Method for the preparation of asymmetric alkynylated α-amino esters of the formula

wherein \( R_1 \) and \( R_2 \) are independently optionally substituted alkyl cycloalkyl, aryl or heteroaryl, and \( Y \) is hydrogen or a nitrogen protecting group.

9 Claims, No Drawings
METHOD FOR ASYMMETRIC ALKYNYLATION OF ALPHA-IMINO ESTERS

This application claims benefit of U.S. Provisional Application No. 60/682,647, filed May 19, 2005.

FIELD OF THE INVENTION

The present invention relates to a method is the addition of a terminal alkyne to an α-imino ester.

BACKGROUND OF THE INVENTION

Enantiomeric α-amino acids, in particular, nonproteinogenic amino acids are of exceptional and rapidly increasing popularity as important tools in protein engineering and peptide-based drug discovery. Intense research has been focused on the preparation of enantiomerically enriched unnatural α-amino acids. Several approaches, for example, bioresolution routes as well as the rhodium-catalyzed asymmetric hydrogenation of enamides have shown good promise. However, there is still a need for an efficient and technically feasible method for the convenient synthesis of different types of unnatural amino acids derivatives.

An attractive strategy to accomplish such syntheses is the enantioselective nucleophilic addition to α-imino esters. This can be useful because a new chiral center and a new carbon-carbon bond can be established in a single operation and an appropriately designed side chain can be introduced as well. Prior work in the field mainly focused on the catalytic asymmetric alkylation of α-imino ester. Nucleophiles that have been used include enol silane, allyl-metal compounds, TMStnitrate, ketones and nitroalkanes.

Recently, the alkylation of α-imino esters by directly adding terminal alkynes to an α-imino ester in the presence of Ag(I) salts under mild reaction conditions has been reported. See, Ji et al., “Efficient Synthesis of β,γ-alkynyl α-amino acid derivatives by Ag(I) catalyzed alkylation of α-imino esters”, 346 Adv. Synth. Catal. 42-44 (2004). However, this reported Ag(I)-catalyzed reaction, is not enantioselective even when a chiral ligand is employed, for example, amiposphoranes, diphasoranes and pybox.

Thus, there is need for a process to provide for the asymmetric terminal alkylation of α-amino esters that can be used to synthesize optically active unnatural α-amino acids. The present invention addresses this need.

SUMMARY OF THE INVENTION

The present invention relates to a method for preparing asymmetric alkylnylated α-amino esters of the formula

wherein R₁ and R₂ are independently optionally substituted alkyl, cycloalkyl, aryl or heteroaryl, and Y is hydrogen or a nitrogen protecting group; which method comprises reacting an α-imino ester of formula

wherein R₁ and Y have meanings as defined for formula III with a terminal alkyne of formula

wherein R₂ has meaning as defined for formula III.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method for the catalytic asymmetric alkylation of α-imino esters.

As used herein, the term “α-imino ester” refers to a compound having the formula (I)

(Compound I)

wherein

R₁ is optionally substituted alkyl, cycloalkyl, aryl or heteroaryl, and
Y is hydrogen or a nitrogen protecting group.

As used herein, the term “optionally substituted alkyl” refers to unsubstituted or substituted straight- or branched-chain hydrocarbon groups having one to twenty carbon atoms, e.g., one to seven carbon atoms. Examples of unsubstituted alkyl groups, include, but are not limited to, methyl, ethyl, propyl, isopropyl (′pr), n-butyl, t-butyl, isobutyl, pentyl, neopentyl, hexyl, isohexyl, heptyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more of the following groups: hydroxyl, alkylamino, dialkylamino, cycloalkyl, alkenyl or alkoxy.

As used herein, the term “lower alkyl” refers to those optionally substituted alkyl groups as described above having one to six carbon atoms.

As used herein, the term “alkenyl” refers to any one of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon double bond at the point of attachment. Useful are groups having two to four carbon atoms.

As used herein, the terms “halogen”, “halide” or “halo” refer to fluorine, chlorine, bromine and iodine.

As used herein, the term “alkoxy” refers to alkyl-O—.

As used herein, the term “cycloalkyl” refers to optionally substituted monocyclic aliphatic hydrocarbon groups of three to six carbon atoms, which may be substituted by one or more substituents, such as alkyl or alkoxy.
Examples of monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

As used herein, the term "aryl" refers to monocyclic or bicyclic aromatic hydrocarbon groups having six to twelve carbon atoms in the ring portion, such as phenyl, biphenyl, naphthyl and tetrahydrophenanthryl, each of which may optionally be substituted by one to four substituents, such as optionally substituted alkyl, cycloalkyl or allyloxy.

As used herein, the term "monocyclic aryl" refers to optionally substituted phenyl as described under aryl.

As used herein, the term "heteroaryl" refers to an aromatic heterocycle, e.g., monocyclic or bicyclic aryl, such as pyrrolyl, pyrazolyl, imidazolyl, triazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furyl, thiophenyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzothiazolyl, benzoxazolyl, benzothienyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzofuryl and the like; optionally substituted by, e.g., lower alkyl or lower alkoxy.

As used herein, the term "nitrogen protecting group" refers to substituents that can be introduced to protect nitrogen from undesired reactions with reaction components under the conditions used for carrying out a particular chemical transformation of the present invention. The need and choice of protecting groups for a particular reaction is known to one skilled in the art and depends on the structure and stability of the molecule of which the substituent is a part and the reaction conditions.


Examples of suitable nitrogen protecting groups for Y include, but are not limited to: p-methoxyphenoxy ("PMP"), benzyl, methyl, and triphenylmethyl. Particularly useful are PMP and benzylic.

As used herein, the term "terminal alkyne" refers to a compound having the formula (II)

```
\[ \text{II} \]
```

wherein

\[ \text{R}_3 \]

is optionally substituted alkyl, cycloalkyl, aryl or heteroaryl.

As used herein, the term "asymmetric alkylnylated \( \alpha \)-imino ester refers to a compound having the formula (III):

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\[ \text{III} \]
```

wherein \( Y, R_1, \) and \( R_2 \) are as defined above.

Catalysts useful in the present invention comprise chiral ligands bound to a transition metal source, e.g., a transition metal, a transition metal salt or a transition metal complex.

Such catalysts can be generated in situ or isolated prior to use.

Suitable transition metals for the catalyst system include, but are not limited to copper (Cu), iridium (Ir), nickel (Ni), palladium (Pd), platinum (Pt), rhodium (Rh) and ruthenium (Ru) and salts and complexes thereof. Particularly useful, e.g., is copper and complexes thereof. Further examples of such transition metal sources can be found, e.g., in Seyden-Penne, Chiral Auxiliaries and Ligands in Asymmetric Synthesis, John Wiley & Sons, Inc., NY (1995), which is hereby incorporated by reference.

Examples of transition metal complexes include, but are not limited to, \( \text{IrCl}_2\text{COD}, \text{Zn(OtTf)}_2, \text{ZnCl}_2, \text{Sco(OtTf)}_3, \text{CuO}_2, \text{CuOAc}, \text{CuCl}, \text{Cu}_2\text{B}_{12}, \text{CuBr}, \text{CuPF}_3\cdot4\text{MeCN}, \text{CuOTf}0.5\text{C}_6\text{H}_6, \text{and Cu(OtTf)}_2. \) However, particularly useful as transition metal sources, are CuPF_3\cdot4MeCN and CuOTf0.5C_6H_6.

Examples of chiral ligands include, but are not limited to, the following chiral ligands designated as 4, 5, 6, 7, 8a, 8b and 9 and enantiomers thereof, and enantiomeric mixtures thereof. However, particularly useful, are chiral ligands: 5, 7, 8a and 9, and enantiomers thereof and enantiomeric mixtures thereof. Chiral ligand 4 is 2,2'-bis (diphenylphosphino)-1,1'-binaphthyl (or, "Binap"). Chiral ligand 6 is 1-(2-Diphenylphosphino-1-naphthyl)isoquinoline (or, "Quinap"). Chiral ligand 9 is bis(oxazolidin-2-yl)pyridine (or, "Pybox").
Examples of amine bases include, but are not limited to, PMP—H₂, Et₃N, Pr₃NH, Pr₂EtN, Cy₂NMe. However, particularly useful is PMP—H₂.

Each of the alkynylation reactions of Compound I (discussed below) is conducted in accordance with the following general procedure:

All reactions are conducted under a nitrogen atmosphere. All chemicals and solvents, e.g., organic solvents, are used without further purification unless otherwise stated. CH₂Cl₂, an organic solvent, is distilled from CaH₂. Compound I is synthesized according to methods known to one of ordinary skill in the art. See, e.g., Andrew Taggi et al., “Amino esters: versatile substrates for the catalytic asymmetric synthesis of α- and β-amino acids and β-lactams,” 36 Acc. Chem. Res. 10-19 (2003).

Pybox (the chiral ligand 9) (0.7 mg, 0.025 mmol) and CuOTf·0.5C₆H₆ (6.5 mg, 0.025 mmol) are added to a dried 10-mL round-bottom flask containing a magnetic stirring bar. CH₂Cl₂ (1.0 mL) is added, and the mixture is stirred at room temperature for one hour. Other organic solvents that can also be used in the present invention are diethyl ether, tetrahydrofuran and dioxane. The solution is cooled to a temperature of about -10°C. The reaction temperature can range from about -40°C to about 30°C; e.g., from about -20°C to 0°C. The α-aminoo ester (Compound I) (52.3 mg, 0.25 mmol) in CH₂Cl₂ (400 µL), the terminal alkyne (Compound II) (0.25 mmol) and PMP—NH₂ (an amine base) (3.2 mg, 0.025 mmol) in CH₂Cl₂ (100 µL) are sequentially added under vigorous stirring. The resulting solution was stirred at -10°C and the reaction was monitored by TLC. Upon completion of the reaction, the mixture is filtered through a 1 cm×1 cm plug of silica gel which is subsequently washed with EtOAc (10 mL). The solution is poured into a separatory funnel and mixed well with EtOAc (25 mL) and H₂O (5 mL). The aqueous layer is discarded, and the organic layer is washed with saturated brine (5 mL). The resulting organic layer is dried over anhydrous Na₂SO₄, filtered, and then concentrated in vacuo. The purification of the residue by flash column chromatography (9:1 hexane-EtOAc as eluents) yields the desired alkynylation products as a light yellow oil.

For analysis, ¹H NMR and ¹³C NMR spectra are recorded in CDCl₃ on a Varian AS 500 (500 and 125 MHz respectively) spectrometer at room temperature. Chemical shifts (δ) are expressed in ppm and J values are given in Hz. HRMS are carried out with ESI method on a Fisons VG platform or a Finnigan Model MAT-95 spectrometer. HPLC analyses are performed using a Waters Model 600 with a Waters 486 UV detector. Optical rotations are measured on a Perkin-Elmer Model 341 polarimeter in a 10 cm cell. Flash column chromatography was performed on silica gel (230-400 mesh).

**Example 1**

 Identification of Appropriate Transition Metals for Catalyst

| TABLE 1 |

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IrCl₂COD, Zn(OTf)₂, ZnCl₂, Sc(OTf)₃, CuO₂, CuOAc</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuCl₂CuBr</td>
<td>&lt;10</td>
</tr>
<tr>
<td>3</td>
<td>CuPF₆·4MeCN</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>CuOTf·0.5C₆H₆</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>CuOTf₂</td>
<td>35</td>
</tr>
</tbody>
</table>

Condition:
1 (0.5 mmol) and
2a (1.0 mmol) in CH₂Cl₂ (5 mL).

*Isolated yields.
A number of transition metals such as Zn(II), Cu(I)/(II), Ir(I) and Sc(III) as listed in Table 1, supra, are investigated. The addition of 4-phenyl-1-butyne 2a to α-imino ester 1 is not observed when IrCl₂COD, Zn(OTf)₂, ZnCl₂ or Sc(OTf)₃ is used as a catalyst precursor (entry 1 of Table 1). The desired product 3a is obtained with good yields when catalyst precursors CuPF₆·4MeCN (entry 3) and CuOTf·0.5C₆H₆ are used (entry 4). Some other copper complexes, e.g., including Cu(OTf)₂ (entry 5), CuCl, CuBr (entry 2), CuO₂ and CuOAc (entry 1) show lower or relatively undetectable catalytic activity.

**EXAMPLE 2**

Effect of the Inclusion of an Amine Base

**TABLE 2**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield* (%)</th>
<th>Ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuPF₆·4MeCN/4</td>
<td>—</td>
<td>trace</td>
<td>nd.</td>
</tr>
<tr>
<td>2</td>
<td>CuPF₆·4MeCN/5</td>
<td>—</td>
<td>92</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>CuPF₆·4MeCN/6</td>
<td>—</td>
<td>trace</td>
<td>nd.</td>
</tr>
<tr>
<td>4</td>
<td>CuPF₆·4MeCN/7</td>
<td>—</td>
<td>75</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>CuPF₆·4MeCN/8a</td>
<td>—</td>
<td>73</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>CuPF₆·4MeCN/8a</td>
<td>A</td>
<td>trace</td>
<td>nd.</td>
</tr>
<tr>
<td>7</td>
<td>CuPF₆·4MeCN/8a</td>
<td>B</td>
<td>trace</td>
<td>nd.</td>
</tr>
<tr>
<td>8</td>
<td>CuPF₆·4MeCN/8a</td>
<td>C</td>
<td>86</td>
<td>57</td>
</tr>
<tr>
<td>9</td>
<td>CuPF₆·4MeCN/8a</td>
<td>D</td>
<td>90</td>
<td>57</td>
</tr>
<tr>
<td>10</td>
<td>CuPF₆·4MeCN/8a</td>
<td>D</td>
<td>93</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>CuPF₆·4MeCN/9</td>
<td>D</td>
<td>91</td>
<td>77</td>
</tr>
<tr>
<td>12</td>
<td>CuOTf·0.5C₆H₆/9</td>
<td>D</td>
<td>91</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td>CuOTf·0.5C₆H₆/9</td>
<td>D</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>14</td>
<td>CuOTf·0.5C₆H₆/9</td>
<td>D</td>
<td>78</td>
<td>56</td>
</tr>
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</table>

Condition:

1. (0.25 mmol) and 2a (0.5 mmol) in CH₂Cl₂ (1.5 mL) at 0°C.

A: 0.5 eq. Et₃N,
B: 0.5 eq. P₂NH₂,
C: 0.5 eq. PMPNH₂,
D: 0.1 eq. PMPNH₂,

*Isolated yields.

*Reaction is conducted at about −10°C.
The addition of amine bases and the use of other copper sources and structurally different Pybox ligands are explored in Table 2. It is known that metal alkynylides employed in C—C bond formation reactions are generated in the presence of an amine base, such as Et$_3$N. Surprisingly, in the alkynylation system of the present invention, the reaction is markedly retarded by adding 0.5 eq Et$_3$N or $^{9}$Pr$_2$NH (entries 6, 7). In contrast, the use of 0.5 or 0.1 equivalent PMP—NH$_2$ as additives increases the yields of 3 from 73% to 86% and 90% respectively with no diminution of enantioselectivity (entries 5, 8, 9). Subsequent careful optimization leads to conditions using CuOTf·0.5C$_6$H$_6$ as a transition metal source and conventionally more restricted Pybox (9) as a chiral ligand at about −10°C. Affer the desired product 3 in 90% and 85% enantiomeric excess (“ee”).

**EXAMPLE 3**

Alkylation of α-imino Esters Catalyzed by CuOTf·0.5C$_6$H$_6$/Pybox (9)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Product</th>
<th>Yield* (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>3a</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>3b</td>
<td>92</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>3c</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>3d</td>
<td>92</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>3e</td>
<td>63</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>3f</td>
<td>55</td>
<td>48</td>
</tr>
</tbody>
</table>

**TABLE 3**

Alkylation of α-imino ester catalyzed by CuOTf·0.5C$_6$H$_6$/Pybox (9)

<table>
<thead>
<tr>
<th>PMP</th>
<th>N</th>
<th>CO$_2$Et</th>
<th>+</th>
<th>“R”</th>
<th>10% cat.</th>
<th>CH$_2$Cl$_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yields.

The direct alkynylation of α-imino ester 1 using a spectrum of terminal alkynes are performed, and the representative results are summarized in Table 3, supra. In a like manner as in the addition of 4-phenyl-1-butyne (entry 1), the addition reactions of 3-phenyl propyne (entry 2), 1-octyne (entry 3) and cyclopentylacetylene (entry 4) provide the corresponding alkynylation products in good yields and enantiomeric excesses. Whereas, using alkynes with bulky substituted groups close to the triple bond, such as trimethylsilylacetylene (entry 6), led to lower reaction rate and enantioselectivity. Noticeably, the present cyclopentylacetylene addition to imino ester 1 (entry 4) represents a new direct and convenient access to α-imino acid derivatives containing conformationally constrained cyclopropene rings.

The following lists the conditions of the analyses of the products in Table 3 of Example 3, i.e., 3a-3f.

Ethyl-2-(p-methoxyphenylamino)-6-phenyl-3-hexynoate. Compound 3a is obtained in 90% yield by using the general procedure. The ee value (85%) is determined by HPLC analysis using a chiral column [Chiralcel OD, 90:10 hexane:i-PrOH, 1.0 mL/min: $t_{R}$ (major)=11.46 min, $t_{R}$ (minor)=16.75 min. [α]$_D^{20}$ = 64.7° (c 0.5, CHCl$_3$); $^{1}$H NMR (500 MHz, CDCl$_3$): δ=7.28-7.27 (m, 2H), 7.10-6.71 (m, 3H), 6.80-6.78 (m, 2H), 6.67-6.65 (m, 2H), 4.69 (t, 1H, J=2.3 Hz), 4.27-4.24 (q, 2H, J=7.5 Hz), 3.76 (s, 3H), 2.80-2.77 (t, 2H, J=7.3 Hz), 2.49-2.46 (dt, 2H, J=7.3, 2.0 Hz), 3.13-3.08 (t, 3H, J=7.3 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): δ=169.5, 153.7, 140.6, 137.6, 128.7, 128.6, 126.6, 116.5, 114.9, 84.8, 75.4, 62.5, 55.9, 50.5, 34.9, 21.1, 14.3; HRMS (ESI) calc. for C$_2$H$_2$N$_2$O$_3$ [M+H]$:^{+}$ 338.1756; found: 338.1782.

Ethyl-2-(p-methoxyphenylamino)-5-phenyl-3-pentynoate. Compound 3b is obtained in 92% yield by using the general procedure. The ee value (83%) is determined by HPLC analysis using a chiral column [Chiralcel OD, 90:10 hexane:i-PrOH, 1.0 mL/min: $t_{R}$ (minor)=21.49 min, $t_{R}$ (major)=35.00 min. [α]$_D^{20}$ = 38.1° (c 0.4, CHCl$_3$); $^{1}$H NMR (500 MHz, CDCl$_3$): δ=7.31-7.24 (m, 5H), 6.83-6.81 (m, 2H), 6.74-6.72 (m, 2H), 4.83 (t, 1H, J=2.2 Hz), 4.32-4.28 (q, 2H, J=7.2 Hz), 3.76 (s, 3H), 3.62 (d, 3H, 2.0 Hz), 1.27 (t, 3H, J=7.3 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): δ=169.5, 153.6, 139.7, 136.3, 128.7, 128.1, 126.9, 116.4, 115.0, 82.9, 72.8, 62.5, 55.8, 50.5, 25.2, 14.3; HRMS (ESI): Calc. for C$_2$H$_2$N$_2$O$_3$ (M+1): 324.1600, found (M+1): 324.1596.

Ethyl-2-(p-methoxyphenylamino)-3-decyynoate. Compound 3c is obtained in 89% yield by using the general procedure. The ee value (91%) is determined by HPLC analysis using a chiral column [Chiralcel OD, 90:10 hexane:i-PrOH, 1.0 mL/min: $t_{R}$ (major)=9.96 min, $t_{R}$ (minor)=12.63 min. [α]$_D^{20}$ = -62.3° (c 0.4, CHCl$_3$); $^{1}$H NMR (500 MHz, CDCl$_3$): δ=6.79-6.77 (m, 2H), 6.70-6.68 (m, 2H), 4.70 (t, 1H, J=2.5 Hz), 4.29-4.24 (q, 2H, 7.3 Hz), 3.75 (s, 3H), 2.19-2.15 (dt, 2H, J=7.3, 2.0 Hz), 1.43-1.44 (m, 2H), 1.34-1.20 (m, 13H), 0.89-0.86 (t, 3H, J=7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): δ=169.6, 153.7, 139.3, 116.6, 114.9, 86.0, 75.0, 62.4, 55.8, 50.6, 31.5, 28.6, 28.5, 22.8, 18.9, 14.3, 14.2; HRMS (ESI) calc. for C$_{22}$H$_{24}$N$_2$O$_3$ [M+H]$:^{+}$ 318.0693; found: 318.0191.

Ethyl-2-(p-methoxyphenylamino)-4-cyclopropyl-3-butyrate. Compound 3d is obtained in 92% yield by using the general procedure. The ee value (79%) is determined by HPLC analysis using a chiral column [Chiralcel OD, 95:15 hexane:i-PrOH, 1.0 mL/min: $t_{R}$ (major)=11.08 min, $t_{R}$ (minor)=19.46 min. [α]$_D^{20}$ = -47.4° (c 0.7, CHCl$_3$); $^{1}$H NMR
Ethyl-2-(p-methoxyphenylamino)-5-(trimethylsilyl)-3-pentynoate. Compound 3e is obtained in 63% yield by using the general procedure. The ee value (77%) is determined by HPLC analysis using a chiral column [Chiralcel AD, 90:10 hexane:i-PrOH, 0.7 mL/min: $t_R$ (major)=18.03 min, $t_R$ (minor)=27.63 min]. $[\alpha]_D^{20}=-36.3^\circ$ (c 0.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta=6.79-6.72$ (m, 2H), 6.68-6.66 (m, 2H), 4.71 (t, 1H, 2.5 Hz), 4.28-4.24 (q, 2H, $J=7.2$ Hz), 3.74 (s, 3H), 1.46-1.45 (d, 2H, $J=3.0$ Hz), 1.32-1.29 (t, 3H, $J=7.3$ Hz), 0.04 (s, 9H); $\delta=169.8, 153.5, 139.6, 116.3, 114.9, 83.7, 73.9, 62.2, 55.9, 50.5, 14.3, 7.3, -19; HRMS (ESI) calc. for C$_{15}$H$_{25}$NO$_3$Si [M+1]$^+$: 320.1682, found: 320.1711.

Ethyl-2-(p-methoxyphenylamino)-4-(trimethylsilyl)-3-butynoate. Compound 3f is obtained in 55% yield by using the general procedure. The ee value (48%) is determined by HPLC analysis using a chiral column [Chiralcel AD, 90:10 hexane:i-PrOH, 1.0 mL/min: $t_R$ (major)=6.97 min, $t_R$ (minor)=9.15 min]. $[\alpha]_D^{20}=-98.5^\circ$ (c 0.3, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$): $\delta=6.65-6.63$ (m, 2H), 6.55-6.53 (m, 2H), 4.58 (s, 1H), 4.15-4.11 (q, 2H, $J=7.0$), 3.60 (s, 3H), 1.15(t, 3H, $J=7.0$ Hz); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta=169.0, 153.6, 139.5, 116.4, 114.9, 100.1, 90.0, 62.5, 55.8, 51.2, 14.2, -0.1; HRMS (ESI) calc. for C$_{16}$H$_{34}$NO$_3$Si [M+1]$^+$: 306.1525, found: 306.1529.

**EXAMPLE 4**

Utility of Asymmetric Alkynylation α-Imino Esters

The products of the processes of the present invention, i.e., asymmetric alkynylation α-imino esters can be used to synthesize optically active unnatural α-amino acid derivatives. An example of this is shown in Scheme 1, below, which is a modification of the product 3b in Example 3 to yield a bis morphenylamine derivative, or (R)-12 in Scheme 1, which is a key intermediate of pharmaceutically interesting peptides used in growth hormone products.
The alkynylation product 3b is hydrogenated to 10 in quantitative yield. Subsequent treatment of 10 with cerium ammonium nitrate (CAN) affords the target molecule in a 76% yield. The absolute configuration of 3b is determined to be R by this transformation ([α]_D^20 \text{~} -11.7^\circ (c 0.4, CHCl_3) for (R)-12; ref 47, [α]_D^20 \text{~} +14.5^\circ (c 0.4, CHCl_3) for its S enantiomer}. In addition, semireduction of 3b in the presence of a Lindlar catalyst yields a (Z)-vinyl amino acid derivative 11, a β,γ-vinyl amino acid derivative. The catalytic asymmetric alkylation of α-imino ester 1, combined with semireduction, provides the first catalylic introduction of vinyl group to amino acid derivatives. The hydrogenation of 11 using Pd/C also furnished intermediate 10 in quantitative yield.
Without being bound to a particular theory, a speculated mechanism for the catalytic alkylation of α-imino ester is outlined in Scheme 2. The successive complexation of substrate 1 and alkyne 2 to the catalyst center produces intermediate 13 which undergoes intramolecular alkyne transfer to afford intermediate 14. Subsequent dissociation of product 3 from 14 concomitantly regenerates the catalyst.

Thus, the present invention provides a method for the asymmetric addition of a terminal alkyne to an α-imino ester that results in a good yield and good ee’s.

It is understood that while the present invention has been described in conjunction with the detailed description thereof that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the following claims. Other aspects, advantages and modifications are within the scope of the claims.

What is claimed is:

1. A method for the preparation of asymmetric alkylation α-amino esters of the formula

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   wherein R₁ and R₂ are independently optionally substituted alkyl, cycloalkyl, aryl or heteroaryl, and Y is hydrogen or a nitrogen protecting group; which method comprises reacting an α-imino ester of formula

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   wherein R₂ has meaning as defined for formula III.

   2. The method of claim 1, wherein said reacting is in the presence of a catalyst.

   3. The method of claim 2, wherein said reacting is in the presence of a catalytic amount of an amine base.

   4. The method of claim 2, wherein said amine base is PMP—N₂.

5. The method of claim 2, wherein said catalyst comprises a transition metal, a transition metal salt, or a transition metal complex.

6. The method of claim 5, wherein said transition metal complex is selected from the group consisting of CuPF₆, 4MeCN and CuOTf·0.5C₇H₆O.

7. The method of claim 5, wherein said catalyst comprises a chiral ligand.

8. The method of claim 7, wherein said chiral ligand is selected from the group consisting of

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   \text{(III)}
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   enantiomers thereof, and enantiomeric mixtures thereof.

9. The method of claim 1, wherein R₁ is alkyl.