the urea intermediate (1.5g, 85% yield).

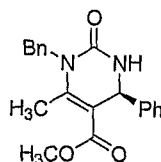
[00161] The 2-[(*R*)-(3-benzyl-ureido)-phenyl-methyl]-3-oxo-butyric acid methyl ester (1.06g, 3.0 mmol) was dissolved in 2.5 mL ethanol and 7.5 mL acetic acid. The solution was subjected to microwave irradiation (300W) at 120 °C for 10 min. The solvent was removed under reduced pressure and residue was purified by flash chromatography over silica gel (elution with 30% ethyl acetate in hexanes) to give the cyclic urea compound shown (0.90 g, 90% yield).



[00162] Yield: 2.95 g, 97%. ¹H NMR (400 MHz, CDCl₃, both diastereomers reported): δ 7.35-7.24 (m, 10H), 6.42 (d, *J* = 9.2 Hz, 1H), 6.15 (d, *J* = 8.4 Hz, 1H), 5.87 (m, 2H), 5.71 (dd, *J* = 9.2, 3.6 Hz, 1H), 5.48 (dd, *J* = 8.8, 6.0 Hz, 1H), 5.28 (m, 2H), 5.20 (m, 2H), 4.55 (s, 2H), 4.54 (s, 2H), 4.06 (d, *J* = 5.6 Hz, 1H), 4.02 (d, *J* = 3.6 Hz, 2H), 3.67 (s, 3H), 3.62 (s, 3H), 2.12 (s, 3H), 2.02 (s, 3H).



[00163] 2-[(*R*)-(3-Benzyl-ureido)-phenyl-methyl]-3-oxo-butyric acid methyl ester. Yield: 1.5 g, 85%. ¹H NMR (400 MHz, CDCl₃, both diastereomers reported): δ 7.28 (m, 20H), 6.17 (d, *J* = 10 Hz, 1H), 5.82 (d, *J* = 9.2 Hz, 1H), 5.78 (dd, *J* = 9.2, 4.4 Hz, 1H), 5.61 (dd, *J* = 9.2, 8.4 Hz, 1H), 4.84 (m, 2H), 4.35 (m, 4H), 4.06 (m, 2H), 3.66 (s, 3H), 3.58 (s, 3H), 2.37 (s, 3H), 2.13 (s, 3H). HRMS: calc'd for (M+H)⁺ C₂₀H₂₂N₂O₄: 355.1613 ; found: 355.1690.



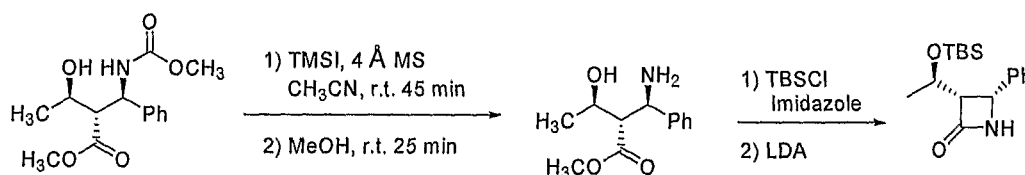
[00164] (*S*)-1-Benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester. Yield: 0.9 g, 90%. ee: 90%. HPLC analysis, *t*_r major: 27.8 min, *t*_r minor: 36.6 min, Chiralcel[®]OD Column, Hexanes : IPA = 95 : 5, 1.0 mL/min. ¹H NMR (400 MHz, CDCl₃): δ 7.29-7.22 (m, 8H), 7.10 (d, *J* = 7.2 Hz, 2H), 5.64 (s, 1H), 5.42

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(d, $J = 3.2$ Hz, 1H), 5.17 (d, $J = 14.8$ Hz, 1H), 4.87 (d, $J = 14.8$ Hz, 1H), 3.61 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 166.5, 153.8, 149.3, 142.9, 137.8, 128.7, 128.6, 127.9, 127.2, 126.4, 126.3, 99.9, 53.9, 51.4, 46.0, 16.5. IR (thin film, cm^{-1}): 3234, 2948, 1685, 1623, 1456, 1387, 1257, 1203, 1164, 1106, 696. HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$: 336.1; found: 336.1. $[\alpha]_{\text{D}}^{23} = -29.8^\circ$ ($c = 1.0$, CHCl_3).

[00165] The ($\pm$)-1-Benzyl-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-pyrimidine-5-carboxylic acid methyl ester was made according to a published procedure.⁶

[00166] The synthesis of the following lactam was performed to compare the enantiomer and diastereomer to a known compound.⁷



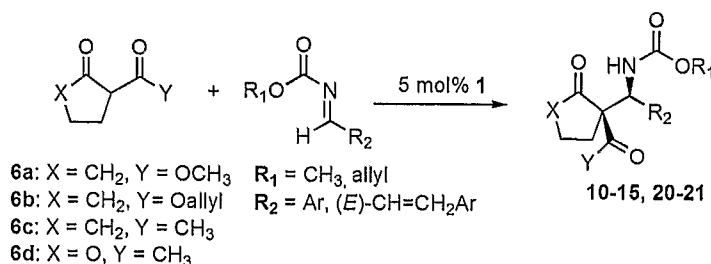
[00167] **(2*S*, 3*R*)-2-((*R*)-Amino-phenyl-methyl)-3-hydroxy-butyric acid methyl ester.**

An oven dried 50 mL round bottom flask was charged with 4 Å molecular sieve (200 mg) and flame dried under high vacuum, purged with nitrogen. (2*S*, 3*R*)-3-Hydroxy-2-((*R*)-methoxycarbonylamino-phenyl-methyl)-butyric acid methyl ester (200 mg, 0.71 mmol), dry acetonitrile (10 mL), and indotrimethylsilane (0.22 mL, 1.56 mmol, 2.2 equiv.) were added successively. The solution were stirred at room temperature for 45 min and concentrated under reduced pressure. The residue was dissolved in anhydrous methanol (10 mL). The solution was stirred at room temperature for 25 min. The solvent was removed under reduced pressure and the residue was treated with CHCl_3 (1 mL). The white precipitate was filtered and washed with hexane to give the desired product (184 mg, 90% yield). ^1H NMR (400 MHz, d_6 -DMSO): δ 7.39 (m, 5H), 7.25 (d, $J = 2.1$ Hz, 2H), 4.54 (d, $J = 9.6$ Hz, 1H), 4.00 (dd, $J = 6.3, 9.0$ Hz, 1H), 3.48 (s, 1H), 3.30 (s, 3H), 2.92 (t, $J = 9.0$ Hz, 1H), 1.12 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (75.0 MHz, d_6 -DMSO): δ 172.0, 129.6, 129.2, 128.4, 67.7, 56.3, 56.2, 52.3, 22.5. IR (thin film, cm^{-1}): 3429, 3043, 2952, 1733, 1608, 1457, 1255, 1112, 848, 763, 700. LRMS: calc'd for $(\text{M})^+$ $\text{C}_{12}\text{H}_{17}\text{NO}_3$: 223.1; found: 223.9. $[\alpha]_{\text{D}}^{23} = +36^\circ$ ($c = 1.5$, CHCl_3).

[00168] **(3*S*, 4*R*)-3-[(*R*)-1-(tert-Butyl-dimethyl-silanyloxy)-ethyl]-4-phenyl-azetidin-2-one (Lactam formation).** To a solution of β -amino alcohol **9** (100 mg, 0.44 mmol) in DMF 3 mL, imidazole (60 mg, 0.88 mmol) and tert-butyldimethylsilyl chloride (75 mg, 0.44 mmol) were added. The solution was stirred at room temperature for 20 h. The mixture was diluted with diethyl ether (10 mL) and successively washed with 5% aqueous HCl (5 mL)

and distilled water (5 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude (2*S*, 3*R*)-2-((*R*)-Amino-phenyl-methyl)-3-(tert-butyl-dimethyl-silanyloxy)-butyric acid methyl ester. This material was used in next step without further purification. The ^1H -NMR spectra data was in agreement with literature value.⁷ ^1H NMR (400 MHz, CDCl_3): δ 7.20 – 7.34 (m, 5H), 4.3 (m, 1H), 4.18 (d, J = 9.6 Hz, 1H), 3.30 (s, 3H), 2.85 (dd, J = 6.8, 9.6 Hz, 1H), 1.31 (d, J = 6.3 Hz, 3H), 0.91 (s, 3H), 0.14 (s, 3H), 0.11(s, 3H).

[00169] In a round bottom flask, diisopropylamine (67.1 mg, 0.66 mmol) was dissolved in 3 mL THF. *n*-BuLi (0.388 mL, 1.6 M, 0.62 mmol) was added at 0°C. The mixture was stirred for 10 minutes and cooled to - 78 °C. TBS ether (70 mg, 0.20 mmol) in 1 mL THF was added. The reaction mixture was stirred at - 78 °C for 10 h and was quenched by the addition of saturated aqueous sodium bicarbonate solution (0.5 mL). The mixture was filtered and the filtrate was concentrated under reduced pressure and residue was purified on silica gel to give the desired lactam (56 mg, 75% yield for two steps). The analytical data was in agreement with the literature value.⁷ ^1H NMR (400 MHz, CDCl_3): δ 7.19-7.36 (m, 5H), 4.25 (m, 1H), 3.85 (d, J = 10.5 Hz, 1H), 2.69 (dd, J = 9.4, 10.5 Hz, 1H), 1.17 (d, J = 6.3 Hz, 3H), 0.97 (s, 9H), 0.35 (s, 6H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 171.9, 151.6, 128.8, 128.2, 127.3, 71.0, 68.2, 59.0, 25.5, 22.1, 19.3, -1.4. LRMS: calc'd for $(\text{M})^+$ $\text{C}_{17}\text{H}_{27}\text{NO}_2\text{Si}$: 305.2; found: 305.1. $[\alpha]_D^{23} = + 85^\circ$ (c = 1.0, CHCl_3). The spectral data of the synthetic material was identical to the reported compound.⁷



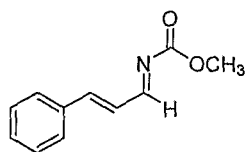
[00170] **General Procedure for Asymmetric Mannich Reaction of Cyclic 1,3-Dicarbonyls (6a-6d) to Acyl Imines.** In an oven dried 17×110 mm round bottom reaction vessel, (+)-cinchonine (8.00 mg, 0.025 mmol) was dissolved in 0.50 mL CH_2Cl_2 . The 1,3-dicarbonyl (6a-6d, 0.50 mmol) was added to catalyst solution and cooled down to appropriate reaction temperature. The acyl imine (1.00 equivalent, 0.50 mmol) in CH_2Cl_2 (0.50 mL) was added drop-wise to the reaction mixture. The solution was stirred at reaction temperature and monitored by TLC (30% ethyl acetate in hexanes). Once the reaction is

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complete, the reaction mixture was flashed through a plug of silica gel and eluted with ethyl acetate (5 mL). The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (elution with 15%-40% ethyl acetate in hexanes) to afford Mannich products **10-15**, and **20-21** as white waxy solids.

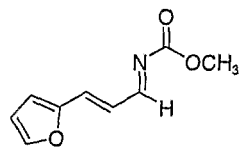
Procedure for 17a (3-phenyl-propenyl) acyl aldimines and 17b (3-furyl-propenyl) acyl aldimine.

[00171] Hexamethyldisilazane (5.54 mL, 26 mmol) was placed under argon in a septum-stoppered 250 mL round bottom. Internal temperature of round bottom was cooled down to 0 °C for drop-wise addition of nBuLi in hexanes (1.60 M, 15.60 mL, 25 mmol). Reaction was stirred at room temperature for 15 minutes and cooled back down to 0 °C for slow addition of freshly distilled 3-aryl-propenal (25 mmol) in THF (10 mL). Reaction was stirred for 30 minutes at room temperature then concentrated under reduced pressure for addition of CH₂Cl₂ (25 mL). Reaction mixture was cooled down to 0 °C for slow addition of methyl chloroformate (125 mmol). Reaction was stirred for 3 hours at room temperature then concentrated under reduced pressure. To the concentrate, diethyl ether (50 mL) and toluene (10mL) were added; resulting in precipitation of LiCl salt that was filtered off quickly with sintered glass funnel over dry Na₂SO₄. The filtrate was dried under reduced pressure. Product comes off as air-sensitive orange solid which is used without further purification.



17a: [(E)-3-Phenyl-prop-2-en-(E)-ylidene]-carbamic acid methyl ester.

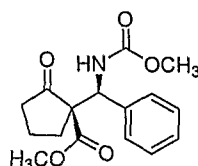
[00172] Yield: 90%. ¹H NMR (400 MHz, CDCl₃): δ 8.74 (d, *J* = 12.8 Hz, 1H), 7.54 (m, 2H), 7.41 (m, 3H), 7.22 (m, 1H), 7.21-6.94 (dd, *J* = 21.2 Hz, 1H), 3.87 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 172.9, 151.3, 134.4, 128.9, 128.5, 128.2, 126.4, 53.8. IR (neat, cm⁻¹): 3335, 3027, 2954, 1714, 1669, 1626, 1527, 1449, 1347, 1251, 1125, 1072, 970, 751, 693. HRMS: calc'd for (M+1)⁺ C₁₁H₁₂NO₂: 190.0823; found: 190.0853.



17b: [(E)-3-Furan-2-yl-prop-2-en-(E)-ylidene]-carbamic acid methyl ester.

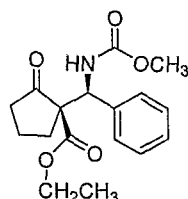
[00173] Yield: 90%. ¹H NMR (400 MHz, CDCl₃): δ 8.70 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 1.6 Hz, 1H), 7.13 (d, *J* = 15.2 Hz, 1H), 6.85 (dd, *J* = 16, 9.2 Hz, 1H), 6.70 (d, *J* = 3.6 Hz), 6.50 (dd, *J* = 3.4, 1.6 Hz, 1H), 3.86 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 172.5, 151.0,

145.7, 136.7, 124.0, 116.0, 112.7, 111.3, 53.6. **IR** (neat, cm^{-1}): 3326, 2956, 2252, 1715, 1624, 1520, 1447, 1358, 1211, 1175, 911, 735. **HRMS**: calc'd for $(\text{M})^+$ $\text{C}_9\text{H}_9\text{NO}_3$: 179.0582; found: 179.0540.



10a: (*R*)-1-((*S*)-Methoxycarbonylamino-phenyl-methyl)-2-oxo-cyclopentane carboxylic acid methyl ester

[00174] According to General Procedure, imine **7a** (benzylidene-carbamic acid methyl ester) was added to β -ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at -40°C for 6 hours to give Mannich product **10a**. **Yield**: 0.150 g (98%), **de**: 98%, **ee**: 90%; **HPLC Analysis**, t_r minor: 29.6 min., t_r major: 39.6 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 90:10, 1.0 mL/min]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.29–7.21 (m, 5H), 6.19 (d, $J = 7.7$ Hz, 1H), 5.15 (d, $J = 9.2$ Hz, 1H), 3.66 (s, 3H), 3.61 (s, 3H), 2.53–2.46 (m, 1H), 2.34 (s, 2H), 2.01–1.94 (m, 3H); $^{13}\text{C NMR}$ (75.0 MHz, CDCl_3): δ 210.9, 169.7, 156.3, 137.9, 128.3, 127.9, 127.8, 64.4, 56.2, 52.1, 37.4, 30.5, 18.8; **IR** (thin film, cm^{-1}): 3333, 2955, 1733, 1537, 1454, 1357, 1231, 1142, 961, 758, 706; **HRMS**: calc'd for $(\text{M})^+$ $\text{C}_{16}\text{H}_{19}\text{NO}_5$: 305.1263; found: 305.1299; $[\alpha]_D^{23} = -22.7^\circ$ ($c = 1.0$, CHCl_3).

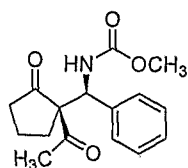


10b: (*R*)-1-((*S*)-Methoxycarbonylamino-phenyl-methyl)-2-oxo-cyclopentane carboxylic acid ethyl ester

[00175] According to General Procedure, imine **7a** (benzylidene-carbamic acid methyl ester) was added to β -ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at -40°C for 6 hours to give Mannich product **10b**. **Yield**: 0.159 g (96%), **de**: 96%, **ee**: 93%; **HPLC Analysis**, t_r minor: 21.5 min., t_r major: 33.1 min., [(*R,R*)-Whelk-O 1 column, Hexanes: IPA = 90:10, 1.0 mL/min]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.30–7.22 (m, 5H), 6.16 (d, $J = 8.4$ Hz, 1H), 5.16 (d, $J = 9.5$ Hz, 1H), 4.13–4.06 (m, 2H), 3.60 (s, 3H), 2.53–2.46 (m, 1H), 2.34–2.32 (m, 2H), 2.01–1.92 (m, 3H), 1.15 (t, $J = 6.9$ Hz, 3H); $^{13}\text{C NMR}$ (75.0 MHz, CDCl_3): δ 211.1, 169.3, 156.4, 38.1, 128.3, 128.1, 127.8, 64.5, 61.8, 56.3, 52.2, 37.5, 30.7, 18.8, 13.8; **IR** (thin film, cm^{-1}): 3334, 2980, 1725, 1533, 1454, 1230, 1118, 1029, 952,

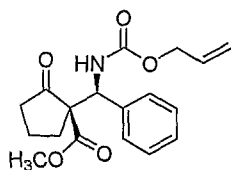
CT/US06/27778

756, 706 ; **HRMS**: calc'd for (M+H)⁺ C₁₇H₂₁NO₅: 319.1420; found: 320.1488; [α]²³_D = -10.3 ° (c = 1.0, CHCl₃).



10c: [(S)-(S)-(1-Acetyl-2-oxo-cyclopentyl)-phenyl-methyl]-carbamic acid methyl ester

[00176] According to General Procedure, imine **7a** (benzylidene-carbamic acid methyl ester) was added to β-diketone **6c** (2-Acetyl-cyclopentanone) and stirred at -55 °C for 2 hours to give Mannich product **10c**. **Yield**: 0.145 g (98%), **de** 98%, **ee**: 93%; **HPLC Analysis**, t_r minor: 22.42 min., t_r major: 28.9 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 90:10, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.20 (m, 5H), 6.69 (d, *J* = 9.5 Hz, 1H), 5.15 (d, *J* = 8.4 Hz, 1H), 3.60 (s, 3H), 2.59–2.61 (m, 1H), 2.33 (s, 3H), 2.16–2.13 (m, 2H), 1.77–1.70 (m, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 213.1, 202.4, 155.9, 137.9, 128.5, 128.1, 127.9, 127.5, 73.5, 57.3, 52.3, 39.0, 25.5, 19.2; **IR (thin film, cm⁻¹)**: 3385, 3354, 3021, 2970, 1711, 1530, 1240, 1195, 1149, 1054, 751, 703; **HRMS**: calc'd for (M+H)⁺ C₁₆H₁₉NO₄: 289.1314; found: 290.1400; [α]²³_D = +71.7 ° (c = 1.0, CHCl₃).

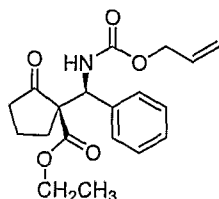


11a: (R)-1-((S)-Allyloxycarbonylamino-phenyl-methyl)-2-oxocyclopentane carboxylic acid methyl ester

[00177] According to General Procedure, imine **8a** (benzylidene-carbamic acid allyl ester) was added to β-ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at -55 °C for 2 hours to give Mannich product **11a**. **Yield**: 0.162 g (98%), **de**: 98%, **ee**: 90%; **HPLC Analysis**, t_r minor: 22.8 min., t_r major: 29.6 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 90:10, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.29–7.21 (m, 5H), 6.22 (d, *J* = 8.1 Hz, 1H), 6.87–6.85 (m, 1H), 5.28–5.24 (br, 1H), 5.16 (9.5 Hz, 2H), 3.66 (s, 3H), 2.53–2.47 (m, 1H), 2.35–2.31 (m, 2H), 2.04–1.92 (m, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 210.8, 169.8, 155.6, 137.9, 132.6, 128.4, 128.0, 127.9, 117.6, 65.7, 64.5, 56.2, 52.7, 37.5, 30.7, 18.8; **IR (thin film, cm⁻¹)**: 3304, 3064, 2954, 1724, 1537, 1454, 1229,

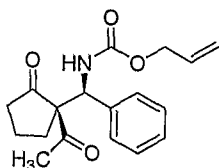
CT/US06/27778

1119, 1052, 934, 758, 707; **HRMS**: calc'd for (M)⁺ C₁₈H₂₁NO₅: 331.1420; found: 331.1417; $[\alpha]_D^{23} = -19.6^\circ$ (c = 1.0, CHCl₃).



11b: (R)-1-((S)-Allyloxycarbonylamino-phenyl-methyl)-2-oxocyclopentane carboxylic acid ethyl ester

[00178] According to General Procedure, imine **8a** (benzylidene-carbamic acid allyl ester) was added to β -ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at -55°C for 2 hours to give Mannich product **11b**. **Yield**: 0.161 g (98%), **de** 99%, **ee**: 90%; **HPLC Analysis**, t_r minor: 16.9 min., t_r major: 24.9 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 90:10, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.15 (m, 5H), 6.19-6.17 (d, J = 9.2 Hz, 1H), 5.90-5.85 (m, 1H), 5.33-5.23 (m, 1H), 5.17 (d, J = 8.4 Hz, 2H), 4.13-4.06 (m, 2H), 2.51-2.48 (m, 1H), 2.33-2.31 (m, 2H), 2.01-1.92 (m, 3H), 1.15 (t, J = 6.9 Hz, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 211.0, 155.5, 138.0, 132.5, 128.3, 128.2, 128.0, 127.7, 125.6, 117.9, 117.5, 65.6, 61.7, 56.2, 37.5, 30.5, 18.8, 13.7; **IR** (thin film, cm⁻¹): 3334, 2979, 2929, 1732, 1523, 1454, 1227, 1142, 1031, 927, 757, 705; **HRMS**: calc'd for (M)⁺ C₁₉H₂₃NO₅: 345.1576; found: 345.1546; $[\alpha]_D^{23} = -8.3^\circ$ (c = 1.0, CHCl₃).

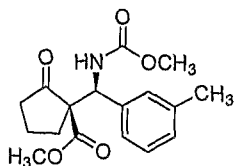


11c: [(S)-(S)-(1-Acetyl-2-oxo-cyclopentyl)-phenyl-methyl]-carbamic acid allyl ester

[00179] According to General Procedure, imine **8a** (benzylidene-carbamic acid allyl ester) was added to β -diketone **6c** (2-Acetyl-cyclopentanone) and stirred at -55°C for 2 hours to give Mannich product **11c**. **Yield**: 0.155 g (98%), **de**: 99%, **ee**: 91%; **HPLC analysis**, t_r minor: 16.6 min., t_r major: 18.9 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 90:10, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.31-7.19 m, 5H), 5.84-5.85 (m, 1H), 5.70 (d, J = 9.5 Hz, 1H), 5.27 (d, J = 8.4 Hz, 1H), 5.18 (d, J = 9.5 Hz, 2H), 4.48 (t, J = 5.6 Hz, 2H), 2.61-2.60 (m, 1H), 2.33 (s, 3H), 2.17-2.12 (m, 1H), 1.77-1.60 (m, 4H); ¹³C NMR (75.0 MHz, CDCl₃): δ 212.9, 202.3, 155.2, 137.9, 132.3, 128.5, 127.9, 127.5, 117.9, 73.5, 65.9, 57.3, 39.0, 25.5, 19.2; **IR** (thin film, cm⁻¹): 3308, 1962, 1706, 1533, 1358, 1295, 1250, 1138, 1054

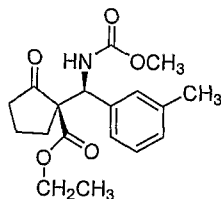
CT/US06/27778

996, 758, 707; **HRMS**: calc'd for (M+H)⁺ C₁₈H₂₁NO₄: 315.1471; found: 316.1591; [α]²³_D = + 85.4 ° (c = 1.0, CHCl₃).



12a: (R)-1-((S)-Methoxycarbonylamino-*m*-tolyl-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester

[00180] According to General Procedure, imine **7b** ((3-Methyl-benzylidene)-carbamic acid methyl ester) was added to β-ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at − 55 ° C for 4 hours to give Mannich product **12a**. **Yield**: 0.168 g (98%), **de**: 93%, **ee**: 96%; **HPLC Analysis**, *t_r* minor: 21.1 min., *t_r* major: 30.2 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.05 (m, 5H), 6.20 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 8.4 Hz, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 2.50-2.47 (m, 1H), 2.36-2.32 (m, 1H), 2.31 (s, 3H), 2.01-1.94 (m, 4H); ¹³C NMR (75.0 MHz, CDCl₃): δ 210.7, 169.4, 156.2, 137.9, 137.7, 128.5, 128.1, 124.7, 58.1, 55.9, 52.5, 52.0, 37.2, 30.5, 21.2, 18.6, 18.1; **IR (thin film, cm^{−1})**: 3335, 2956, 1726, 1512, 1453, 1234, 1141, 1118, 1051, 757, 711; **HRMS**: calc'd for (M+H)⁺ C₁₇H₂₁NO₅: 319.1420; found: 320.1490; [α]²³_D = − 20.9 ° (c = 1.0, CHCl₃).

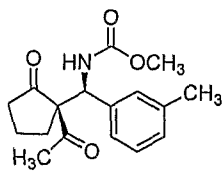


12b: (R)-1-((S)-Methoxycarbonylamino-*m*-tolyl-methyl)-2-oxocyclopentane carboxylic acid ethyl ester

[00181] According to General Procedure, imine **7b** ((3-Methyl-benzylidene)-carbamic acid methyl ester) was added to β-ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at − 55 ° C for 4 hours to give Mannich product **12b**. **Yield**: 0.118 g (98%), **de**: 98%, **ee**: 92%; **HPLC Analysis**, *t_r* minor: 15.4 min., *t_r* major: 25.5 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.18-7.04 (m, 4H), 6.17 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 9.2 Hz, 1H), 4.13-4.05 (m, 2H), 3.60 (s, 3H), 2.51-2.42 (m, 2H), 2.33 (s, 3H), 2.02-1.93 (m, 4H), 1.67 (t, *J* = 6.6 Hz, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 211.1, 169.3, 156.4, 138.0, 137.9, 128.8, 128.6, 128.2, 125.1, 64.4, 61.8, 56.2, 52.2, 37.5, 30.8, 21.4, 18.8, 13.8; **IR (thin film, cm^{−1})**: 3340, 2958, 1723, 1512, 1461,

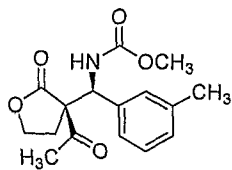
CT/US06/27778

1230, 1141, 1118, 731, 711; **HRMS**: calc'd for (M)⁺ C₁₈H₂₃NO₅: 333.1576; found: 333.1559; [α]_D²³ = − 9.0 ° (c = 1.0, CHCl₃).



12c: [(S)-(S)-(1-Acetyl-2-oxo-cyclopentyl)-*m*-tolyl-methyl]-carbamic acid methyl ester

[00182] According to General Procedure, imine **7b** ((3-Methyl-benzylidene)-carbamic acid methyl ester) was added to β-diketone **6c** (2-Acetyl-cyclopentanone) and stirred at − 55 ° C for 2 hours to give Mannich product **12c**. **Yield**: 0.149 g (98%), **de**: 94%, **ee**: 94%; **HPLC Analysis**, *t_r* minor: 14.5 min., *t_r* major: 16.6 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **¹H NMR** (400 MHz, CDCl₃): δ 7.18-7.14 (m, 1H), 7.04-6.98 (m, 3H), 5.66 (d, *J* = 9.2 Hz, 1H), 5.27 (d, *J* = 8.8 Hz, 1H), 3.59 (s, 3H), 2.62-2.61 (m, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 2.16-2.11 (m, 1H), 1.78-1.58 (m, 4H); **¹³C NMR** (75.0MHz,CDCl₃):δ 212.8, 202.2, 155.7, 137.9, 137.6, 128.5, 128.2, 127.9, 124.3, 76.4, 73.2, 57.1, 52.1, 38.8, 25.3, 21.2, 19.0 ; **IR (thin film, cm⁻¹)**: 3329, 2958, 1705, 1532, 1358, 1243, 1196, 1143, 1055, 917, 757, 732; **HRMS**: calc'd for (M+H)⁺ C₁₇H₂₁NO₄: 303.1471; found: 304.1537; [α]_D²³ = + 83.3 ° (c = 1.0, CHCl₃).

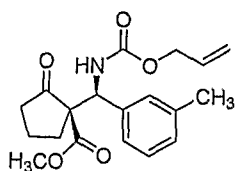


12d: [(S)-(S)-(3-Acetyl-2-oxo-tetrahydro-furan-3-yl)-*m*-tolyl-methyl]-carbamic acid methyl ester

[00183] According to General Procedure, imine **7b** ((3-Methyl-benzylidene)-carbamic acid methyl ester) was added to β-diketone **6d** (3-Acetyl-dihydro-furan-2-one) and stirred at − 78 ° C for 2 hours to give Mannich product **12d**. **Yield**: 0.135 g (88%), **de**: 38%, **ee**: 91%, (major diastereomer); **HPLC Analysis**, *t_r* minor: 24.4 min., *t_r* major: 25.7 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **¹H NMR** (400 MHz, CDCl₃): δ 7.22-7.20 (m, 1H), 7.11-7.08 (m, 3H), 5.75 (d, *J* = 9.9 Hz, 1H), 5.04 (d, *J* = 8.1 Hz, 1H), 3.99-3.94 (m, 1H), 3.66-3.63 (m, 1H), 3.63 (s, 3H), 2.89-2.83 (m, 1H), 2.45 (s, 3H), 2.32 (s, 3H), 2.10-2.09 (m, 1H); **¹³C NMR** (75.0 MHz, CDCl₃): δ 200.9, 173.1, 155.9, 138.6, 136.5, 129.3, 128.7, 127.9, 124.1, 66.8, 66.2, 56.7, 52.6, 25.5, 24.2, 21.5; **IR (thin film, cm⁻¹)**: 3327, 2956, 2922 1760, 1716, 1537, 1361, 1248, 1170, 1028,

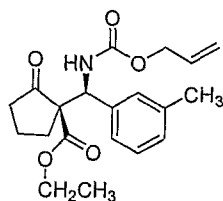
PCT/US2006/027778

914, 733; **HRMS**: calc'd for (M+H)⁺ C₁₆H₁₉NO₅: 305.1263; found: 306.1309; [α]²³_D = − 6.1° (c = 1.0, CHCl₃).



13a: (R)-1-((S)-Allyloxycarbonylamino-*m*-tolyl-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester

[00184] According to General Procedure, imine **8b** ((3-Methyl-benzylidene)-carbamic acid allyl ester) was added to β-ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at − 55 °C for 2 hours to give Mannich product **13a**. **Yield**: 0.165 g (96%), **de**: 97%, **ee**: 92%; **HPLC** analysis, *t_r* minor: 16.7 min., *t_r* major: 22.2 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.15 (m, 2H), 7.08-7.05 (m, 3H), 6.23 (d, *J* = 8.4 Hz, 1H), 5.85 (br, 1H), 5.28-5.24 (m, 1H), 5.13 (dd, *J* = 21.6, 9.2 Hz, 2H), 4.95 (s, 2H), 3.67 (s, 3H), 2.52-2.47 (m, 1H), 2.36-2.33 (br, 1H), 2.31 (s, 3H), 2.03-1.94 (m, 4H); ¹³CNMR (75.0 MHz, CDCl₃): δ 210.8, 169.7, 155.5, 137.9, 137.8, 132.6, 128.7, 128.6, 128.2, 124.9, 117.5, 65.6, 64.4, 56.1, 52.6, 37.4, 30.5, 21.4, 18.7; **IR** (thin film, cm^{−1}): 3336, 2954, 1731, 1507, 1436, 1233, 1140, 1119, 1048, 917, 732; **HRMS**: calc'd for (M)⁺ C₁₉H₂₃NO₅: 345.1657; found: 345.1587; [α]²³_D = − 25.1° (c = 1.0, CHCl₃).

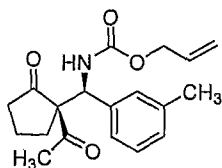


13b: (R)-1-((S)-Allyloxycarbonylamino-*m*-tolyl-methyl)-2-oxo-cyclopentanecarboxylic acid ethyl ester

[00185] According to General Procedure, imine **8b** ((3-Methyl-benzylidene)-carbamic acid allyl ester) was added to β-ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at − 55 °C for 2 hours to give Mannich product **13b**. **Yield**: 0.177 g (98%), **de**: 98%, **ee**: 99%; **HPLC** analysis, *t_r* minor: 19.2 min., *t_r* major: 25.5 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.04 (m, 5H), 6.20 (d, *J* = 8.8 Hz, 1H), 5.87 (br, 1H), 5.28-5.24 (m, 1H), 5.18-5.11 (m, 2H), 4.50-4.49 (m, 2H), 4.10 (m, 2H), 2.50-2.47 (m, 2H), 2.30 (s, 3H), 2.00-1.92 (m, 4H), 1.85 (t, *J* = 6.0 Hz, 3H); ¹³C NMR (75.0 MHz,

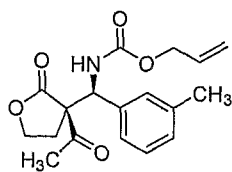
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CDCl₃): δ 210.9, 169.3, 155.5, 137.9, 137.9, 132.6, 128.8, 128.6, 128.2, 125.1, 117.50, 65.63, 64.4, 61.8, 56.2, 37.5, 30.6, 21.4, 18.8, 13.8; **IR** (thin film, cm⁻¹): 3339, 2978, 1722, 1529, 1641, 1229, 1139, 1118, 1048, 922, 711; **HRMS**: calc'd for (M)⁺ C₂₀H₂₅NO₅: 359.1733; found: 359.1719; $[\alpha]^{23}_D = -15.2^\circ$ (c = 1.0, CHCl₃).



13c: [(S)-(S)-(1-Acetyl-2-oxo-cyclopentyl)-*m*-tolyl-methyl]-carbamic acid allyl ester

[00186] According to General Procedure, imine **8b** ((3-Methyl-benzylidene)-carbamic acid allyl ester) was added to β -diketone **6c** (2-Acetyl-cyclopentanone) and stirred at -55°C for 2 hours to give Mannich product **13c**. **Yield**: 0.152 g (92%), **de**: 92%, **ee**: 98%; **HPLC Analysis**, t_r minor: 14.5 min., t_r major: 15.5 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.19-7.15 (m, 2H), 7.06-6.98 (m, 3H), 5.85 (br, 1H), 5.67 (d, $J = 9.9$ Hz, 1H), 5.27 (m, 1H), 5.18 (d, $J = 10.2$, 2H), 4.50-4.48 (m, 2H), 2.62-2.59 (m, 1H), 2.33 (s, 3H), 2.31 (s, 3H), 2.17-1.12 (m, 1H), 1.78-1.52 (m, 4H); ¹³C NMR (75.0 MHz, CDCl₃): δ 213.4, 202.7, 155.6, 138.5, 138.2, 132.7, 129.1, 128.7, 128.6, 124.9, 118.3, 73.9, 66.2, 57.7, 39.4, 29.9, 25.9, 21.8, 19.6; **IR** (thin film, cm⁻¹): 3331, 2598, 1700, 1607, 1533, 1360, 1238, 1142, 1050, 998, 917, 732; **HRMS**: calc'd for (M+H)⁺ C₁₉H₂₃NO₄: 329.1627; found: 330.1695; $[\alpha]^{23}_D = +70.5^\circ$ (c = 1.0, CHCl₃).

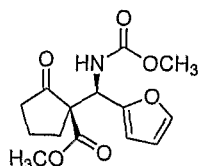


13d: [(S)-(S)-(3-Acetyl-2-oxo-tetrahydro-furan-3-yl)-*m*-tolyl-methyl]-carbamic acid allyl ester

[00187] According to General Procedure, imine **8b** ((3-Methyl-benzylidene)-carbamic acid allyl ester) was added to β -diketone **6d** (3-Acetyl-dihydro-furan-2-one) and stirred at -55°C for 2 hours to give Mannich product **13d**. **Yield**: 0.130 g (78%), **de**: 38%, **ee**: 99% (major diastereomer); **HPLC Analysis**, t_r minor: 19.3 min., t_r major: 20.5 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min].; ¹H NMR (400 MHz, CDCl₃): δ 7.22-7.20 (m, 1H), 7.12-7.09 (m, 3H), 5.85 (br, 1H), 5.76 (d, $J = 9.9$ Hz, 1H), 5.28-5.19 (m, 2H), 5.10 (d, $J = 8.0$ Hz, 1H), 4.52-4.49 (m, 2H), 3.97 (q, $J = 16.1, 8.3$ Hz, 1H), 3.72-3.66 (m, 2H), 2.90-2.84 (m, 1H), 2.45 (s, 3H), 2.32 (s, 3H), 2.14-2.03 (m, 1H).; ¹³C NMR (75.0

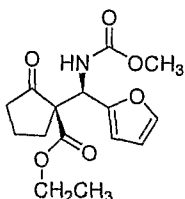
PCT/US2006/027778

MHz, CDCl_3): δ 200.9, 173.1, 155.2, 138.6, 136.5, 132.2, 129.3, 128.7, 128.0, 124.2, 118.2, 66.8, 66.1, 56.7, 25.5, 24.2, 21.5.; IR (thin film, cm^{-1}): 3327, 2923, 1760, 1716, 1533, 1376, 1242, 1168, 1027, 916, 732, 649; HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{18}\text{H}_{21}\text{NO}_5$: 331.1420; found: 331.1376; $[\alpha]_D^{23} = -14.2^\circ$ ($c = 1.0$, CHCl_3).



14a: (R)-1-((S)-Furan-2-yl-methoxycarbonylamino-methyl)-2-oxo-cyclopentanecarboxylic acid methyl ester

[00188] According to General Procedure, imine **7c** (Furan-2-ylmethylene-carbamic acid methyl ester) was added to β -ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at -78°C for 3 hours to give Mannich product **14a**. Yield: 0.145 g (98%), de: 99%, ee: 99%; HPLC Analysis, t_r minor: 22.6 min., t_r major: 23.1 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.29 (d, $J = 1.1$ Hz, 1H), 6.28 (dd, $J = 2.9, 1.8$ Hz, 1H), 6.21 (d, $J = 2.9$ Hz, 1H), 5.83 (d, $J = 9.2$ Hz, 1H), 5.35 (d, $J = 9.9$ Hz, 1H), 3.71 (s, 3H), 3.65 (s, 3H), 2.61-2.45 (m, 1H), 2.36-2.33 (m, 2H), 2.06-1.94 (m, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 210.6, 156.4, 151.2, 142.1, 110.5, 108.3, 63.9, 52.8, 52.4, 50.9, 37.6, 30.6, 29.6, 18.9; IR (thin film, cm^{-1}): 3330, 2956, 1726, 1526, 1451, 1321, 1240, 1142, 1042, 1011, 745; HRMS: calc'd for $(\text{M})^+$ $\text{C}_{14}\text{H}_{17}\text{NO}_6$: 295.1056; found: 295.1030; $[\alpha]_D^{23} = -41.8^\circ$ ($c = 1.0$, CHCl_3).

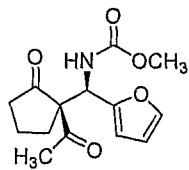


14b: (R)-1-((S)-Furan-2-yl-methoxycarbonylamino-methyl)-2-oxo-cyclopentanecarboxylic acid ethyl ester

[00189] According to General Procedure, imine **7c** (Furan-2-ylmethylene-carbamic acid methyl ester) was added to β -ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at -78°C for 3 hours to give Mannich product **14b**. Yield: 0.151g (98%) de: 99%, ee: 99%; HPLC Analysis, t_r minor: 15.8, min., t_r major: 16.6 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.29 (d, $J = 1.1$ Hz, 1H), 6.28 (dd, $J = 3.3, 1.8$ Hz, 1H), 6.22 (s, 2H), 5.80 (d, $J = 9.2$ Hz), 5.36 (d, $J = 9.5$ Hz, 1H), 4.21-4.11 (m, 2H), 3.64 (s, 3H), 2.61-2.54 (m, 1H), 2.36-2.32 (m, 2H), 2.05-1.93 (m,

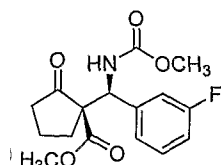
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3H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): 210.7, 156.3, 151.4, 141.9, 110.5, 108.3, 63.9, 61.9, 52.4, 50.9, 37.6, 30.7, 29.7, 18.9, 13.9; IR (thin film, cm^{-1}): 3333, 2960, 1723, 1526, 1456, 1319, 1235, 1071, 1141, 1015, 743; HRMS: calc'd for $(\text{M})^+$ $\text{C}_{15}\text{H}_{19}\text{NO}_6$: 309.1212; found: 309.1238; $[\alpha]_D^{25} = -26.5^\circ$ ($c = 1.0$, CHCl_3).



14c: [(S)-(S)-(1-Acetyl-2-oxo-cyclopentyl)-furan-2-yl-methyl]-carbamic acid methyl ester

[00190] According to General Procedure, imine **7c** (Furan-2-ylmethylene-carbamic acid methyl ester) was added to β -diketone **6c** (2-Acetyl-cyclopentanone) and stirred at -78°C for 3 hours to give Mannich product **14c**. Yield: 0.138 g (98%), **de**: 99%, **ee**: 99%; HPLC Analysis, t_r minor: 16.6 min., t_r major: 17.2 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.30 (d, $J = 1.1$ Hz, 1H), 6.28 (dd, $J = 2.9, 1.8$ Hz, 1H), 6.15 (d, $J = 2.9$ Hz, 1H), 5.77 (d, $J = 9.2$ Hz, 1H), 5.08 (d, $J = 8.8$ Hz, 1H), 3.64 (s, 3H), 2.67-2.64 (m, 1H), 2.31 (s, 3H), 2.26-2.17 (m, 1H), 2.09-2.02 (m, 1H), 1.75-1.59 (m, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 212.3, 156.1, 150.9, 142.3, 119.6, 110.6, 108.2, 72.9, 52.6, 52.4, 38.5, 26.5, 25.7, 19.1; IR (thin film, cm^{-1}): 3321, 2959, 2242, 1708, 1532, 1244, 1141, 1052, 1010, 925, 739; HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{14}\text{H}_{15}\text{NO}_6$: 279.1107; found: 280.1159; $[\alpha]_D^{25} = +146.0^\circ$ ($c = 1.0$, CHCl_3).



15a: (R)-1-[(S)-(3-Fluoro-phenyl)-methoxycarbonylamino-methyl]-2-oxo-cyclopentanecarboxylic acid methyl ester

[00191] According to General Procedure, imine **7d** (3-Fluoro-benzylidene)-carbamic acid methyl ester) was added to β -ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at -85°C for 2 hours to give Mannich product **15a**. Yield: 0.159 g (98%), **de**: 99%, **ee**: 90%; HPLC Analysis, t_r minor: 17.9 min., t_r major: 22.7 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.26-6.93 (m, 2H), 7.08-7.04 (m, 1H), 6.97-6.93 (m, 1H), 6.17 (s, 1H), 5.12 (d, $J = 8.1$ Hz, 1H), 3.67 (s, 3H), 3.61 (s, 3H), 2.49-2.48 (m, 1H), 2.35-2.34 (m, 2H), 1.95 (m, 3H); ^{13}C NMR (75.0 MHz,

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CDCl₃): δ 210.7, 164.3, 156.3, 140.7, 129.9, 123.9, 115.2, 115.1, 114.9, 114.8, 55.9, 52.8, 52.3, 37.5, 30.9, 18.9; **IR (thin film, cm⁻¹)**: 331, 2957, 1726, 1590, 1523, 1237, 1134, 1049, 918, 785, 705; **HRMS**: calc'd for (M)⁺ C₁₆H₁₈FNO₅: 323.1169; found 324.1270; ; $[\alpha]_D^{23} = -17.4^\circ$ (c = 2.0, CHCl₃). The X-ray structure of compound **15a** is depicted in **Figure 1**. X-ray analysis of compound **15a** provided the following data:

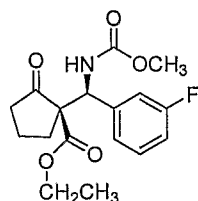
Crystal data and structure refinement for **15a**.

Identification code	15a	
Empirical formula	C ₁₅ H ₂₀ F N O ₅	
Formula weight	313.32	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.754(2) Å	$\alpha = 90^\circ$.
	b = 12.086(2) Å	$\beta = 90^\circ$.
	c = 13.614(3) Å	$\gamma = 90^\circ$.
Volume	1605.0(6) Å ³	
Z	4	
Density (calculated)	1.297 Mg/m ³	
Absorption coefficient	0.104 mm ⁻¹	
F(000)	664	
Crystal size	0.40 x 0.10 x 0.05 mm ³	
Theta range for data collection	2.25 to 30.53°.	
Index ranges	-13 ≤ h ≤ 13, -17 ≤ k ≤ 16, -19 ≤ l ≤ 19	
Reflections collected	27484	
Independent reflections	4884 [R(int) = 0.0367]	
Completeness to theta = 30.53°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9948 and 0.9595	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	4884 / 0 / 280	
Goodness-of-fit on F ²	1.016	
Final R indices [I > 2σ(I)]	R1 = 0.0357, wR2 = 0.0935	
R indices (all data)	R1 = 0.0435, wR2 = 0.0981	
Absolute structure parameter	0.0(6)	
Largest diff. peak and hole	0.244 and -0.188 e.Å ⁻³	

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Table A. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **15a**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	2974(1)	-1032(1)	987(1)	56(1)
O(1)	8305(1)	-193(1)	-2246(1)	42(1)
O(2)	6205(1)	2753(1)	-2907(1)	48(1)
O(3)	8117(1)	2325(1)	-2053(1)	38(1)
O(4)	7686(1)	2717(1)	399(1)	32(1)
O(5)	5577(1)	3532(1)	485(1)	38(1)
N(1)	5822(1)	2056(1)	-463(1)	25(1)
C(1)	6489(1)	1049(1)	-838(1)	24(1)
C(2)	6295(1)	1017(1)	-1979(1)	25(1)
C(3)	7135(1)	49(1)	-2460(1)	28(1)
C(4)	6236(1)	-533(1)	-3210(1)	35(1)
C(5)	5018(1)	253(1)	-3374(1)	37(1)
C(6)	4819(1)	804(1)	-2358(1)	32(1)
C(7)	6841(1)	2128(1)	-2381(1)	32(1)
C(8)	8676(2)	3406(1)	-2284(1)	49(1)
C(9)	5978(1)	5(1)	-319(1)	26(1)
C(10)	6838(1)	-923(1)	-230(1)	37(1)
C(11)	6380(2)	-1882(1)	241(1)	45(1)
C(12)	5069(2)	-1937(1)	644(1)	43(1)
C(13)	4251(1)	-1009(1)	567(1)	37(1)
C(14)	4664(1)	-41(1)	97(1)	30(1)
C(15)	6474(1)	2758(1)	164(1)	24(1)
C(16)	6125(2)	4330(2)	1169(2)	61(1)

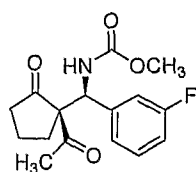


15b: (R)-1-[(S)-(3-Fluoro-phenyl)-methoxycarbonylamino-methyl]-2-oxo-cyclopentanecarboxylic acid ethyl ester

[00192] According to General Procedure, imine **7d** (3-Fluoro-benzylidene)-carbamic acid methyl ester) was added to β -ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester)

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and stirred at -90°C for 3 hours to give Mannich product **15b**. Yield: 0.165 g (98%), **de**: 99%, **ee**: 92%; HPLC analysis, t_r minor: 14.9 min., t_r major: 20.7 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.23–7.21 (m, 1H), 7.10–7.06 (m, 2H), 6.96–6.92 (m, 1H), 6.15 (d, $J = 6.6$ Hz, 1H), 5.14 (d, $J = 8.4$ Hz, 1H), 4.14–4.07 (m, 2H), 3.60 (s, 3H), 2.49–2.48 (m, 1H), 2.34–2.31 (m, 2H), 2.10–1.94 (m, 3H), 1.16 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 210.9, 164.3, 156.3, 140.8, 129.9, 124.0, 115.3, 115.0, 114.7, 61.9, 55.9, 52.3, 37.5, 30.9, 18.9, 13.7; IR (thin film, cm^{-1}): 3334, 2960, 1724, 1590, 1529, 1453, 1351, 1236, 1123, 11028, 782, 706; HRMS: calc'd for $(\text{M}+\text{H})^+$ $\text{C}_{17}\text{H}_{20}\text{FNO}_5$: 337.1326; found: 338.1377; $[\alpha]_D^{23} = -4.6^{\circ}$ ($c = 1.2$, CHCl_3).



15c: [(*S*)-(*S*)-(1-Acetyl-2-oxo-cyclopentyl)-(3-fluoro-phenyl)-methyl]-carbamic acid methyl ester

[00193] According to General Procedure, imine **7d** (3-Fluoro-benzylidene)-carbamic acid methyl ester) was added to β -diketone **6c** (2-Acetyl-cyclopentanone) and stirred at -78°C for 2 hours to give Mannich product **15c**. Yield: 0.150 g (98%) **de**: 99%, **ee**: 93%; HPLC Analysis, t_r minor: 13.5 min., t_r major: 15.8 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.26–7.24 (m, 1H), 6.99–6.92 (m, 3H), 5.67 (d, $J = 9.2$ Hz, 1H), 5.22 (br, 1H), 3.60 (s, 3H), 2.62–2.61 (m, 1H), 2.31 (s, 3H), 2.20–2.16 (m, 1H), 1.82–1.64 (m, 4H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 212.9, 164.3, 156.0, 140.8, 130.1, 123.3, 115.0, 114.8, 114.4, 73.4, 56.9, 52.4, 38.9, 25.6, 25.5, 19.2; IR (thin film, cm^{-1}): 3325, 2961, 1706, 1591, 1532, 1452, 1357, 1245, 11945, 1143, 732; HRMS: calc'd for $(\text{M})^+$ $\text{C}_{16}\text{H}_{18}\text{FNO}_4$: 307.1220; found: 307.1234; $[\alpha]_D^{23} = +1.17^{\circ}$ ($c = 1.0$, CHCl_3). The X-ray structure of compound **15c** is depicted in Figure 2. X-ray analysis of compound **15c** provided the following data:

Crystal data and structure refinement for **15c**.

Identification code	15c
Empirical formula	$\text{C}_{16}\text{H}_{18}\text{FNO}_4$
Formula weight	307.31
Temperature	173(2) K

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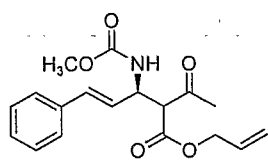
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 9.6137(19) Å	$\alpha = 90^\circ$.
	b = 11.512(2) Å	$\beta = 90^\circ$.
	c = 13.536(3) Å	$\gamma = 90^\circ$.
Volume	1498.1(5) Å ³	
Z	4	
Density (calculated)	1.363 Mg/m ³	
Absorption coefficient	0.106 mm ⁻¹	
F(000)	648	
Crystal size	0.40 x 0.10 x 0.03 mm ³	
Theta range for data collection	2.32 to 25.67°.	
Index ranges	-11 ≤ h ≤ 11, -13 ≤ k ≤ 14, -12 ≤ l ≤ 16	
Reflections collected	7386	
Independent reflections	2839 [R(int) = 0.0406]	
Completeness to theta = 25.67°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9974 and 0.9589	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2839 / 0 / 271	
Goodness-of-fit on F ²	0.953	
Final R indices [I > 2σ(I)]	R1 = 0.0380, wR2 = 0.0705	
R indices (all data)	R1 = 0.0668, wR2 = 0.0778	
Absolute structure parameter	2.2(9)	
Largest diff. peak and hole	0.135 and -0.220 e.Å ⁻³	

Table B. Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for **15c**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
F(1)	6690(1)	11008(1)	3838(1)	52(1)
O(1)	1603(2)	9986(2)	7392(1)	39(1)
O(2)	3838(2)	7114(2)	8022(1)	46(1)
O(3)	2260(1)	7191(1)	4556(1)	28(1)
O(4)	4345(1)	6287(1)	4481(1)	29(1)

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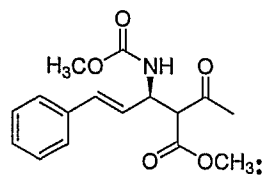
N(1)	4097(2)	7798(2)	5480(1)	24(1)
C(1)	3428(2)	8828(2)	5886(2)	25(1)
C(2)	3669(2)	8830(2)	7021(2)	26(1)
C(3)	2828(2)	9799(2)	7535(2)	29(1)
C(4)	3760(3)	10461(2)	8225(2)	35(1)
C(5)	5025(3)	9679(2)	8351(2)	35(1)
C(6)	5168(2)	9078(3)	7348(2)	31(1)
C(7)	3132(3)	7662(2)	7448(2)	32(1)
C(8)	1721(3)	7246(3)	7140(2)	40(1)
C(9)	3885(2)	9933(2)	5365(2)	24(1)
C(10)	3054(2)	10920(2)	5383(2)	35(1)
C(11)	3467(3)	11935(2)	4912(2)	42(1)
C(12)	4700(3)	11982(2)	4391(2)	37(1)
C(13)	5473(2)	10995(2)	4369(2)	34(1)
C(14)	5122(2)	9982(2)	4839(2)	27(1)
C(15)	3471(2)	7112(2)	4812(2)	23(1)
C(16)	3742(3)	5448(3)	3818(2)	40(1)



(E)-(R)-2-Acetyl-3-methoxycarbonylamino-5-phenyl-pent-4-enoic acid allyl ester.

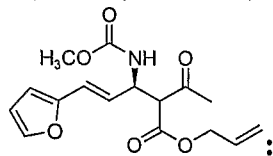
[00194] According to General Procedure, imine **17a** (3-Phenyl-allylidene)-carbamic acid methyl ester) was added to β -ketoester **16a** and stirred at -78°C for 2 hours to give the title Mannich product. **Yield:** 0.325 g (98%), **ee:** 95%; **HPLC** analysis, t_r major: 12.0 min, t_r minor: 13.6 min, [Chiralcel[®]OD Column, Hexanes : IPA = 90 : 10, 1.0 mL/min.]; **¹H NMR** (400 MHz, CDCl_3 , both isomers were reported): δ 7.33-7.19 (m, 10H), 6.60-6.55 (dd, $J = 8.8$, 3.2 Hz, 2H), 6.22-6.13 (m, 2H), 5.98 (d, $J = 9.2$ Hz, 1H), 5.88-5.80 (m, 2H), 5.75 (d, $J = 8$ Hz, 1H), 5.29 (d, $J = 17.2$ Hz, 2H), 5.21 (d, $J = 8.8$ Hz, 2H), 5.08 (m, 1H), 4.98 (m, 1H), 4.60 (m, 4H), 3.92 (d, $J = 4.4$ Hz, 1H), 3.87 (d, $J = 4.4$ Hz, 1H), 3.65 (s, 6H), 2.30 (s, 3H), 2.26 (s, 3H); **¹³C NMR** (75.0 MHz, CDCl_3 , both isomers were reported): δ 202.2, 201.2, 168.2, 167.2, 156.3, 156.1, 136.0, 135.9, 132.4, 132.2, 131.1, 131.0, 128.5, 128.4, 127.9, 127.8, 126.5, 126.5, 126.2, 126.0, 119.2, 119.1, 66.3, 66.1, 62.7, 62.4, 52.6, 52.2, 52.1, 30.2, 29.2; **IR** (neat, cm^{-1}): 3337, 2954, 1712, 1722, 1508, 1450, 1361, 1242, 1047, 750; **HRMS**: calc'd for $(\text{M})^+ \text{C}_{18}\text{H}_{21}\text{NO}_5$: 331.1420; found: 331.1420; $[\alpha]_D^{23} = -3.9^{\circ}$ ($c = 1.0$, CHCl_3).

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(E)-(R)-2-Acetyl-3-methoxycarbonylamino-5-phenyl-pent-4-enoic acid methyl ester.

[00195] According to General Procedure, imine **17a** (3-Phenyl-allylidene)-carbamic acid methyl ester) was added to β -ketoester **16b** and stirred at -78°C for 2 hours to give the title Mannich product. **Yield:** 0.295g (97%), **de:** 67%, **ee:** 92%; **HPLC Analysis**, t_{r} major: 10.7 min, t_{r} minor: 12.2 min, [Chiralcel[®]OD Column, Hexanes : IPA = 90 : 10, 1.0 mL/min]; **¹H NMR** (400 MHz, CDCl_3 , major isomer was reported): δ 7.31-7.12 (m, 5H), 6.52 (d, $J = 8.8$ Hz, 1H), 6.16-6.11 (dd, $J = 16, 7.2$ Hz, 1H), 5.69 (d, $J = 8.8$ Hz, 1H), 4.90 (dd, $J = 14.8, 6.8$ Hz, 1H), 3.85 (d, $J = 6.8$ Hz, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 2.20 (s, 3H); **¹³C NMR** (75.0 MHz, CDCl_3): δ 202.3, 168.0, 156.2, 136.0, 132.4, 128.5, 127.9, 126.5, 126.2, 126.0, 62.2, 52.6, 52.2, 30.2; **IR** (thin film, cm^{-1}): 3363, 3003, 2960, 1750, 1701, 1519, 1444, 1356, 1302, 1228, 1047, 735; **HRMS**: calc'd for $(\text{M})^+$ $\text{C}_{16}\text{H}_{19}\text{NO}_5$: 305.1263; found: 305.1293; $[\alpha]_{\text{D}}^{23} = -22.7^{\circ}$ ($c = 1.0$, CHCl_3).

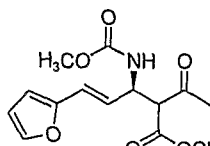


(E)-(R)-2-Acetyl-5-furan-2-yl-3-methoxycarbonylamino-pent-4-enoic acid allyl ester.

[00196] According to General Procedure, imine **17b** (3-Furan-allylidene)-carbamic acid methyl ester) was added to β -ketoester **16a** and stirred at -78°C for 2 hours to give the title Mannich product. **Yield:** 0.325g (98%), **ee:** 90%; **HPLC Analysis**, t_{r} minor: 11.6 min, t_{r} major: 12.4 min, [Chiralcel[®]OD Column, Hexanes : IPA = 90 : 10, 1.0 mL/min.]; **¹H NMR** (400 MHz, CDCl_3 , both isomers were reported): δ 7.27 (m, 2H), 6.35 (d, $J = 16$ Hz, 2H), 6.29 (m, 2H), 6.19 (t, $J = 4$ Hz, 2H), 6.04 (m, 2H), 5.92 (d, 9.2 Hz), 5.83 (m, 2H), 5.70 (d, $J = 9.2$ Hz), 5.25 (m, 2H), 5.17 (m, 2H), 5.02 (m, 1H), 4.91 (dd, $J = 14.8, 6.4$ Hz, 1H), 4.56 (m, 4H), 3.85 (d, $J = 5.2$ Hz, 1H), 3.81 (d, $J = 4$ Hz, 1H), 3.61 (s, 6H), 2.26 (s, 3H), 2.22 (s, 3H); **¹³C NMR** (75.0 MHz, CDCl_3 , both isomers were reported): δ 202.5, 201.4, 168.5, 167.4, 156.7, 156.4, 151.8, 151.8, 142.5, 142.4, 131.4, 131.3, 124.9, 124.8, 120.9, 120.7, 119.5, 119.4, 111.6, 111.5, 109.2, 109.1, 66.6, 66.4, 62.9, 62.4, 52.7, 52.5, 52.4, 52.0, 30.6, 29.5; **IR**

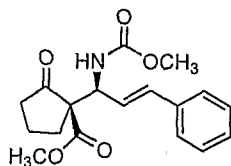
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(neat, cm^{-1}): 3343, 2954, 1720, 1510, 1454, 1361, 1242, 1156, 1048, 964, 742. 700; **HRMS**: calc'd for $(\text{M})^+$ $\text{C}_{16}\text{H}_{19}\text{NO}_6$: 321.1212; found: 321.1199; $[\alpha]^{23}_{\text{D}} = -7.5^\circ$ ($c = 1.0$, CHCl_3).



(E)-(R)-2-Acetyl-5-furan-2-yl-3-methoxycarbonylamino-pent-4-enoic acid methyl ester.

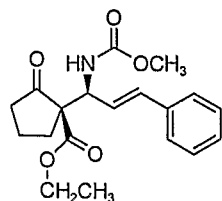
[00197] According to General Procedure, imine **17b** (3-Furan-allylidene)-carbamic acid methyl ester) was added to β -ketoester **16b** and stirred at -78°C for 2 hours to give the title Mannich product. **Yield**: 0.290g (98%), **ee**: 90%; **HPLC** analysis, t_{r} major: 25.6 min, t_{r} minor: 29.3 min, [Chiralcel[®]AD Column, Hexanes : IPA = 90 : 10, 1.0 mL/min.]; **^1H NMR** (400 MHz, CDCl_3 , both isomers were reported): δ 7.26 (m, 2H), 6.35 (dd, $J = 16, 2.4$ Hz, 2H), 6.28 (m, 2H), 6.18 (m, 2H), 6.04 (m, 2H), 5.94 (d, $J = 9.2$ Hz), 5.73 (d, $J = 8.8$ Hz), 4.99 (m, 1H), 4.90 (m, 1H), 3.83 (d, $J = 5.6$ Hz, 1H), 3.79 (d, $J = 4$ Hz, 1H), 3.68 (s, 6H), 3.60 (s, 6H), 2.25 (s, 3H), 2.21 (s, 3H); **^{13}C NMR** (75.0 MHz, CDCl_3 , both isomers were reported): δ 202.6, 201.5, 169.2, 168.2, 156.6, 156.5, 151.8, 151.7, 142.5, 142.4, 124.9, 124.8, 120.9, 120.7, 111.6, 111.5, 109.3, 109.2, 62.8, 62.2, 52.9, 52.7, 52.5, 52.4, 30.5, 29.4; **IR** (neat, cm^{-1}): 3346, 2957, 1722, 1511, 1440, 1362, 1245, 1157, 1047, 743; **HRMS**: calc'd for $(\text{M})^+$ $\text{C}_{14}\text{H}_{17}\text{NO}_6$: 295.1056; found: 295.1050; $[\alpha]^{23}_{\text{D}} = -5.7^\circ$ ($c = 1.0$, CHCl_3).



20a: (R)-1-((E)-(S)-1-Methoxycarbonylamino-3-phenyl-allyl)-2-oxo-cyclopentanecarboxylic acid methyl ester

[00198] According to General Procedure, imine **17a** (3-Phenyl-allylidene)-carbamic acid methyl ester) was added to β -ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at -78°C for 2 hours to give Mannich product **20a**. **Yield**: 0.160 g (98%), **de**: 90%, **ee**: 99%; **HPLC** analysis, t_{r} minor: 21.6 min., t_{r} major: 23.6 min., [(R,R)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **^1H NMR** (400 MHz, CDCl_3): δ 7.34-7.21 (m, 5H), 6.58 (d, $J = 15.8$ Hz, 1H), 6.17 (dd, $J = 15.8, 7.7$ Hz, 1H), 5.60 (d, $J = 8.8$ Hz, 1H), 4.68 (t, $J = 8.7$ Hz, 1H), 3.69 (s, 3H), 3.64 (s, 3H), 2.54-2.47 (m, 1H), 2.46-2.33 (m, 2H), 2.03 (br, 3H); **^{13}C NMR** (75.0 MHz, CDCl_3): δ 211.8, 170.5, 156.5, 136.1, 133.9, 128.5, 128.0, 126.6, 124.7, 64.2, 55.1, 52.7, 52.3, 37.5, 31.4, 18.9; **IR** (thin film, cm^{-1}): 3334, 2955, 1726, 1508, 1449, 1233, 1192, 1148, 970, 753,

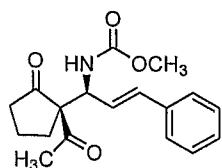
695; **HRMS**: calc'd for $(M)^+$ $C_{18}H_{21}NO_5$: 331.1420 ; found: 331.1448; $[\alpha]^{23}_D = -73.9^\circ$ (c = 1.0, $CHCl_3$).



20b: (R)-1-((E)-(S)-1-Methoxycarbonylamino-3-phenyl-allyl)-2-oxo-cyclopentanecarboxylic acid ethyl ester

[00199] According to General Procedure, imine **17a** (3-Phenyl-allylidene)-carbamic acid methyl ester) was added to β -ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at $-78^\circ C$ for 2 hours to give Mannich product **20b**. **Yield**: 0.170 g (98%), **de**: 94%, **ee**: 98%; **HPLC** analysis, t_r minor: 16.9 min., t_r major: 19.5 min, [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **1H NMR** (400 MHz, $CDCl_3$): δ 7.34-7.21 (m, 5H), 6.58 (d, $J = 15.8$ Hz, 1H), 6.20 (dd, $J = 15.8, 7.7$ Hz, 1H), 5.59 (d, $J = 8.1$ Hz, 1H), 4.68 (t, $J = 8.8$ Hz, 1H), 3.64 (s, 3H), 2.54-2.47 (m, 1H), 2.39-2.38 (m, 2H), 2.15-2.12 (m, 1H), 2.11-1.97 (m, 2H), 1.23 (t, $J = 7.6$ Hz, 3H); **^{13}C NMR** (75.0 MHz, $CDCl_3$): δ 211.9, 156.5, 136.1, 133.8, 128.5, 127.9, 126.6, 124.8, 64.1, 61.7, 55.1, 52.3, 37.5, 31.4,

[00200] - 29.6, 18.9, 13.9; **IR** (thin film, cm^{-1}): 3437, 2957, 1720, 1506, 1451, 1269, 1229, 1192, 909, 733, 647; **HRMS**: calc'd for $(M+H)^+$ $C_{19}H_{23}NO_5$: 345.1576; found: 345.1540; $[\alpha]^{23}_D = -56.9^\circ$ (c = 1.0, $CHCl_3$).



20c: [(E)-(S)-1-((S)-1-Acetyl-2-oxo-cyclopentyl)-3-phenyl-allyl]-carbamic acid methyl ester

[00201] According to General Procedure, imine **17a** (3-Phenyl-allylidene)-carbamic acid methyl ester) was added to β -diketone **6c** (2-Acetyl-cyclopentanone) and stirred at $-78^\circ C$ for 2 hours to give Mannich product **20c**. **Yield**: 0.150 g (98%), **de**: 95%, **ee**: 99%; **HPLC Analysis**, t_r minor: 19.5 min., t_r major: 20.9 min, [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **1H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.24 (m, 5H), 6.53 (d, $J = 15.8$ Hz, 1H), 6.01 (dd, $J = 16.0, 6.4$ Hz, 1H), 5.15-5.105 (m, 1H), 4.87 (d, $J = 9.9$ Hz, 1H), 3.65 (s, 3H), 2.59-2.56 (m, 1H), 2.32-2.23 (m, 3H), 1.95-1.89 (m, 1H), 1.86-1.84 (m, 1H); **^{13}C NMR** (75.0 MHz, $CDCl_3$): δ 213.4, 156.2, 135.8, 133.3, 128.6,

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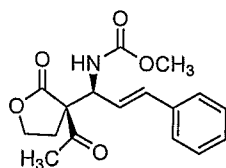
128.1, 126.6, 124.7, 72.68, 55.8, 52.4, 38.6, 29.6, 27.1, 26.0, 19.7; IR (thin film, cm^{-1}): 3328, 2956, 2927, 1702, 1527, 1358, 1449, 1238, 1196, 1144, 755; HRMS: calc'd for $(\text{M})^+$ $\text{C}_{18}\text{H}_{21}\text{NO}_4$: 315.1471; found: 315.1332; $[\alpha]_D^{23} = +63.6^\circ$ ($c = 1.0$, CHCl_3). The X-ray structure of compound **20c** is depicted in **Figure 3**. X-ray analysis of compound **20c** provided the following data:

Crystal data and structure refinement for **20c**.

Identification code	20c
Empirical formula	$\text{C}_{18}\text{H}_{21}\text{NO}_4$
Formula weight	315.36
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2(1)2(1)2(1)$
Unit cell dimensions	$a = 6.3666(4)$ Å $\alpha = 90^\circ$ $b = 15.3404(9)$ Å $\beta = 90^\circ$ $c = 17.1852(13)$ Å $\gamma = 90^\circ$
Volume	$1678.41(19)$ Å ³
Z	4
Density (calculated)	1.248 Mg/m^3
Absorption coefficient	0.088 mm^{-1}
F(000)	672
Crystal size	$0.40 \times 0.10 \times 0.05 \text{ mm}^3$
Theta range for data collection	1.78 to 28.28°
Index ranges	$-8 \leq h \leq 8$, $-20 \leq k \leq 20$, $-22 \leq l \leq 15$
Reflections collected	12635
Independent reflections	4169 [$R(\text{int}) = 0.0264$]
Completeness to $\theta = 28.28^\circ$	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9956 and 0.9656
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4169 / 0 / 292
Goodness-of-fit on F^2	1.018
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0331$, $wR2 = 0.0785$
R indices (all data)	$R1 = 0.0455$, $wR2 = 0.0835$
Absolute structure parameter	1.0(8)
Largest diff. peak and hole	0.177 and -0.157 e.Å^{-3}

Table C. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **20c**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

O(1)	8617(1)	2714(1)	1781(1)	30(1)
O(2)	3778(2)	2189(1)	162(1)	36(1)
O(3)	3372(2)	309(1)	2247(1)	37(1)
O(4)	-43(2)	692(1)	2101(1)	33(1)
N(1)	2353(2)	1726(1)	2097(1)	23(1)
C(1)	4414(2)	2128(1)	2169(1)	21(1)
C(2)	4915(2)	2659(1)	1422(1)	19(1)
C(3)	7121(2)	3072(1)	1491(1)	20(1)
C(4)	7048(2)	3995(1)	1202(1)	26(1)
C(5)	4926(2)	4074(1)	804(1)	29(1)
C(6)	3517(2)	3452(1)	1268(1)	24(1)
C(7)	4876(2)	2031(1)	715(1)	23(1)
C(8)	6182(2)	1225(1)	761(1)	29(1)
C(9)	4634(2)	2672(1)	2894(1)	24(1)
C(10)	3224(2)	2788(1)	3450(1)	24(1)
C(11)	3587(2)	3264(1)	4184(1)	25(1)
C(12)	2092(3)	3213(1)	4775(1)	32(1)
C(13)	2455(3)	3598(1)	5494(1)	41(1)
C(14)	4290(3)	4041(1)	5632(1)	42(1)
C(15)	5775(3)	4119(1)	5048(1)	40(1)
C(16)	5411(2)	3737(1)	4327(1)	34(1)
C(17)	2039(2)	866(1)	2157(1)	24(1)
C(18)	-613(3)	-212(1)	2039(1)	46(1)

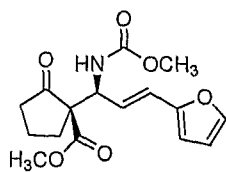


20d: [(*E*)-(*S*)-1-((*S*)-3-Acetyl-2-oxo-tetrahydro-furan-3-yl)-3-phenyl-allyl]-carbamic acid methyl ester

[00202] According to General Procedure, imine **17a** (3-Phenyl-allylidene)-carbamic acid methyl ester) was added to β -diketone **6d** (3-Acetyl-dihydro-furan-2-one) and stirred at -78

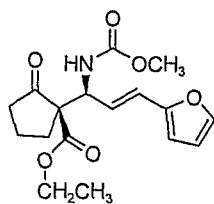
PCT/US06/27778

$^{\circ}\text{C}$ for 2 hours to give Mannich product **20d**. **Yield:** 0.132 g (88%), **de:** 38%, **ee:** 98% (major diastereomer); **HPLC** analysis, t_{r} minor: 30.2 min., t_{r} major: 34.7 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.35-7.24 (m, 5H), 6.58 (d, $J = 15.0$ Hz, 1H), 6.15 (dd, $J = 15.8, 5.9$ Hz, 1H), 5.29 (t, 1H), 4.71 (d, $J = 8.7$, 1H), 4.39-4.26 (m, 2H), 4.16-4.07 (m, 1H), 3.67 (s, 3H), 2.85-2.73 (m, 1H), 2.44 (s, 3H), 2.33-2.21 (m, 1H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 175.5, 156.2, 136.1, 135.3, 128.7, 128.6, 128.5, 126.7, 122.9, 65.8, 63.8, 55.8, 52.5, 29.8, 26.2; **IR** (thin film, cm^{-1}): 3399, 2955, 2925, 1765, 1716, 1225, 1194, 1028, 972; **HRMS**: calc'd for (M) $^{+}$ $\text{C}_{17}\text{H}_{19}\text{NO}_5$: 317.1263; found: 317.1230; $[\alpha]_{\text{D}}^{23} = -43.2^{\circ}$ ($c = 1.0$, CHCl_3).



21a: (*R*)-1-((*E*)-(*S*)-3-Furan-2-yl-1-methoxycarbonylamino-allyl)-2-oxocyclopentanecarboxylic acid methyl ester

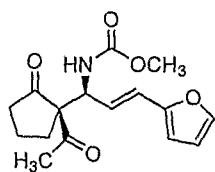
[00203] According to General Procedure, imine **17b** (3-Furan-allylidene)-carbamic acid methyl ester) was added to β -ketoester **6a** (2-oxo-cyclopentanecarboxylic acid methyl ester) and stirred at -78°C for 2 hours to give Mannich product **21a**. **Yield:** 0.158 g (98%) **de:** 99%, **ee:** 99%; **HPLC Analysis**, t_{r} minor: 25.8 min., t_{r} major: 27.2 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; ^1H NMR (400 MHz, CDCl_3): δ 7.31 (d, $J = 1.5$ Hz, 1H), 6.40 (d, $J = 15.7$ Hz, 1H), 6.34 (dd, $J = 3.3, 1.8$ Hz, 1H), 6.23 (d, $J = 3.3$ Hz, 1H), 6.07 (dd, $J = 15.6, 7.5$ Hz, 1H), 5.6 (br, 1H), 4.65 (t, $J = 8.6$ Hz, 1H), 3.69 (s, 3H), 3.63 (s, 3H), 2.56-2.49 (m, 1H), 2.40-2.34 (m, 3H), 2.13-2.08 (m, 1H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 211.6, 163.2, 156.6, 142.3, 123.2, 121.9, 111.3, 109.1, 64.0, 54.8, 52.7, 52.3, 37.5, 31.3, 29.7, 19.0; **IR** (thin film, cm^{-1}): 3339, 2956, 1725, 1514, 1455, 1236, 1151, 1014, 956, 736; **HRMS**: calc'd for ($\text{M}+\text{H}$) $^{+}$ $\text{C}_{16}\text{H}_{19}\text{NO}_6$: 321.1212; found: 322.1301; $[\alpha]_{\text{D}}^{23} = -39.1^{\circ}$ ($c = 0.8$, CHCl_3).



21b: (*R*)-1-((*E*)-(*S*)-3-Furan-2-yl-1-methoxycarbonylamino-allyl)-2-oxocyclopentanecarboxylic acid ethyl ester

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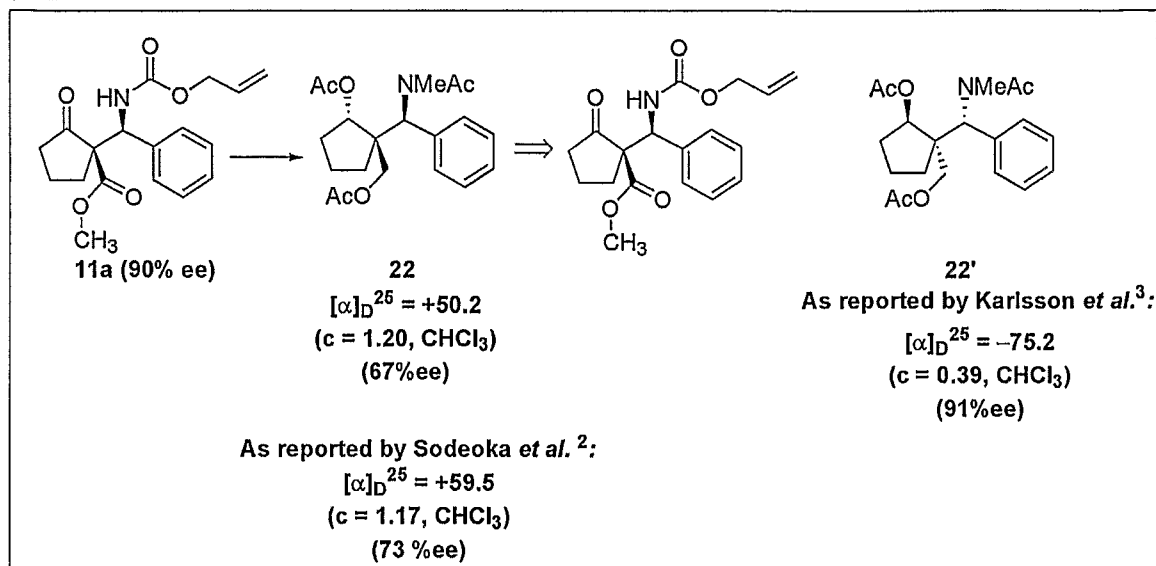
[00204] According to General Procedure, imine **17b** (3-Furan-allylidene)-carbamic acid methyl ester) was added to β -ketoester **6b** (2-oxo-cyclopentanecarboxylic acid ethyl ester) and stirred at -85°C for 3 hours to give Mannich product **21b**. **Yield:** 0.165 g (98%), **de:** 98%, **ee:** 93%; **HPLC Analysis**, t_r minor: 18.2, t_r major: 19.9 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **^1H NMR** (400 MHz, CDCl_3): δ 7.30 (d, $J = 1.5$ Hz, 1H), 6.39 (d, $J = 15.7$ Hz, 1H), 6.33 (dd, $J = 3.3, 1.8$ Hz, 1H), 6.22 (d, $J = 3.3$ Hz, 1H), 6.09 (dd, $J = 15.5, 7.5$ Hz, 1H), 5.58 (d, $J = 8.4$ Hz, 1H), 4.65 (t, $J = 7.8$ Hz, 1H), 4.19-4.11 (m, 2H), 3.63 (s, 3H), 2.55-2.48 (m, 1H), 2.39-2.36 (m, 2H), 2.12-2.07 (m, 1H), 2.02-1.97 (m, 2H), 1.21 (t, $J = 7.2$ Hz, 3H); **^{13}C NMR** (75.0 MHz, CDCl_3): δ 211.7, 151.7, 142.2, 123.3, 121.9, 111.3, 108.9, 61.8, 54.9, 53.5, 53.4, 52.3, 37.6, 31.4, 29.7, 19.0, 13.9; **IR (thin film, cm^{-1}):** 3356, 2959, 2361, 1723, 1514, 1232, 1150, 1018, 965; **HRMS:** calc'd for (M) $^+$ $\text{C}_{17}\text{H}_{21}\text{NO}_6$: 335.1369; found: 335.1357; $[\alpha]_D^{23} = -24.3^{\circ}$ ($c = 0.5$, CHCl_3)



21c: [(*E*)-(*S*)-1-((*S*)-1-Acetyl-2-oxo-cyclopentyl)-3-furan-2-yl-allyl]-carbamic acid methyl ester

[00205] According to General Procedure, imine **17b** (3-Furan-allylidene)-carbamic acid methyl ester) was added to β -diketone **6c** (2-Acetyl-cyclopentanone) and stirred at -78°C for 2 hours to give Mannich product **21c**. **Yield:** 0.150 g (98%), **de:** 94%, **ee:** 98%; **HPLC Analysis**, t_r minor: 23.3, t_r major: 24.4 min., [(*R,R*)-Whelk-O 1 column, Hexanes:IPA = 85:15, 1.0 mL/min]; **^1H NMR** (400 MHz, CDCl_3): δ 7.30 (s, 1H), 6.35-6.31 (m, 2H), 6.23 (d, $J = 3.3$ Hz, 1H), 5.90 (dd, $J = 15.7, 6.5$ Hz, 1H), 5.14-5.10 (m, 1H), 4.80 (d, $J = 9.9$ Hz, 1H), 3.64 (s, 3H), 2.60-2.57 (m, 1H), 2.30-2.71 (m, 2H), 2.25 (s, 3H), 1.96-1.85 (m, 3H); **^{13}C NMR** (75.0 MHz, CDCl_3): δ 211.6, 170.3, 156.6, 151.6, 142.3, 123.2, 121.9, 111.3, 109.1, 54.8, 52.7, 52.3, 37.5, 31.3, 29.6, 18.9; **IR (thin film, cm^{-1}):** 3327, 2965, 1707, 1527, 1357, 1241, 1147, 1012, 965, 921, 735; **HRMS:** calc'd for (M) $^+$ $\text{C}_{16}\text{H}_{19}\text{NO}_5$: 305.1263; found: 305.1283; $[\alpha]_D^{23} = +71.3^{\circ}$ ($c = 1.0$, CHCl_3).

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[00206] To Mannich product **11a** (130 mg, 0.37 mmol, 90% ee) in dry THF was slowly added LiAlH_4 (414.9 mg, 10.9 mmol, 30.0 equivalents) at room temperature. The reaction was refluxed for 24 h under N_2 . Reaction was diluted with CH_2Cl_2 (13.0 ml) at -78°C . To the mixture, H_2O (0.4 mL), aqueous 1N NaOH (0.4 mL), and H_2O (1.5 mL) was added sequentially. The mixture was warmed to room temperature and filtered through Celite. Solvent was removed under reduced pressure to afford yellow oil. To the yellow oil, pyridine (5.5 mL) and acetic anhydride (3.0 mL) were added and reaction was stirred for 12 h at room temperature. Toluene (5.0 mL) was added to reaction and mixture was subjected to reduced pressure vacuum pump to yield product **22** (73.0 mg, 56.1 % yield) confirmed by $^1\text{H-NMR}$. Comparison of the sign of optical rotation to compound **22** and **22'** (as reported by Sodeoka *et al.* ²) confirmed the absolute stereochemistry of major diastereomer of Mannich product **11a** as the (2*R*,1*S*) enantiomer.

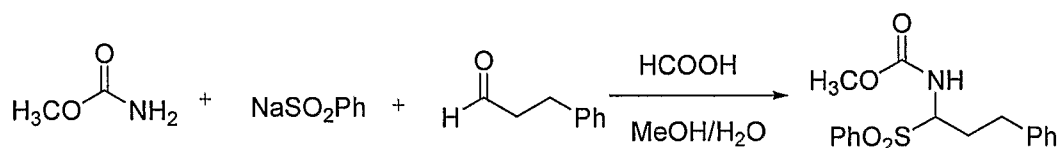
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- 1) a) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.C.; Aubry, A.; Collet, A. *Chem. Eur. J.* **1997**, *3*, 1691; b) Hart, D. J.; Kanai, K.; Thomas, D. G.; Yang, T. -K. *J. Org. Chem.* **1983**, *48*, 289.
- 2) Lou, S.; Westbrook, J. A.; Schaus, S. E. *J. Am. Chem. Soc.* **2004**, *126*, 11440.
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- 4) Zinc borohydride was made according to a published procedure: Gensler, W. J.; Johnson, F.; Sloan, A. David B. *J. Am. Chem. Soc.* **1960**, *82*, 6074.

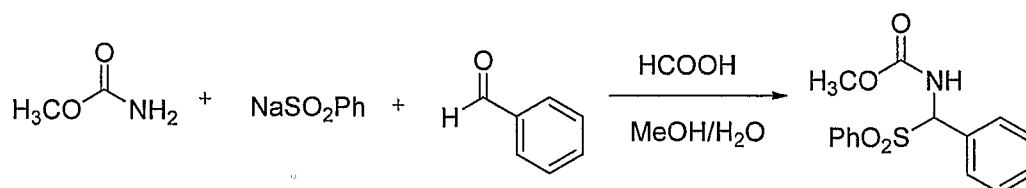
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- 5) a) Gerald, O. D.; Gert, P. V. *J. Am. Chem. Soc.* **1963**, *85*, 2697; b) George, D. H.; Richard D. H.; David, W. C. *J. Org. Chem.* **1983**, *48*, 4119.
- 6) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624.
- 7) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840.
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General procedure to synthesize α -amido sulfones

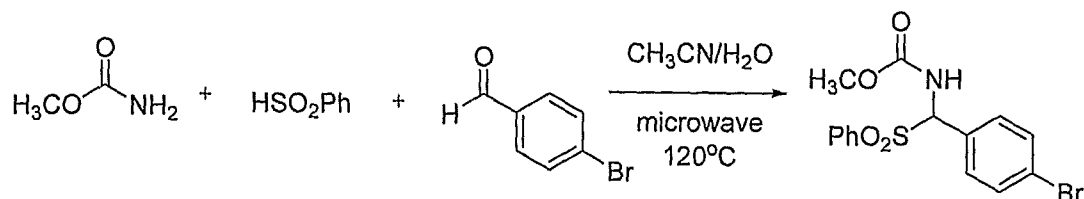


[00207] Method A for aliphatic α -amido sulfones: A 250mL one neck round bottom flask was charged with stir bar, sodium benzenesulfinate (3.0g, 15mmol), carbamate (1.12g, 15mmol), methanol (10mL) and water (20mL). Aldehyde (10 mmol) and formic acid (1.9mL, 50mmol) was added subsequently. The reaction mixture was stirred for two days. The solution was extracted with CH_2Cl_2 (3 $\times$ 50mL). The combined organic layers were dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (elution with 20%-40% ethyl acetate in hexanes) to afford corresponding α -amido sulfones as white solids.

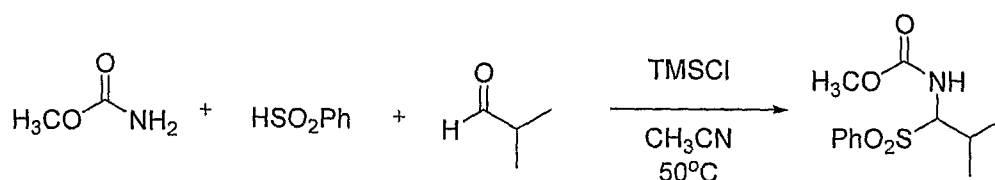


[00208] Method B for aromatic α -amido sulfones: A 250mL one neck round bottom flask was charged with stir bar, sodium benzenesulfinate (3.0g, 15.0mmol), carbamate (1.12g, 15.0mmol), methanol (10mL) and water (20mL). Aldehyde (10.0mmol) and formic acid (50.0mmol) was added subsequently. The reaction mixture was stirred overnight. The white precipitate was filtered, washed with petroleum ether and azeotropic with toluene. The product was used in the Mannich reaction without further purification.

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[00209] **Method C for aromatic α -amido sulfones:** The microwave tube was charged with stir bar, carbamate (150mg, 2.0mmol), benzenesulfinic acid (280mg, 2 mmol), aldehyde (1 mmol) and 4.0 mL acetonitrile and 1 drop water. The solution was subjected to microwave irradiation (300W) at 120 °C for 30 min and stirred at room temperature for 4 hours. The solution was concentrated under reduced pressure and diluted with water. The resulting white precipitate was filtered, washed with petroleum ether and azeotropic with toluene. The product was used in the Mannich reaction without further purification.

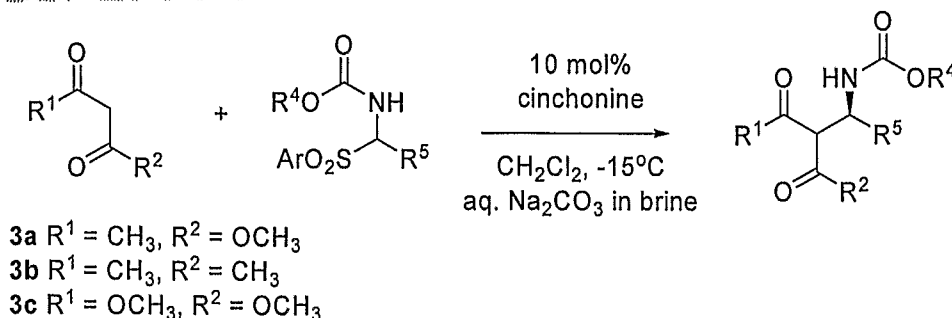


[00210] **Method D for α -foramido sulfones:** A 50 mL one neck round bottom flask was charged with stir bar, benzenesulfinic acid (853mg, 6.0mmol), foramide (338mg, 7.5mmol), acetonitrile (20 mL) and aldehyde (3.0mmol). TMSCl (0.38mL, 3 mmol) was added. The reaction solution was heated and stirred at 50°C for 5 hours. The solution was concentrated and the residue was purified by flash chromatography over silica gel (elution with 20%-40% ethyl acetate in hexanes) to afford corresponding α -amido sulfones as white solids.

Preparation of aqueous sodium carbonate solution for Mannich reactions.

[00211] Sodium carbonate (5.0g) was dissolved in water (100 mL). The resulting solution was saturated with sodium chloride solids appear.

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General Procedure for Asymmetric Mannich Reaction of Dicarbonyls to α -Amido sulfones.

[00212] A 25 mL one neck round bottom flask was charged with stir bar, (+)-cinchonine (16.0 mg, 0.05 mmol), α -amido sulfones (0.50 mmol) and CH_2Cl_2 (5mL). The solution was cooled to -15°C and dicarbonyl compound (1.50 mmol) was added. Aqueous sodium carbonate in brine (5.0mL) was added in slowly. The reaction mixture was stirred for 48 hours at -15°C . 10 mL CH_2Cl_2 and 10 mL water were added to dilute the solution. The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (elution with 15%-40% ethyl acetate in hexanes) to afford Mannich products as white solids.

General Procedure for preparation of racemic Mannich products.

[00213] A 25mL one neck round bottom flask was charged with stir bar, DABCO (11.0 mg, 0.10mmol), α -amido sulfones (0.5 mmol) and CH_2Cl_2 (5mL). Dicarbonyl compound (1.50 mmol) 5% sodium carbonate in water (5.0mL) were added subsequently. The reaction mixture was stirred for 48 hours at -15°C . CH_2Cl_2 (10mL) and water (10mL) were added to dilute the solution. The organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers was dried over sodium sulfate and filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography over silica gel (elution with 15%-40% ethyl acetate in hexanes) to afford Mannich products as white solids.

General procedure for the preparation of (Z)-enamines (17a – 17p, 18a – 18l).³

[00214] An oven dried 17×110 mm round bottom reaction vessel was charged with $\text{Yb}(\text{OTf})_3$ (2.0 mg, 0.003 mmol). This metal salt was flamed dried under high vacuum and

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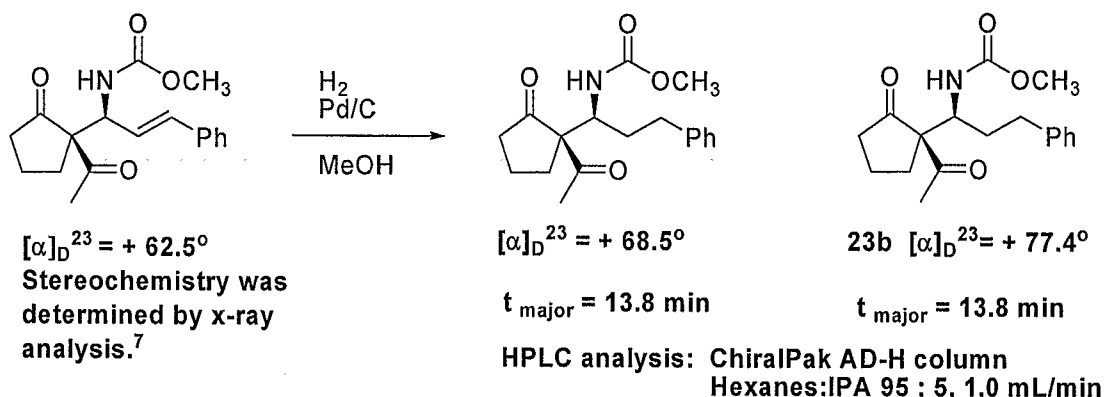
purged with nitrogen. The vessel was cooled to room temperature and the Mannich product (0.30 mmol) was added. Trimethyl orthoformate (1 mL) and benzyl amine (0.070 mL, 0.60 mmol) were added successively. The solution was stirred for 4.0 h. The reaction mixture was subjected directly to the flash chromatography over silica gel (elution with 15-20% ethyl acetate in hexanes) to give the enamines (**17a–17p**, **18a–18l**). The (*Z*) configuration of enamines (**8**, **9**) were determined by ^1H -NMR analogy of reported compounds.⁴

[00215] The absolute stereochemistry of **17** and **18** was determined by comparison of HPLC retention time and optical rotation with reported compounds.³

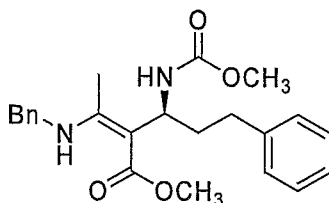
[00216] The absolute stereochemistry of **26**, **17b** and **17d** was determined by comparison of HPLC retention time, NMR data with reported compounds.⁵

[00217] The absolute stereochemistry of **21**, **22** and **25c** was determined by comparison of HPLC retention time, optical rotation NMR data with reported compounds.⁶

[00218] Determination of relative diastereoselectivity and absolute stereochemistry of **23**⁷

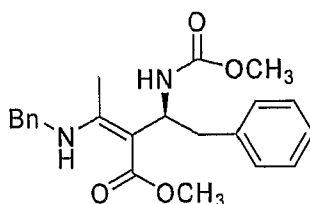


[00219] H-cube system was charged with Pd/C CatCart column and was heated to 50°C. Hydrogen pressure was set at 50 bars. [(*E*)-(*S*)-1-((*S*)-1-Acetyl-2-oxo-cyclopentyl)-3-phenyl-allyl]-carbamic acid methyl ester (50mg, 0.158mmol) was dissolved in methanol (5.0 mL). The solution was pumped through H-Cube system in a flow rate at 1 mL/min. The collected solution was concentrated under reduced pressure to give pure product 50mg (99%yield). ^1H NMR was identical with **23b**.

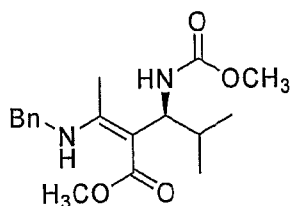


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[00220] **17a: methyl (*S,Z*)-4-(methoxycarbonyl)-5-(benzylamino)-1-phenylhex-4-en-3-ylcarbamate.** Yield: 81 mg, 71%; ee: 90%; **HPLC Analysis**, t_r major: 14.5 min., t_r minor: 18.0 min., [Chiralcel®OD-H column, Hexanes:IPA = 98:2, 1.0 mL/min]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.81 (t, J = 6.0 Hz, 1H), 7.34 (m, 2H), 7.24 (m, 5H), 7.15 (m, 3H), 5.58 (d, J = 9.6 Hz, 1H), 4.46 (dd, J = 15.2, 9.6 Hz, 1H), 4.39 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H), 3.63 (s, 3H), 2.56 (t, J = 7.6 Hz, 2H), 2.14 (m, 1H), 1.95 (m, 1H), 1.93 (s, 3H). $^{13}\text{C NMR}$ (75.0 MHz, CDCl_3): δ 166.7, 157.8, 152.9, 142.1, 134.7, 125.1, 124.8, 124.7, 124.6, 123.7, 123.2, 122.0, 90.1, 48.1, 46.5, 45.7, 43.6, 33.4, 31.0, 18.9; **IR (thin film, cm^{-1}):** 3333, 3050, 2953, 1720, 1657, 1580, 1498, 1230, 1081; $[\alpha]_D^{23} = -33.7^\circ$ (c = 1.0, CHCl_3).



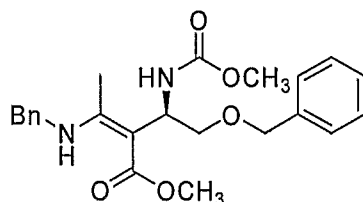
[00221] **17b: methyl (*S,Z*)-3-(methoxycarbonyl)-4-(benzylamino)-1-phenylpent-3-en-2-ylcarbamate.** Yield: 99 mg, 84%; ee: 90%; **HPLC Analysis**, t_r major: 25.5 min., t_r minor: 31.5 min., [Chiralcel®OD column, Hexanes:IPA = 98:2, 1.0 mL/min]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.77 (br, 1H), 7.25-6.92 (m, 10H), 5.73 (d, J = 10.4 Hz, 1H), 4.77 (m, 1H), 4.25 (d, J = 4 Hz, 2H), 3.74 (s, 3H), 3.58 (s, 3H), 2.96 (m, 2H), 2.13 (s, 3H). $^{13}\text{C NMR}$ (75.0 MHz, CDCl_3): δ 171.3, 162.0, 158.0, 143.5, 128.7, 129.8, 129.0, 128.3, 127.4, 126.7, 89.7, 52.1, 47.2, 45.7, 42.2, 32.9, 15.9; **IR (thin film, cm^{-1}):** 3345, 3040, 2953, 1715, 1650, 1581, 1488, 1250, 1029; $[\alpha]_D^{23} = -34.5^\circ$ (c = 1.0, CHCl_3).



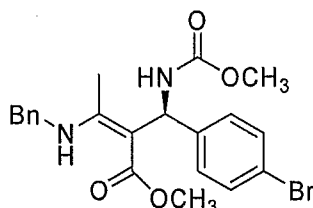
[00222] **17c: Methyl (*S,Z*)-4-(methoxycarbonyl)-5-(benzylamino)-2-methylhex-4-en-3-ylcarbamate.** Yield: 73 mg, 73%; ee: 93%; **HPLC Analysis**, t_r major: 15.9 min., t_r minor: 19.4min., [Chiralcel®OD-H column, Hexanes:IPA = 98:2, 1.0 mL/min]; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 9.85 (t, J = 5.6 Hz, 1H), 7.31 (m, 2H), 7.24 (m, 3H), 5.50 (d, J = 10 Hz, 1H), 4.43 (d, J = 5.6 Hz, 2H), 4.27 (t, J = 10 Hz, 1H), 3.68 (s, 3H), 3.61 (s, 3H), 2.05 (s, 3H), 1.85 (m, 1H), 0.98 (t, J = 6.0 Hz, 6H). $^{13}\text{C NMR}$ (75.0 MHz, CDCl_3): δ 169.3, 162.4, 155.2, 142.1,

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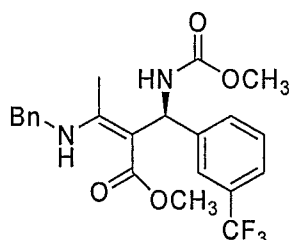
129.2, 128.3, 126.1, 95.2, 52.3, 48.1, 46.2, 32.5, 18.5, 15.4; IR (thin film, cm^{-1}): 3415, 3035, 2930, 1720, 1564, 1470, 1380, 1215; $[\alpha]^{23}_{\text{D}} = -38.0^{\circ}$ ($c = 1.0$, CHCl_3).



[00223] 17d: methyl (*R,Z*)-3-(methoxycarbonyl)-4-(benzylamino)-1-(benzyloxy)pent-3-en-2-ylcarbamate. Yield: 96 mg, 78%; ee: 95%; HPLC Analysis, t_{r} major: 7.3 min., t_{r} minor: 8.9 min., [Chiralcel[®]OD-H column, Hexanes:IPA = 95:5, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl_3): δ 9.84 (br, 1H), 7.30-7.15 (m, 10H), 5.53 (d, $J = 9.6$ Hz, 1H), 4.90 (dd, $J = 17.2, 7.2$ Hz, 1H), 4.45 (s, 2H), 4.43-4.37 (m, 4H), 3.59 (s, 3H), 3.56 (s, 3H), 2.09 (s, 3H); ¹³C NMR (75.0 MHz, CDCl_3): δ 170.4, 162.7, 157.0, 138.7, 138.5, 129.1, 128.5, 128.0, 127.7, 127.6, 127.1, 91.4, 72.8, 72.4, 52.2, 50.5, 49.6, 47.6, 15.8. IR (thin film, cm^{-1}): 3430, 3255, 2933, 1715, 1649, 1553, 1484, 1350, 1200, 1003; $[\alpha]^{23}_{\text{D}} = -47.3^{\circ}$ ($c = 1.0$, CHCl_3).

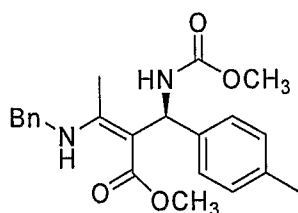


[00224] 17f: methyl (*S,Z*)-2-(methoxycarbonyl)-3-(benzylamino)-1-(4-bromophenyl)but-2-enylcarbamate. Yield: 111 mg, 83%; ee: 90%; HPLC Analysis, t_{r} major: 12.3 min., t_{r} minor: 16.9 min., [Chiralcel[®]OD column, Hexanes:IPA = 95:5, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl_3): δ 9.84 (br, 1H), 7.28 (m, 3H), 7.23 (m, 3H), 7.05 (d, $J = 8.4$ Hz, 2H), 5.82 (s, 2H), 4.44 (d, $J = 5.6$ Hz, 2H), 3.65 (s, 3H), 3.40 (s, 3H), 2.14 (s, 3H). ¹³C NMR (75.0 MHz, CDCl_3): δ 172.2, 162.1, 157.5, 146.5, 140.2, 131.2, 129.2, 127.8, 127.3, 127.1, 121.1, 94.1, 52.4, 52.2, 50.5, 47.7, 15.8; IR (thin film, cm^{-1}): 3330, 3011, 2945, 1715, 1630, 1581, 1477, 1250, 1095, 1003; $[\alpha]^{23}_{\text{D}} = -82.5^{\circ}$ ($c = 1.0$, CHCl_3).

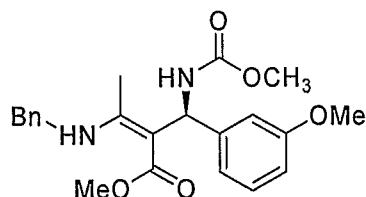


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[00225] 17h: methyl (*S,Z*)-2-(methoxycarbonyl)-3-(benzylamino)-1-(3-(trifluoromethyl)phenyl) but-2-enylcarbamate. Yield: 109 mg, 84%; ee: 92%; HPLC Analysis, t_r major: 11.2 min., t_r minor: 14.5 min., [Chiralcel[®]OD column, Hexanes:IPA = 95:5, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 9.93 (t, J = 5.2 Hz, 1H), 7.50 (s, 1H), 7.42 (t, J = 6.8 Hz, 2H), 7.36 (t, J = 8.0 Hz, 3H), 7.28 (m, 3H), 5.97(d, J = 9.6 Hz, 1H), 5.92 (d, J = 9.6 Hz, 1H), 4.53 (d, J = 4.6 Hz, 2H), 3.73 (s, 3H), 3.44 (s, 3H), 2.23 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 170.0, 162.2, 157.3, 144.9, 138.4, 129.2, 128.7, 127.8, 127.0, 123.3, 122.5, 94.1, 52.4, 51.5, 50.4, 47.7, 15.7.; IR (thin film, cm⁻¹): 3450, 3340, 2955, 1720, 1651, 1497, 1339, 1250, 1135, 1085; [α]_D²³ = -57.5° (c = 1.0, CHCl₃).



[00226] 17i: methyl (*S,Z*)-2-(methoxycarbonyl)-3-(benzylamino)-1-p-tolylbut-2-enylcarbamate. Yield: 110 mg, 96%; ee: 90%; HPLC Analysis, t_r major: 14.5 min., t_r minor: 18.0 min., [Chiralcel[®]OD column, Hexanes:IPA = 95:5, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 9.91 (br, 1H), 7.06-7.40 (9H), 5.90 (d, J = 10.4, 2H), 5.25 (d, J = 10.4 Hz, 1H), 4.49 (d, J = 5.6 Hz, 2H), 3.71(s, 3H), 3.45(s, 3H), 2.33(s, 3H), 2.19(s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 170.1, 161.6, 156.4, 142.8, 138.4, 135.5, 130.0, 129.2, 129.1, 128.9, 127.6, 127.1, 125.8, 125.7, 94.3, 52.1, 50.1, 47.3, 21.5, 15.4; IR (thin film, cm⁻¹): 3390, 2949, 1719, 1651, 1593, 1497, 1454, 1251, 1192; [α]_D²³ = -45.8° (c = 1.0, CHCl₃).

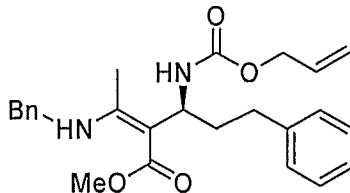


[00227] 17j: methyl (*S,Z*)-2-(methoxycarbonyl)-3-(benzylamino)-1-(3-methoxyphenyl) but-2-enylcarbamate. Yield: 102 mg, 86%; ee: 91%; HPLC Analysis, t_r major: 11.5 min., t_r minor: 15.3 min., [Chiralcel[®]OD column, Hexanes:IPA = 95:5, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 9.92 (t, J = 5.4 Hz, 1H), 7.16-7.40 (9H), 5.95 (d, J = 10.0 Hz, 1H), 5.25 (d, J = 10 Hz, 1H), 4.53 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.61 (s, 3H), 3.48 (s, 3H), 2.18 (s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 170.4, 161.9, 159.8, 156.5, 145.5, 138.6, 129.2,

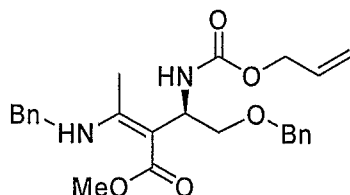
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129.1, 127.7, 127.1, 94.5, 65.9, 55.4, 52.5, 50.5, 47.6, 15.7; IR (thin film, cm^{-1}): 3331, 2933, 1715, 1652, 1583, 1350, 1280, 1005; $[\alpha]_{\text{D}}^{23} = -53.2^\circ$ ($c = 1.0$, CHCl_3).

For 18a-18h, the condensation reactions were run in 0.2mmol scale.

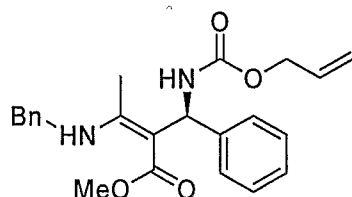


[00228] **18a: (S,Z)-methyl 3-(allyloxycarbonylamino)-2-(1-(benzylamino)ethylidene)-5-phenylpentanoate** Yield: 76mg, 81%; ee: 90%; HPLC analysis, t_{r} major: 4.7 min, t_{r} minor: 5.5 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ¹H NMR (400 MHz, CDCl_3): δ 9.85 (t, $J = 5.5$ Hz, 1H), 7.12-7.38 (10H), 5.94 (m, 1H), 5.68 (d, $J = 10.2$ Hz, 1H), 5.31 (d, $J = 17.2$ Hz, 1H), 5.21 (d, $J = 11.0$ Hz, 1H), 4.68 (m, 1H), 4.59 (dd, $J = 13.3, 5.5$ Hz, 1H), 4.51 (dd, $J = 13.3, 5.5$ Hz, 1H), 4.40 (d, $J = 6.3$ Hz, 2H), 3.71 (s, 3H), 2.59 (t, $J = 7.8$ Hz, 2H), 2.18 (m, 1H), 2.00 (m, 1H), 1.94 (s, 3H); ¹³C NMR (75.0 MHz, CDCl_3): δ 170.6, 161.7, 156.1, 142.1, 138.7, 133.4, 129.0, 128.7, 128.5, 127.6, 127.1, 126.0, 117.8, 94.0, 66.6, 50.5, 49.6, 47.5, 37.4, 33.4, 15.5; IR (thin film, cm^{-1}): 3328, 3030, 2943, 1715, 1646, 1590, 1498, 1235, 1091, 1041; $[\alpha]_{\text{D}}^{23} = -38.6^\circ$ ($c = 1.9$, CHCl_3).

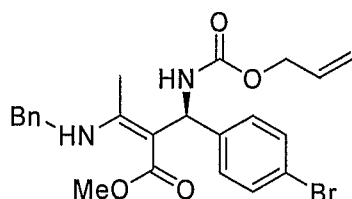


[00229] **18b: (R,Z)-methyl 2-(1-(allyloxycarbonylamino)-2-phenoxyethyl)-3-(benzylamino) but-2-enoate** Yield: 66 mg, 76%; ee: 90%; HPLC analysis, t_{r} major: 12.9 min, t_{r} minor: 18.5 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 96:4, 1.0 mL/min); ¹H NMR (400 MHz, CDCl_3): δ 9.93 (t, $J = 5.5$ Hz, 1H), 7.22-7.36 (10H), 5.92 (m, 1H), 5.66 (d, $J = 10.2$ Hz, 1H), 5.31 (d, $J = 16.4$ Hz, 1H), 5.20 (d, $J = 10.2$ Hz, 1H), 4.99 (m, 1H), 4.59 (dd, $J = 13.3, 5.5$ Hz, 1H), 4.54-4.51 (3H), 4.44 (d, $J = 6.3$ Hz, 2H), 3.69 (dd, $J = 9.4, 8.6$ Hz, 1H), 3.64 (s, 3H), 3.52 (dd, $J = 9.4, 7.0$ Hz, 1H), 2.16 (s, 3H); ¹³C NMR (75.0 MHz, CDCl_3): δ 170.4, 162.7, 156.2, 138.7, 138.5, 133.3, 129.1, 128.7, 128.5, 127.69, 127.65, 127.0, 117.9, 91.4, 72.8, 72.4, 65.7, 51.5, 49.6, 47.6, 15.8; IR (thin film, cm^{-1}): 3261, 2945, 1717, 1649, 1593, 1498, 1240, 1087, 1003; $[\alpha]_{\text{D}}^{23} = -42.4^\circ$ ($c = 1.2$, CHCl_3).

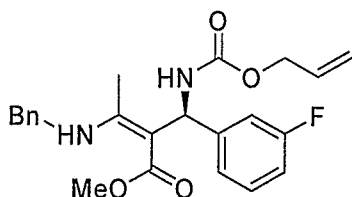
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[00230] **18c: (S,Z)-methyl 2-((allyloxycarbonylamino)(phenyl)methyl)-3-(benzylamino)but-2-enoate:** Yield: 64 mg, 81%; ee: 91%; HPLC analysis, t_r major: 8.5 min, t_r minor: 9.7 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 96:4, 1.0 mL/min); The spectra of this compound has been reported before.³



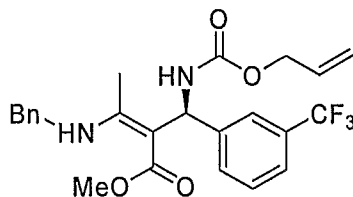
[00231] **18d: (S,Z)-methyl 2-((allyloxycarbonylamino)(4-bromophenyl)methyl)-3-(benzylamino)but-2-enoate:** Yield: 76 mg, 80%; ee: 90%; HPLC analysis, t_r major: 8.5 min, t_r minor: 9.6 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 96:4, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 9.91 (t, J = 5.5 Hz, 1H), 7.10-7.42 (9H), 5.89-6.02 (3H), 5.35 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 9.4 Hz, 1H), 4.65 (dd, J = 12.5, 5.5 Hz, 1H), 4.58 (dd, J = 12.5, 5.5 Hz, 1H), 4.51 (d, J = 6.3 Hz, 2H), 3.46 (s, 3H), 2.20 (s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 156.4, 142.8, 138.4, 133.1, 131.5, 131.2, 129.1, 127.9, 127.8, 127.6, 127.4, 127.1, 118.2, 66.0, 52.2, 50.5, 47.7, 15.7; IR (thin film, cm⁻¹): 3324, 3031, 2945, 1716, 1650, 1591, 1492, 1260, 1086, 1005; $[\alpha]_D^{23}$ = -24.9° (c = 1.3, CHCl₃).



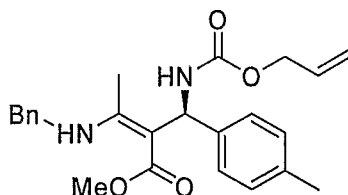
[00232] **18e: (S,Z)-methyl 2-((allyloxycarbonylamino)(3-fluorophenyl)methyl)-3-(benzylamino)but-2-enoate:** Yield: 68 mg, 83%; ee: 90%; HPLC analysis, t_r major: 10.2 min, t_r minor: 11.9 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 96:4, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 9.92 (t, J = 5.5 Hz, 1H), 7.18-7.40 (9H), 5.91-6.04 (3H), 5.35 (d, J = 17.2 Hz, 1H), 5.26 (d, J = 10.2 Hz, 1H), 4.66 (dd, J = 13.3, 5.5 Hz, 1H), 4.58 (dd, J = 13.3, 6.3 Hz, 1H), 4.51 (d, J = 6.3 Hz, 2H), 3.46 (s, 3H), 2.21 (s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 169.9, 164.1, 161.8, 161.7, 156.2, 146.5, 146.4, 138.2, 132.9, 129.4, 129.3, 128.9,

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127.5, 126.8, 121.0, 117.9, 113.0, 112.8, 112.6, 112.4, 94.0, 77.3, 77.0, 76.7, 65.7, 52.0, 50.2, 47.4, 15.4; **IR** (thin film, cm^{-1}): 3323, 3030, 2943, 1716, 1650, 1591, 1495, 1261, 1087; $[\alpha]^{23}_{\text{D}} = -31.6^{\circ}$ ($c = 1.2$, CHCl_3).

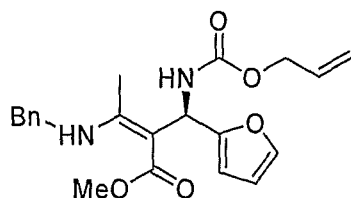


[00233] 18f: (S,Z)-methyl 2-((allyloxycarbonylamino)(3-(trifluoromethyl)phenyl)methyl)-3-(benzylamino)but-2-enoate: Yield: 76 mg, 82%; **ee:** 91%; **HPLC analysis**, t_{r} major: 4.7 min, t_{r} minor: 5.5 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); **^1H NMR** (400 MHz, CDCl_3): δ 9.94 (t, $J = 5.5$ Hz, 1H), 7.27-7.52 (9H), 5.95-6.01 (3H), 5.37 (d, $J = 17.2$ Hz, 1H), 5.27 (d, $J = 10.2$ Hz, 1H), 4.57-4.69 (2H), 4.53 (d, $J = 5.4$ Hz, 2H), 3.45 (s, 3H), 2.23 (s, 3H); **^{13}C NMR** (75.0 MHz, CDCl_3): δ 170.0, 162.3, 156.5, 144.9, 138.4, 133.1, 129.2, 128.8, 128.7, 128.4, 127.8, 127.0, 123.3, 122.5, 118.3, 94.1, 66.1, 52.4, 50.5, 47.7, 15.8; **IR** (thin film, cm^{-1}): 3331, 2945, 1717, 1651, 1592, 1496, 1329, 1242, 1166, 1124, 1075; $[\alpha]^{23}_{\text{D}} = -31.5^{\circ}$ ($c = 1.3$, CHCl_3).



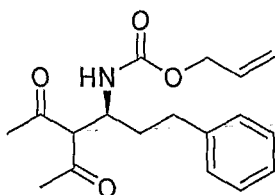
[00234] 18g: (S,Z)-methyl 2-((allyloxycarbonylamino)(p-tolyl)methyl)-3-(benzylamino)but-2-enoate: Yield: 69 mg, 84%; **ee:** 90%; **HPLC analysis**, t_{r} major: 18.5 min, t_{r} minor: 19.6 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 98:2, 1.0 mL/min); **^1H NMR** (400 MHz, CDCl_3): δ 9.91 (t, $J = 5.5$ Hz, 1H), 7.06-7.40 (9H), 5.90-6.04 (3H), 5.35 (d, $J = 17.2$ Hz, 1H), 5.25 (d, $J = 10.2$ Hz, 1H), 4.65 (dd, $J = 13.3, 5.5$ Hz, 1H), 4.58 (dd, $J = 13.3, 5.5$ Hz, 1H), 4.51 (d, $J = 5.5$ Hz, 2H), 3.48 (s, 3H), 2.31 (s, 3H), 2.20 (s, 3H); **^{13}C NMR** (75.0 MHz, CDCl_3): δ 156.4, 142.8, 138.4, 135.5, 130.0, 129.2, 129.1, 128.9, 127.6, 127.1, 125.8, 125.7, 118.2, 66.0, 52.2, 50.5, 47.6, 21.2, 15.7; **IR** (thin film, cm^{-1}): 3335, 3031, 2943, 1716, 1649, 1592, 1497, 1256, 1192, 1088; $[\alpha]^{23}_{\text{D}} = -53.1^{\circ}$ ($c = 1.9$, CHCl_3).

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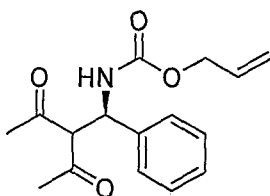


[00235] **18h:** (*R,Z*)-methyl 2-((allyloxycarbonylamino)(furan-2-yl)methyl)-3-(benzylamino)but-2-enoate: Yield: 62 mg, 81%; ee: 90%; HPLC analysis, t_r major: 11.1 min, t_r minor: 15.1 min, (Chiralcel[®]OD-H Column, Hexane:IPA = 96:4, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 9.92 (t, J = 5.5 Hz, 1H), 7.25-7.38 (6H), 6.27 (m, 1H), 5.90-6.04 (3H), 5.34 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 9.4 Hz, 1H), 4.64 (dd, J = 13.3, 5.5 Hz, 1H), 4.56 (dd, J = 13.3, 6.3 Hz, 1H), 4.49 (d, J = 5.5 Hz, 2H), 3.58 (s, 3H), 2.21 (s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 161.9, 156.0, 141.1, 132.9, 131.7, 128.9, 127.5, 126.9, 117.8, 117.7, 117.2, 117.0, 116.6, 115.4, 110.2, 65.7, 50.3, 48.2, 47.4, 15.4; IR (thin film, cm⁻¹): 3329, 2924, 1717, 1649, 1591, 1497, 1238, 1086; [α]_D²³ = -6.5° (c = 1.0, CHCl₃).

For 26a-26f, reactions were run in 4.0 mmol scale.

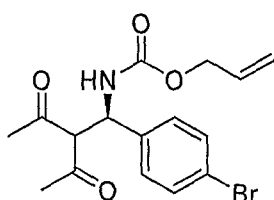


[00236] **26a:** (*S*)- Allyl 4-acetyl-5-oxo-1-phenylhexan-3-ylcarbamate: Yield: 1.12 g, 88%, ee: 90%; HPLC analysis, t_r minor: 9.4 min, t_r major: 12.3 min, (ChiralPak[®]AD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 7.16-7.32 (5H), 5.90 (m, 1H), 5.61 (d, J = 10.2 Hz, 1H), 5.25 (m, 2H), 4.54 (m, 2H), 4.35 (m, 1H), 3.88 (d, J = 4.7 Hz, 1H), 2.74 (m, 1H), 2.61 (m, 1H), 2.24 (s, 3H), 2.10 (s, 3H), 1.96 (m, 1H), 1.74 (m, 1H); ¹³C NMR (75.0 MHz, CDCl₃): δ 205.2, 203.8, 156.3, 141.1, 132.8, 128.8, 128.6, 126.4, 117.9, 69.6, 65.9, 50.8, 35.9, 33.0, 31.1, 30.1; IR (thin film, cm⁻¹): 3323, 1720, 1694, 1536, 1363, 1278, 1149, 1060, 700; [α]_D²³ = -56.2° (c = 1.0, CHCl₃). Enantiomer of **26a** was obtained as a white crystal 89% yield and 90% ee from a reaction catalyzed by cinchonidine at -20 °C to -15°C for 48 h.

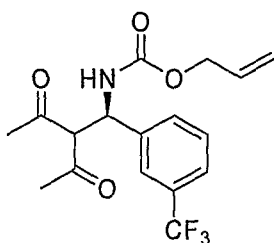


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[00237] **26b: (R)- Allyl 2-acetyl-3-oxo-1-phenylbutylcarbamate:** Yield: 1.05 g, 91%; ee: 93%; **HPLC analysis**, t_r minor: 9.0 min, t_r major: 9.8 min, (ChiralPak[®]AD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 7.21-7.34 (5H), 6.22 (d, J = 9.4 Hz, 1H), 5.83 (m, 1H), 5.53 (dd, J = 8.6, 7.8 Hz, 1H), 5.23 (d, J = 17.2 Hz, 2H), 5.15 (d, J = 10.2 Hz, 1H), 4.50 (m, 2H), 4.26 (d, J = 7.0 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 204.6, 202.4, 155.9, 139.7, 132.7, 129.0, 128.1, 126.7, 118.0, 71.8, 66.1, 54.5, 30.6, 30.3; **IR** (thin film, cm⁻¹): 3320, 1727, 1693, 1538, 1360, 1262, 1148, 1049, 702; $[\alpha]_D^{23}$ = +8.4 ° (c = 1.0, CHCl₃). Enantiomer of **26b** was obtained as a white crystal 90% yield and 91% ee from a reaction catalyzed by cinchonidine at -15 °C for 16 h.



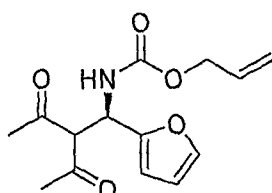
[00238] **26c: (R)- Allyl 2-acetyl-1-(4-bromophenyl)-3-oxobutylcarbamate:** Yield: 1.32 g, 90%; ee: 91%; **HPLC analysis**, t_r minor: 8.5 min, t_r major: 9.6 min, (ChiralPak[®]AD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 7.45 (d, J = 8.6 Hz, 2H), 7.17 (d, J = 8.6 Hz, 2H), 6.09 (d, J = 8.6 Hz, 1H), 5.85 (m, 1H), 5.47 (t, J = 7.8 Hz, 1H), 5.26 (d, J = 17.2 Hz, 2H), 5.20 (d, J = 11.0 Hz, 1H), 4.52 (d, J = 5.5 Hz, 2H), 4.19 (d, J = 6.3 Hz, 1H), 2.23 (s, 3H), 2.11 (s, 3H); ¹³C NMR (75.0 MHz, CDCl₃): δ 206.8, 204.5, 158.8, 138.8, 132.6, 132.2, 128.4, 122.1, 118.2, 71.2, 66.2, 53.9, 30.9, 30.2; **IR** (thin film, cm⁻¹): 3321, 1726, 1694, 1531, 1414, 1361, 1252, 1149, 1010, 826; $[\alpha]_D^{23}$ = +9.9 ° (c = 1.0, CHCl₃). Enantiomer of **26c** was obtained as a white crystal 90% yield and 90% ee from a reaction catalyzed by cinchonidine at -15 °C for 16 h.



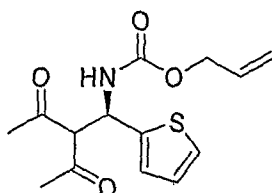
[00239] **26d: (R)-Allyl 2-acetyl-3-oxo-1-(3-(trifluoromethyl)phenyl)butylcarbamate:** Yield: 1.24 g, 87 %; ee: 92%; **HPLC analysis**, t_r minor: 10.8 min, t_r major: 12.1 min, (ChiralPak[®]AD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ¹H NMR (400 MHz, CDCl₃): δ 7.42-7.56 (4H), 6.25 (d, J = 8.6 Hz, 1H), 5.85 (m, 1H), 5.58 (dd, J = 8.6, 7.0 Hz, 1H), 5.26 (d, J = 17.2 Hz, 2H), 5.19 (d, J = 11.0 Hz, 1H), 4.53 (d, J = 5.5 Hz, 2H), 4.26 (d, J = 6.3 Hz,

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1H), 2.25 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 204.3, 201.8, 155.6, 132.2, 130.0, 129.3, 125.1, 124.7, 123.1, 118.0, 70.7, 66.1, 53.6, 30.7, 29.9; IR (thin film, cm^{-1}): 3320, 1721, 1699, 1530, 1329, 1260, 1163, 1126, 1074, 705; $[\alpha]_D^{23} = -10.9^\circ$ ($c = 1.0$, CHCl_3). Enantiomer of **26d** was obtained as a white crystal 86% yield and 91% ee from a reaction catalyzed by cinchonidine at -15°C for 16 h.

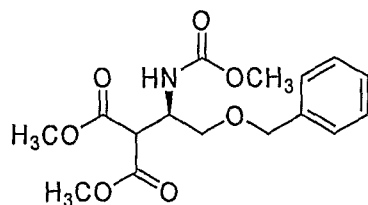


[00240] **26e: (R)- Allyl 2-acetyl-1-(furan-2-yl)-3-oxobutylcarbamate:** Yield: 982 mg, 88%; ee: 91%; HPLC analysis, t_r minor: 9.0 min, t_r major: 10.2 min, (ChiralPak[®] AD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ^1H NMR (400 MHz, CDCl_3): δ 7.17 (d, $J = 3.9$ Hz, 1H), 6.86-6.93 (2H), 6.13 (d, $J = 8.6$ Hz, 1H), 5.85 (m, 1H), 5.77 (dd, $J = 8.6, 6.3$ Hz, 1H), 5.16-5.27 (2H), 4.53 (m, 2H), 4.33 (d, $J = 6.3$ Hz, 1H), 2.22 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 204.1, 202.0, 155.8, 143.4, 132.6, 127.3, 125.3, 125.2, 118.1, 71.7, 66.2, 50.6, 30.7, 30.2; IR (thin film, cm^{-1}): 3349, 1727, 1702, 1526, 1268; $[\alpha]_D^{23} = +24.0^\circ$ ($c = 1.0$, CHCl_3). Enantiomer of **26e** was obtained as a white crystal 87% yield and 90% ee from a reaction catalyzed by cinchonidine at -15°C for 16 h.

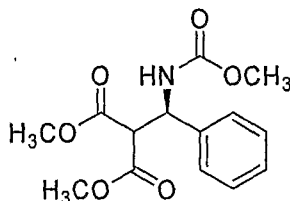


[00241] **26f: (R)- Allyl 2-acetyl-3-oxo-1-(thiophen-2-yl)butylcarbamate:** Yield: 1.01 g, 86%; ee: 93%; HPLC analysis, t_r minor: 14.0 min, t_r major: 14.8 min, (ChiralPak[®] AD-H Column, Hexane:IPA = 95:5, 1.0 mL/min); ^1H NMR (400 MHz, CDCl_3): δ 7.27 (d, $J = 1.6$ Hz, 1H), 6.28 (dd, $J = 3.1, 1.6$ Hz, 1H), 6.19 (d, $J = 3.1$ Hz, 1H), 5.95 (d, $J = 9.4$ Hz, 1H), 5.85 (m, 1H), 5.59 (dd, $J = 9.4, 7.0$ Hz, 1H), 5.16-5.30 (2H), 4.53 (m, 2H), 4.35 (d, $J = 7.0$ Hz, 1H), 2.23 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (75.0 MHz, CDCl_3): δ 204.0, 202.2, 155.9, 152.2, 142.3, 132.6, 118.1, 111.0, 107.4, 68.7, 66.2, 48.8, 30.4, 30.0; IR (thin film, cm^{-1}): 3329, 1725, 1697, 1526, 1361, 1264, 1149, 1048, 707; $[\alpha]_D^{23} = +20.3^\circ$ ($c = 1.0$, CHCl_3). Enantiomer of **26f** was obtained as a white crystal 86% yield and 91% ee from a reaction catalyzed by cinchonidine at -15°C for 16 h.

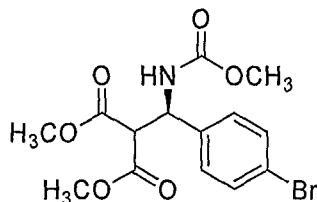
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[00242] **21a: methyl (R)-1,1-di(methoxycarbonyl)-3-(benzyloxy)propan-2-ylcarbamate:** Yield: 69 mg, 82%. ee: 91%. HPLC analysis, t_r major: 35.5 min, t_r minor: 41.7 min, [Chiralcel[®]OD-H column, Hexanes:IPA 99 : 1, 1.0 mL/min]. ¹H NMR (400 MHz, CDCl₃): δ 7.30 (m, 5H), 5.75 (d, J = 8.0 Hz, 1H), 5.31 (br, 1H), 4.55 (m, 2H), 3.87 (d, J = 4.4 Hz, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.62 (s, 3H), 3.60 (m, 1H), 3.50 (m, 1H); ¹³C NMR (75.0 MHz, CDCl₃): δ 169.5, 167.3, 155.7, 137.1, 129.7, 129.2, 128.9, 75.5, 72.4, 56.5, 54.3, 53.2, 52.5, 43.1. IR (thin film, cm⁻¹): 3350, 2935, 1730, 1715, 1496, 1150; $[\alpha]_D^{23} = -12.3^\circ$ (c = 1.0, CHCl₃).

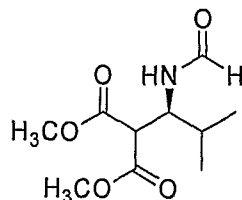


[00243] **21b: methyl (R)-2,2-di(methoxycarbonyl)-1-phenylethylcarbamate :** Yield: 122 mg, 83%; ee: 90%; HPLC Analysis, t_r major: 9.2 min., t_r minor: 12.7 min., [Chiralcel[®]OD-H column, Hexanes:IPA = 95:5, 1.0 mL/min]; ¹H NMR (400 MHz, CDCl₃): δ 7.33 – 7.22 (m, 5H), 6.39 (d, J = 8.4 Hz, 1H), 5.51 (dd, J = 8.4, 4.0 Hz, 1H), 3.92 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), 3.65 (s, 3H), 3.63 (s, 3H). ¹³C NMR (75.0 MHz, CDCl₃): δ 168.6, 167.6, 156.6, 139.3, 128.9, 128.1, 126.4, 56.7, 54.2, 53.2, 52.8, 52.5; IR (thin film, cm⁻¹): 3387, 1720, 1500, 1220, 1130; $[\alpha]_D^{23} = -15.3^\circ$ (c = 1.0, CHCl₃).

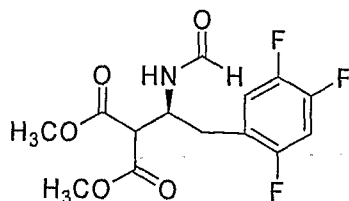


[00244] **21c: methyl (R)-2,2-di(methoxycarbonyl)-1-(4-bromophenyl)ethylcarbamate:** Yield: 89 mg, 95%. ee: 90%. HPLC analysis, t_r major: 11.0 min, t_r minor: 18.0 min, [Chiralcel[®]OD-H column, Hexanes:IPA 98 : 2, 1.0 mL/min]. ¹H NMR (400 MHz, CDCl₃): δ 7.44 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.38 (d, J = 6.4 Hz, 1H), 5.44 (br, 1H), 3.87 (d, J = 3.2 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 6H). ¹³C NMR (75.0 MHz, CDCl₃): δ 168.5,

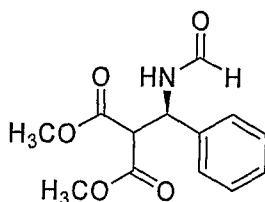
167.3, 156.5, 138.5, 132.1, 128.2, 122.1, 56.4, 53.7, 53.0, 52.7. IR (thin film, cm^{-1}): 3350, 1717, 1496, 1230, 1120; $[\alpha]^{23}_{\text{D}} = -25.1^{\circ}$ ($c = 1.0$, CHCl_3).



[00245] **22a: (S)-1,1-di(methoxycarbonyl)-3-methylbutan-2-ylformate:** Yield: 55 mg, 72%. ee: 96%. HPLC analysis, t_{r} major: 17.2 min, t_{r} minor: 23.0 min, [(*R,R*)-Whelk-O 1 column, Hexanes:IPA 95 : 5, 1.0 mL/min] ^1H NMR (400 MHz, CDCl_3): δ 8.18 (s, 1H), 4.35 (m, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.50 (d, $J = 8.4$ Hz, 1H), 1.65 (m, 1H), 0.92 (t, $J = 8.0$ Hz, 6H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 168.3, 166.2, 160.9, 53.3, 53.0, 52.4, 44.0, 31.8, 19.9, 19.8. IR (thin film, cm^{-1}): 3355, 2935, 1720, 1670, 1444, 1110; $[\alpha]^{23}_{\text{D}} = -17.6^{\circ}$ ($c = 1.0$, CHCl_3).

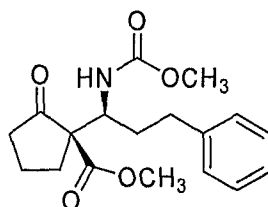


[00246] **22b: (S)-1,1-di(methoxycarbonyl)-3-(2,4,5-trifluorophenyl)propan-2-ylformate:** Yield: 61 mg, 73%. ee: 90%. HPLC analysis, t_{r} major: 17.2 min, t_{r} minor: 23.0 min, [(*R,R*)-Whelk-O 1, Hexanes:IPA 95 : 5, 1.0 mL/min. ^1H NMR (400 MHz, CDCl_3): δ 8.27 (s, 1H), 7.31 (d, $J = 9.6$ Hz, 1H), 7.17 (dd, $J = 15.6, 10.4$ Hz, 1H), 6.96 (m, 1H), 6.02 (dd, $J = 9.2, 4.4$ Hz, 1H), 3.98 (d, $J = 4.4$ Hz, 1H), 3.78 (s, 3H), 3.74 (d, $J = 9.2$ Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 168.3, 167.2, 160.7, 157.8, 148.4, 145.3, 123.8, 106.6, 53.3, 53.0, 52.4, 43.6, 29.8. IR (thin film, cm^{-1}): 3343, 2940, 1720, 1680, 1440, 1135; $[\alpha]^{23}_{\text{D}} = -22.8^{\circ}$ ($c = 1.0$, CHCl_3).

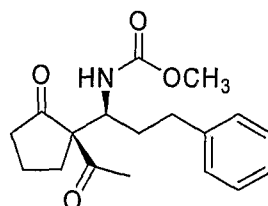


[00247] **22c: (R)-2,2-di(methoxycarbonyl)-1-phenylethylformate:** Yield: 63 mg, 95%. ee: 98%. HPLC analysis, t_{r} major: 14.2 min, t_{r} minor: 17.1 min, [ChiralPak[®]AD-H column, Hexanes:IPA 90 : 10, 1.0 mL/min]. ^1H NMR (400 MHz, CDCl_3): δ 8.29 (s, 1H), 7.30 (m,

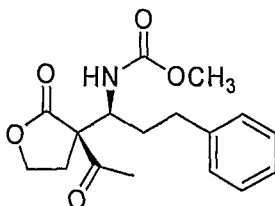
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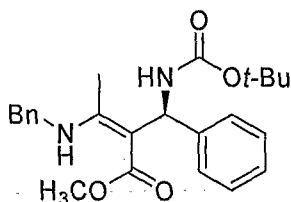
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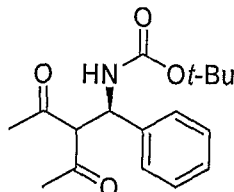
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[00250] **23c: methyl (S)-1-((S)-3-acetyl-tetrahydro-2-oxofuran-3-yl)-3-phenylpropyl carbamate:** Yield: 133 mg, 84%. ee: 97%. HPLC analysis, t_r major: 13.7 min, t_r minor: 11.3 min, [ChiralPak[®]AD-H column, Hexanes:IPA 95 : 5, 1.0 mL/min ¹H NMR (400 MHz, CDCl₃, major diastereomer was reported): δ 7.24 (m, 2H), 7.15 (m, 3H), 4.55 (m, 2H), 4.24 (td, J = 10.4, 2.0 Hz, 1H), 4.05 (dd, J = 12.4, 8.0 Hz, 1H), 3.67 (s, 3H), 2.73 (m, 1H), 2.63 (m, 1H), 2.55 (m, 1H), 2.28 (m, 1H), 1.83 (m, 2H). ¹³C NMR (75.0 MHz, CDCl₃): δ 200.9, 175.3, 155.5, 138.7, 129.3, 128.7, 127.9, 67.3, 66.2, 56.7, 52.6, 34.5, 30.4, 25.5, 24.2. IR (thin film, cm⁻¹): 3327, 2956, 2922 1760, 1716, 1537, 1361, 1248, 1170, 1028; $[\alpha]^{23}_D = -15.6^\circ$ (c = 1.0, CHCl₃).



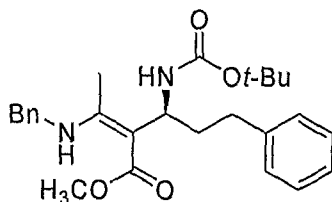
[00251] **tert-Butyl (S,Z)-2-(methoxycarbonyl)-3-(benzylamino)-1-phenylbut-2-enyl carbamate:** Yield: 77 mg, 84%. ee: 96%. HPLC analysis, t_r major: 15.8 min, t_r minor: 14.6 min, [(R,R)-Whelk-O 1 column, Hexanes:IPA 95 : 5, 1.0 mL/min ¹H NMR (400 MHz, CDCl₃): δ 9.82 (br, 1H), 7.30-7.09 (m, 10H), 5.85 (d, J = 9.6 Hz, 1H), 5.69 (d, J = 9.6 Hz, 1H), 4.43 (d, J = 5.2 Hz, 2H), 3.39 (s, 3H), 2.13 (s, 3H), 1.37 (s, 9H). ¹³C NMR (75.0 MHz, CDCl₃): δ 170.6, 161.8, 156.1, 144.1, 138.7, 129.1, 128.9, 128.8, 128.1, 127.7, 127.1, 126.3, 126.2, 125.8, 95.0, 79.4, 51.8, 51.5, 50.4, 47.6, 28.7, 28.5, 15.8. IR (thin film, cm⁻¹): 3446, 3395, 2949, 1717, 1651, 1593, 1497, 1455, 1239; $[\alpha]^{23}_D = -18.2^\circ$ (c = 1.0, CHCl₃).



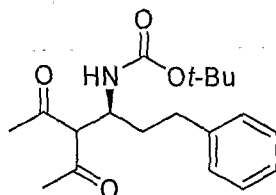
[00252] **25b: tert-butyl (R)-3-oxo-2-acyl-1-phenylbutyl carbamate:** Yield: 147 mg, 97%. ee: 95%. HPLC analysis, t_r major: 18.3 min, t_r minor: 17.1 min, [ChiralPak[®]AD-H, Hexanes:IPA 99 : 1, 1.0 mL/min ¹H NMR (400 MHz, CDCl₃): δ 7.26 (m, 5H), 5.82 (br, 1H),

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5.48 (br, 1H), 4.20 (d, $J = 8.8$ Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 204.9, 202.8, 155.4, 140.1, 129.0, 127.4, 126.6, 125.9, 80.3, 71.9, 53.9, 28.6, 28.4.



[00253] **tert-Butyl (S,Z)-4-(methoxycarbonyl)-5-(benzylamino)-1-phenylhex-4-en-3-ylcarbamate**: Yield: 84 mg, 81%. ee: 90%. HPLC analysis, t_r major: 30.5 min, t_r minor: 29.0 min, [(R,R)-Whelk-O 1 column, Hexanes:IPA 98 : 2, 1.0 mL/min ^1H NMR (400 MHz, CDCl_3): δ 9.75 (br, 1H), 7.30-7.07 (m, 10H), 5.36 (d, $J = 9.6$ Hz, 1H), 4.75 (m, 1H), 4.35 (d, $J = 6.0$ Hz, 2H), 3.28 (s, 3H), 2.63 (m, 2H), 1.90 (s, 3H), 1.87 (m, 1H), 1.77 (m, 1H), 1.39 (s, 9H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 169.4, 161.5, 154.5, 146.6, 135.7, 127.4, 127.3, 127.2, 126.4, 125.8, 125.0, 93.7, 54.3, 47.7, 46.3, 36.4, 30.3, 27.3, 14.4. IR (thin film, cm^{-1}): 3451, 3390, 2949, 1719, 1651, 1593, 1497, 1454, 1251, 1192; $[\alpha]_D^{23} = -36.1^\circ$ ($c = 1.0$, CHCl_3).



[00254] **25e: tert-Butyl (S)-5-oxo-4-acyl-1-phenylhexan-3-ylcarbamate**: Yield: 150 mg, 90%. ee: 90%. HPLC analysis, t_r major: 8.5 min, t_r minor: 6.1 min, [(R,R)-Whelk-O 1 column, Hexanes:IPA 85 : 15, 1.0 mL/min ^1H NMR (400 MHz, CDCl_3): δ 7.30-7.15 (m, 5H), 5.40 (d, $J = 10$ Hz, 1H), 4.32 (br, 1H), 3.83 (d, $J = 4.4$ Hz, 1H), 2.81-2.55 (m, 2H), 2.22 (s, 3H), 2.09 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (75.0 MHz, CDCl_3): δ 205.3, 204.0, 155.9, 141.3, 128.8, 128.5, 126.3, 79.8, 70.0, 50.3, 36.0, 32.9, 30.9, 30.2, 28.5. IR (thin film, cm^{-1}): 3446, 3390, 2951, 1720, 1650, 1591, 1499, 1453, 1253, 1193, 1090; $[\alpha]_D^{23} = -19.3^\circ$ ($c = 1.0$, CHCl_3).

References and Notes

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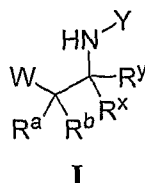
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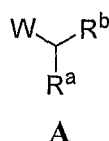
CLAIMS

We claim:

1. A method for preparing a compound of formula **I**:



wherein said method comprises the step of:
reacting a compound of formula **A**:



wherein:

W is C(O)R, C(O)OR, C(OSR), C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, NO₂, CN, or P(O)(OR)₂;

each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3-8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

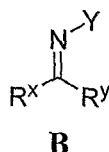
two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3-8-membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R' is independently hydrogen or R;

R^a is R', halo, N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂; and

R^b is R', halo, C(O)R, C(O)OR, C(OSR), C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, NO₂, CN, or P(O)(OR)₂;

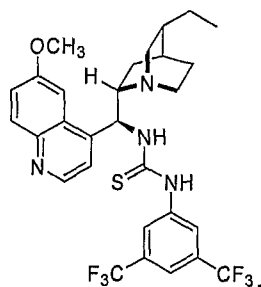
with a compound of formula **B**:



wherein:

Y is R', C(O)R, C(O)OR, C(O)SR, C(S)OR, C(O)NR'₂, S(O)₂R, S(O)₂NR'₂, S(O)R, P(O)(OR)₂, N(R')C(O)R', N(R')C(O)OR, N(R')C(O)NR'₂, N(R')S(O)₂R, or N(S(O)₂R)₂; each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or: two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each R' is independently hydrogen or R; and R^x and R^y are each independently R'; in the presence of a chiral amine base and optionally in a suitable medium.

2. The method of claim 1, wherein the amine base is cinchonine or cinchonidine.
3. The method of claim 1, wherein the amine base is quinine, or quinidine.
4. The method of claim 1, wherein the amine base is:



5. The method of claim 1, wherein one enantiomer makes up at least 80% of the preparation.
6. The method of claim 1, wherein the ratio of one pair of enantiomers to its diastereomic pair of enantiomers is other than 1:1.
7. The method of claim 6, wherein the ratio is at least 5:1.

8. The method of claim 6, wherein the ratio is at least 20:1.
9. The method of claim 1, wherein the amine base is used in less than 1 mole equivalent relative to the compound of formula A.
10. The method of claim 9, wherein the amine base is employed in less than 0.1 mole equivalents.
11. The method of claim 9, wherein the amine base is employed in less than 0.05 mole equivalents.
12. The method of claim 1, wherein the W group of formulae A and I is C(O)R, NO₂, or C(O)OR.
13. The method of claim 12, wherein the W group of formulae A and I is C(O)R, wherein the R group is optionally substituted C₁₋₆ aliphatic.
14. The method of claim 13, wherein the R group is CH₃.
15. The method of claim 1, wherein the R^a group of formulae A and I is hydrogen or optionally substituted C₁₋₆ aliphatic.
16. The method of claim 1, wherein the R^a group of formulae A and I is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
17. The method of claim 1, wherein an R group on W and an R group on R^a of formulae A and I are taken together with their intervening atoms to form an optionally substituted 5–8-membered saturated or partially unsaturated monocyclic ring having 0–3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

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18. The method of claim 17, wherein an R group on W and an R group on R^a of formulae A and I are taken together with their intervening atoms to form an optionally substituted cyclopentanone, γ -lactone, or γ -lactam.
19. The method of claim 1, wherein the R^b group of formulae A and I is C(O)OR or C(O)R.
20. The method of claim 19, wherein the R is optionally substituted C₁₋₆ aliphatic.
21. The method of claim 19, wherein the R group CH₂CHCH₂ or CH₃.
22. The method of claim 1, wherein the Y group of formulae B and I is R.
23. The method of claim 1, wherein the Y group of formulae B and I is C(O)R, C(O)OR, C(O)SR, C(S)OR, or C(O)NR'₂.
24. The method of claim 23, wherein the Y group of formulae B and I is C(O)OR.
25. The method of claim 24, wherein the R group is CH₃, CH₂CH₃, CH₂CHCH₂, or C(CH₃)₃.
26. The method of claim 1, wherein at least one of the R^x and R^y groups of formulae B and I is hydrogen.
27. The method of claim 1 wherein at least one of the R^x and R^y groups of formulae B and I is optionally substituted C₁₋₆ aliphatic.
28. The method of claim 1, wherein at least one of the R^x and R^y groups of formulae B and I is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

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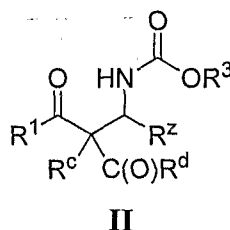
29. The method of claim 28, wherein at least one of the R^x and R^y groups of formulae **B** and **I** is optionally substituted phenyl.

30. The method of claim 1, wherein at least one of the R^x and R^y groups of formulae **B** and **I** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

31. The method of claim 30, wherein at least one of the R^x and R^y groups of formulae **B** and **I** is an optionally substituted naphthyl.

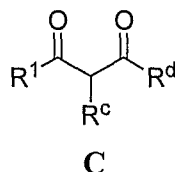
32. The method of claim 1, wherein at least one of the R^x and R^y groups of formulae **B** and **I** is phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-bromophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3,4-(OCH_2O) C_6H_3 -, furan-2-yl, thien-2-yl, naphth-2-yl, $PhCH=CH$ -, $(2-C_4H_3O)CH=CH$ -, or $PhCH_2CH_2$ -.

33. A method for preparing a compound of formula **II**:



wherein said method comprises the step of:

reacting a compound of formula **C**:



wherein:

R^1 is R, OR, SR, or NR'_2 ;

each R is independently an optionally substituted group selected from C_{1-6} aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

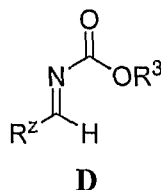
two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R' is independently hydrogen or R;

R^c is R', halo, N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂; and

R^d is R or OR;

with a compound of formula **D**:



wherein:

R^z is R'; and,

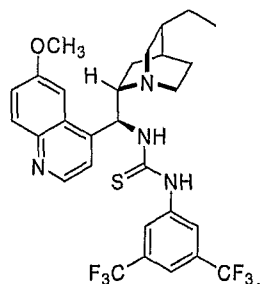
R³ is R;

in the presence of a chiral amine base and optionally in a suitable medium.

34. The method of claim 33, wherein the amine base is cinchonine or cinchonidine.

35. The method of claim 33, wherein the amine base is quinine, or quinidine.

36. The method of claim 33, wherein the amine base is:



37. The method of claim 33, wherein one enantiomer makes up at least 80% of the preparation.

38. The method of claim 33, wherein the ratio of one pair of enantiomers to its diastereomeric pair of enantiomers is other than 1:1.

Full Subsearch

39. The method of claim 33, wherein the ratio is at least 5:1.
40. The method of claim 33, wherein the ratio is at least 20:1.
41. The method of claim 33, wherein the amine base is used in less than 1 mole equivalent relative to the compound of formula **C**.
42. The method of claim 41, wherein the amine base is employed in less than 0.1 mole equivalents.
43. The method of claim 41, wherein the amine base is employed in less than 0.05 mole equivalents.
44. The method of claim 33, wherein the R^1 group of formulae **C** and **II** is R.
45. The method of claim 33, wherein the R^1 group of formulae **C** and **II** is OR, SR, or NR'_2 .
46. The method of claim 33, wherein the R^1 group of formulae **C** and **II** is optionally substituted C_{1-6} aliphatic.
47. The method of claim 33, wherein the R^1 group of formulae **C** and **II** is CH_3 .
48. The method of claim 33, wherein the R^c group of formulae **C** and **II** is R' .
49. The method of claim 33, wherein the R^c group of formulae **C** and **II** is hydrogen or optionally substituted C_{1-6} aliphatic.
50. The method of claim 33, wherein an R group on R^1 and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted 5–8-membered saturated or partially unsaturated monocyclic ring having 0–3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

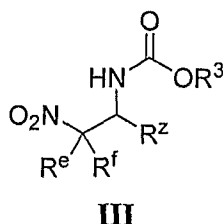
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51. The method of claim 50, wherein an R group on R¹ and an R group on R^c of formulae **C** and **II** are taken together with their intervening atoms to form an optionally substituted cyclopentanone, γ -lactone, or γ -lactam.
52. The method of claim 33, wherein the R^d group of formulae **C** and **II** is R or OR, wherein R is optionally substituted C₁₋₆ aliphatic.
53. The method of claim 52, wherein the R is CH₃, CH₂CH₃, CH₂CHCH₂, C(CH₃)₃, or optionally substituted phenyl.
54. The method of claim 33, wherein the R^z group of formulae **D** and **II** is hydrogen.
55. The method of claim 33, wherein the R^z group of formulae **D** and **II** is optionally substituted C₁₋₆ aliphatic.
56. The method of claim 33, wherein the R^z group of formulae **D** and **II** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
57. The method of claim 56, wherein the R^z group of formulae **D** and **II** is optionally substituted phenyl.
58. The method of claim 33, wherein the R^z group of formulae **D** and **II** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.
59. The method of claim 58, wherein the R^z group of formulae **D** and **II** is optionally substituted naphthyl.
60. The method of claim 33, wherein the R^z group of formulae **D** and **II** is phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-bromophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3,4-(OCH₂O)C₆H₃-, furan-2-yl, thien-2-yl, naphth-2-yl, PhCH=CH-, (2-C₄H₃O)CH=CH-, or PhCH₂CH₂-.

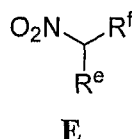
61. The method of claim 33, wherein the R^3 group of formulae **D** and **II** is optionally substituted C_{1-6} aliphatic.

62. The method of claim 61, wherein the R^3 group of formulae **D** and **II** is optionally substituted CH_3 , CH_2CH_3 , CH_2CHCH_2 , $C(CH_3)_3$.

63. A method for preparing a compound of formula **III**:



wherein said method comprises the step of:
reacting a compound of formula **E**:



wherein:

R^e is R' , halo, $N(R')C(O)R'$, $N(R')C(O)OR$, or $N(R')C(O)NR'_2$;

each R' is independently hydrogen or R ;

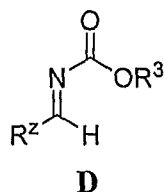
each R is independently an optionally substituted group selected from C_{1-6} aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;
and

R^f is halo or R' ;

with a compound of formula **D**:

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wherein:

R^Z is R' ; and

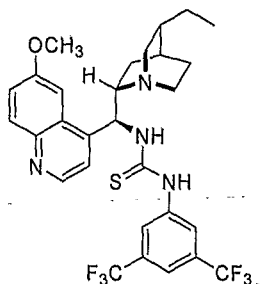
R^3 is R ;

in the presence of a chiral amine base and optionally in a suitable medium.

64. The method of claim 63, wherein the amine base is cinchonine or cinchonidine.

65. The method of claim 63, wherein the amine base is quinine, or quinidine.

66. The method of claim 63, wherein the amine base is:



67. The method of claim 63, wherein one enantiomer makes up at least 80% of the preparation.

68. The method of claim 63, wherein the ratio of one pair of enantiomers to its diastereomeric pair of enantiomers is other than 1:1.

69. The method of claim 68, wherein the ratio is at least 5:1.

70. The method of claim 68, wherein the ratio is at least 20:1.

71. The method of claim 63, wherein the amine base is used in less than 1 mole equivalent relative to the compound of formula E.

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72. The method of claim 71, wherein the amine base is employed in less than 0.1 mole equivalents.

73. The method of claim 71, wherein the amine base is employed in less than 0.05 mole equivalents.

74. The method of claim 63, wherein the R^e group of formulae **E** and **III** is hydrogen or optionally substituted C₁₋₆ aliphatic.

75. The method of claim 63, wherein the R^f group of formulae **E** and **III** is hydrogen optionally substituted C₁₋₆ aliphatic.

76. The method of claim 63, wherein at least one of the R^e and R^f groups of formulae **E** and **III** is hydrogen.

77. The method of claim 63, wherein both of the R^e and R^f groups of formulae **E** and **III** are hydrogen.

78. The method of claim 63, wherein the R^z group of formulae **D** and **III** is hydrogen.

79. The method of claim 63, wherein the R^z group of formulae **D** and **III** is optionally substituted C₁₋₆ aliphatic.

80. The method of claim 63, wherein the R^z group of formulae **D** and **III** is an optionally substituted 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

81. The method of claim 80, wherein the R^z group of formulae **D** and **III** is optionally substituted phenyl.

82. The method of claim 63, wherein the R^z group of formulae **D** and **III** is an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

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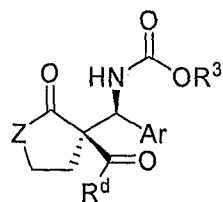
83. The method of claim 82, wherein the R^z group of formulae **D** and **III** is optionally substituted naphthyl.

84. The method of claim 63, wherein the R^z group of formulae **D** and **III** is phenyl, 4-chlorophenyl, 4-fluorophenyl, 3-fluorophenyl, 4-bromophenyl, 3-methylphenyl, 3-trifluoromethylphenyl, 3,4-(OCH₂O)C₆H₃-, furan-2-yl, thien-2-yl, naphth-2-yl, PhCH=CH-, (2-C₄H₃O)CH=CH-, or PhCH₂CH₂-.

85. The method of claim 63, wherein the R^3 group of formulae **D** and **III** is optionally substituted C₁₋₆ aliphatic.

86. The method of claim 85, wherein the R^3 group of formulae **D** and **III** is optionally substituted CH₃, CH₂CH₃, CH₂CHCH₂, C(CH₃)₃.

87. A method for preparing a compound of formula **IV**:



IV

wherein:

Z is -O-, -S-, -NR'-, or -C(R')₂;

each R' is independently hydrogen or R;

each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring

having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

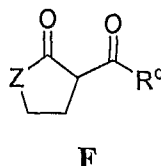
R^3 is R;

R^d is R or OR; and

Ar is an optionally substituted group selected from 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10-membered aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

wherein said method comprises the step of:

reacting a compound of formula F:



wherein:

Z is -O-, -S-, -NR'-, or -C(R')₂;

each R' is independently hydrogen or R;

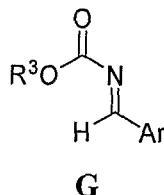
each R is independently an optionally substituted group selected from C₁₋₆ aliphatic, or a 3-8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3-8-membered saturated or partially unsaturated ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^3 is R; and

R^d is R or OR;

with a compound of formula G:



wherein:

Ar is an optionally substituted group selected from 5-6 membered aromatic monocyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8-10-membered aromatic bicyclic ring having 0-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; and

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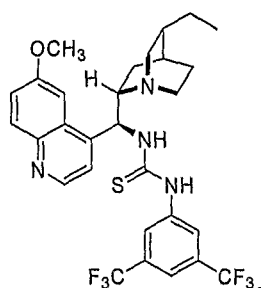
R^3 is R,

in the presence of a chiral amine base and optionally in a suitable medium.

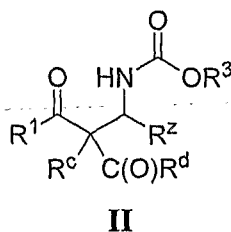
88. The method of claim 87, wherein the amine base is cinchonine or cinchonidine.

89. The method of claim 87, wherein the amine base is quinine, or quinidine.

90. The method of claim 87, wherein the amine base is:

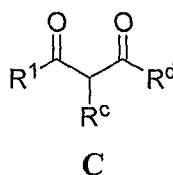


91. A method for preparing a compound of formula **II**:



wherein said method comprises the step of:

reacting a compound of formula **C**:



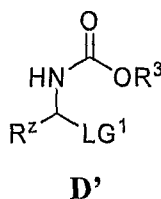
wherein:

R^1 is R, OR, SR, or NR'_2 ;

each R is independently an optionally substituted group selected from C_{1-6} aliphatic, or a 3–8-membered saturated, partially unsaturated, or aromatic monocyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 8–10-membered saturated, partially unsaturated, or aromatic bicyclic ring having 0–5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or:

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two occurrences of R are taken together with their intervening atom(s) to form an optionally substituted 3–8-membered saturated or partially unsaturated ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; each R' is independently hydrogen or R; R^c is R', halo, N(R')C(O)R', N(R')C(O)OR, or N(R')C(O)NR'₂; and R^d is R or OR; with a compound of formula **D'**:



wherein:

LG¹ is a suitable leaving group;

R^z is R'; and

R³ is R;

in the presence of a chiral amine base and optionally in a suitable medium.

X-ray crystal structure of compound 15a: ((*R*)-1-[(*S*)-(3-Fluoro-phenyl)-methoxycarbonylamino-methyl]-2-oxo-cyclopentanecarboxylic acid methyl ester).

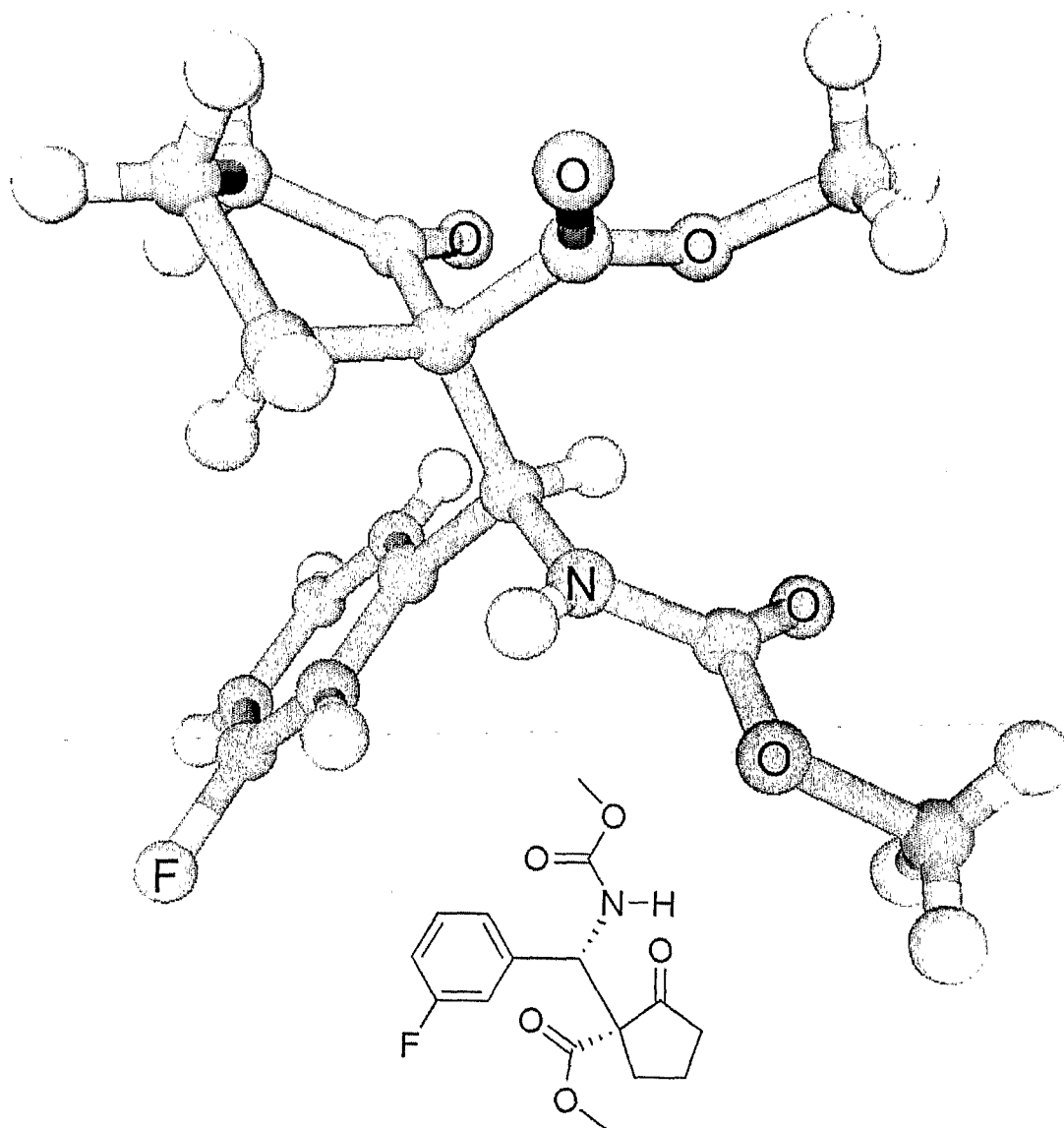


FIGURE 1 of 3

X-ray crystal structure of compound 15c: [(*S*)-(*S*)-(1-Acetyl-2-oxo-cyclopentyl)-(3-fluoro-phenyl)-methyl]-carbamic acid methyl ester)

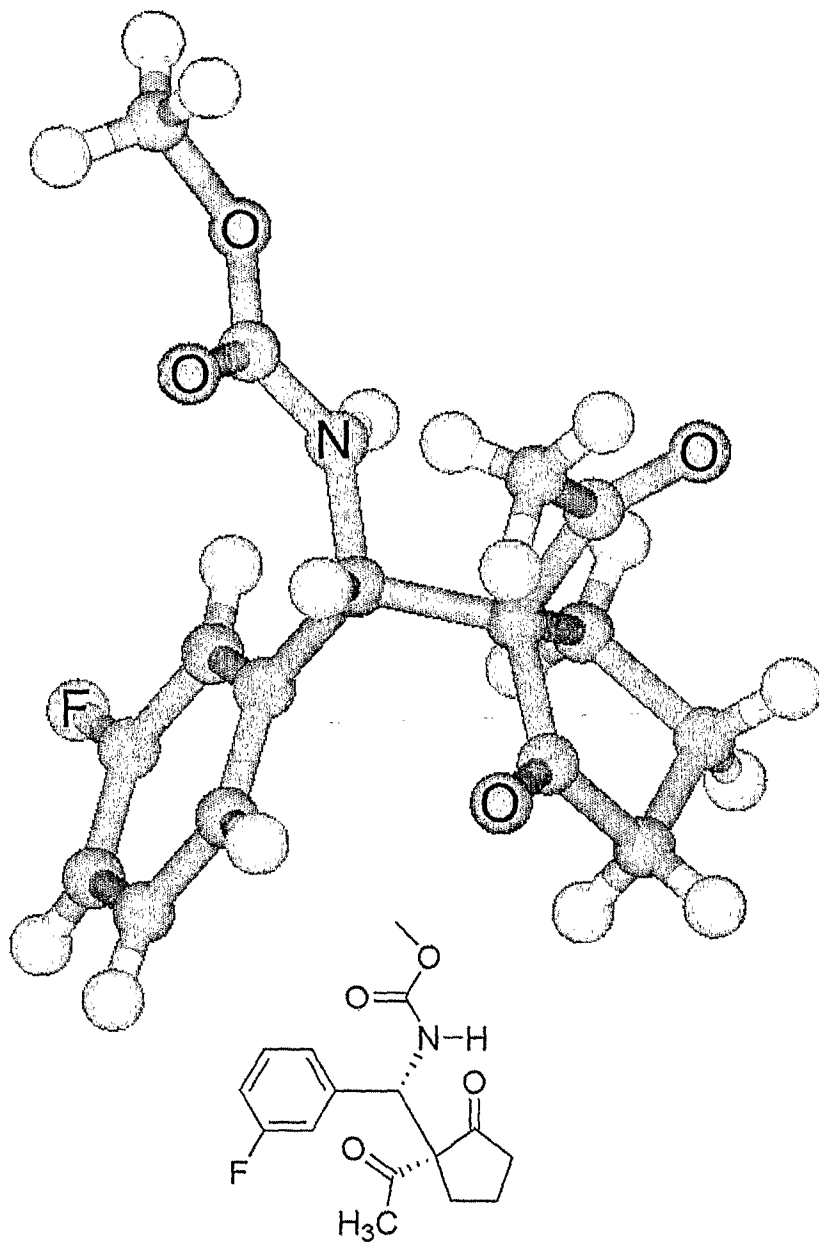


FIGURE 2 of 3

X-Ray crystal structure of compound 20c: ([(*E*)-(*S*)-1-((*S*)-1-Acetyl-2-oxo-cyclopentyl)-3-phenyl-allyl]-carbamic acid methyl ester)

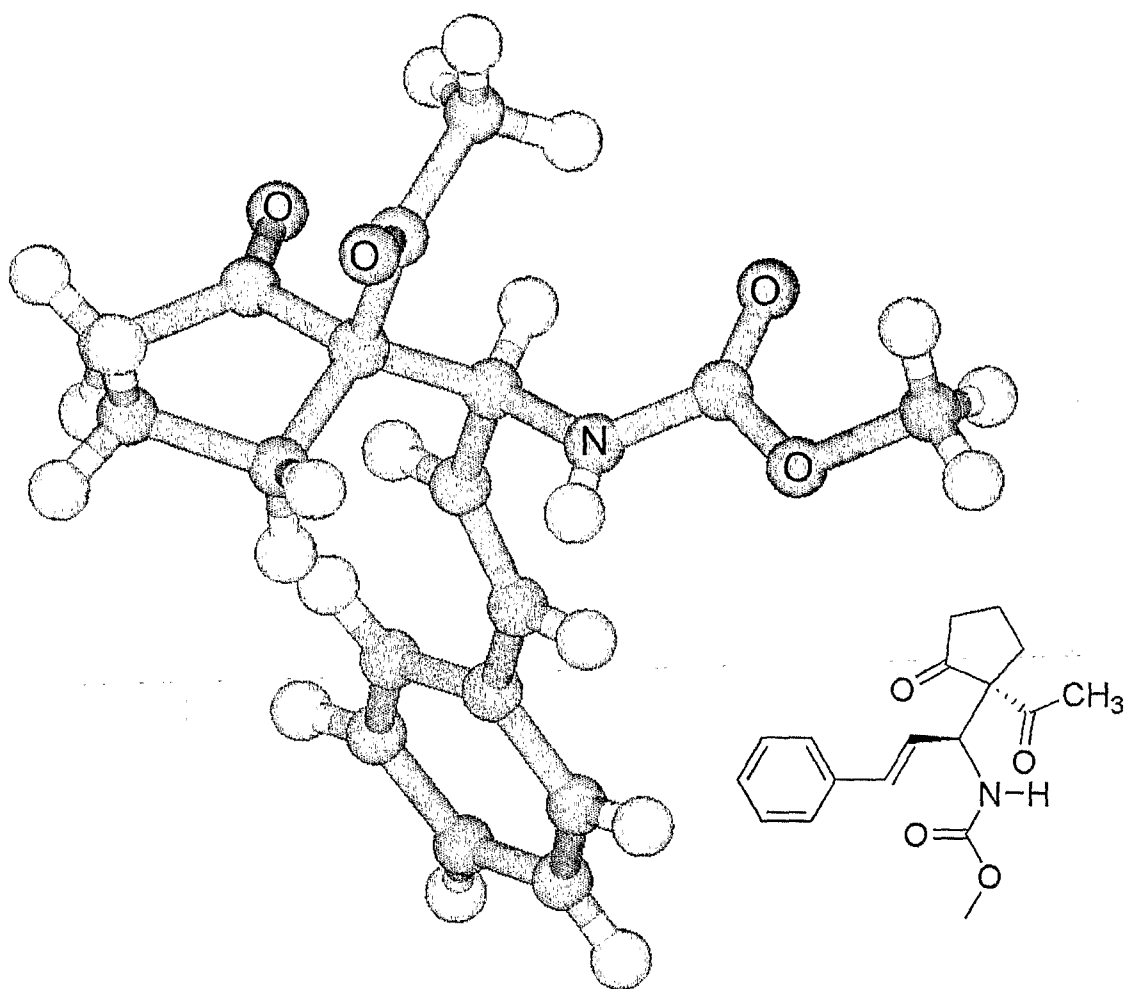


FIGURE 3 of 3