

**N-HETEROCYCLIC CARBENE CATALYZED SYNTHESIS OF
N-PHENYLISOXAZOLIDIN-5-ONE DERIVATIVE AND SYNTHESIS OF
 β -AMINO ACID ESTER DERIVATIVE**

This invention relates to a process for preparing
5 a *N*-phenylisoxazolidin-5-one derivative comprising reacting
an α,β -unsaturated aldehyde with nitrosobenzene in the
presence of a *N*-heterocyclic carbene (NHC) catalyst. The
invention also relates to a process for preparing an
N-alkoxyphenyl protected β -amino acid ester derivative
10 comprising reacting an α,β -unsaturated aldehyde with
nitrosobenzene in the presence of a *N*-heterocyclic carbene
catalyst to form a *N*-phenylisoxazolidin-5-one derivative,
and then treating the *N*-phenylisoxazolidin-5-one derivative
with an alcohol in the presence of an acid catalyst. The
15 invention further relates to a process for preparing an
N-alkoxyphenyl protected β -amino acid ester derivative
comprising treating a *N*-phenylisoxazolidin-5-one derivative
with an alcohol in the presence of an acid catalyst.

BACKGROUND

20 *N*-Phenylisoxazolidin-5-one derivatives may be used
as intermediates in the preparation of β -amino acid esters,
which can be further converted into other biologically
important compounds, for example, β -amino acids. β -Amino
acids possess biologically important properties, occur in
25 natural products, and are the building blocks to several
bioactive compounds.

The preparation of *N*-phenylisoxazolidin-5-one
derivatives may involve carbon-nitrogen (C-N) bond forming
reactions. Catalytic methods for C-N bond formation have
30 been reported and have been applied in organic synthesis,
including in the preparation of pharmaceuticals and natural
products.

Organocatalytic reactions for forming C-N bonds are of interest, as these reactions may avoid the use of toxic and/or expensive metal catalysts. Examples of organocatalytic C-N bond formation reactions, including
5 proline-catalyzed direct α -aminations of carbonyl compounds, have been reported. *N*-Nitroso aldol reaction of enamines selectively forming *N*-hydroxyaminoketones have also been reported (see, for example, Yamamoto, H. and Momiyama, N. *J. Am. Chem. Soc.* 2005, 127, 1080; Momiyama, N.; Yamamoto, Y.;
10 Yamamoto, H. *J. Am. Chem. Soc.* 2007, 129, 1190). The enantioselective conjugate addition of *N*-silyloxy carbamates to enals using imidazolidinone catalysts has been used to obtain enantio-enriched β -amino aldehydes. The reaction of enals and *N*-protected hydroxylamine in the presence of
15 chiral pyrrolidine catalysts, forming 5-hydroxyisoxazolidines that are further converted to the corresponding β -amino acids or γ -amino alcohols, has been reported.

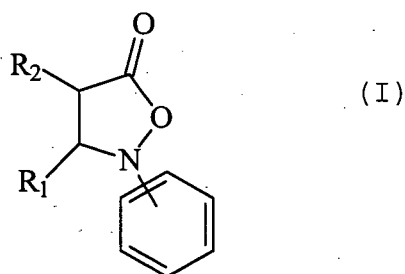
In addition to C-N bond formation, organocatalytic
20 reactions for forming carbon-carbon (C-C) bonds have been reported. For example, NHC-catalyzed activation of carbonyl compounds has been reported as a potential method for metal-free C-C bond forming reactions via the nucleophilic "Breslow intermediate", or the homoenolate equivalent
25 species (see, for example, Sohn, S. S.; Rosen, E. L.; Bode, J. F. *J. Am. Chem. Soc.* 2004, 126, 14370; Burstein, C. and Glorius, F. *Angew. Chem., Int. Ed.* 2004, 43, 6205). The ability of thiamine-dependent enzymes to convert aromatic nitroso compounds into hydroxamic acids has been reported.

30 Additional approaches to synthesizing *N*-phenylisoxazolidin-5-one derivatives and β -amino acid ester derivatives involving readily available reactants and catalysts are desirable.

SUMMARY

In one broad aspect of the present invention, there is provided a process for preparing a *N*-phenylisoxazolidin-5-one derivative comprising reacting an α,β -unsaturated aldehyde with nitrosobenzene in the presence of a *N*-heterocyclic carbene (NHC) catalyst.

In an embodiment of the present invention, there is provided a process for preparing a *N*-phenylisoxazolidin-5-one derivative represented by the formula (I):



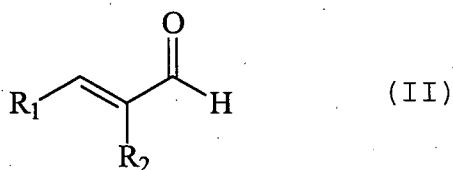
wherein:

- 15 R_1 is a hydrogen atom, a halogen atom, a nitrile group, a C_{1-6} alkyl group which may be substituted with one or more substituents which are the same or different, a C_{2-6} alkenyl group which may be substituted with one or more substituents which are the same or different, a C_{2-6} alkynyl group which
- 20 may be substituted with one or more substituents which are the same or different, a C_{3-8} cycloalkyl group which may be substituted with one or more substituents which are the same or different, a C_{3-8} cycloalkenyl group which may be substituted with one or more substituents which are the same
- 25 or different, a C_{6-14} aryl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl- C_{1-6} alkyl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl- C_{2-6} alkenyl group which may be substituted with one or

more substituents which are the same or different, a C₆₋₁₄ aryl-C₂₋₆ alkynyl group which may be substituted with one or more substituents which are the same or different, a 4- to 10-membered non-aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen and which group may be substituted with one or more substituents which are the same or different, a 5- to 14-membered aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen and which group may be substituted with one or more substituents which are the same or different or a C₁₋₆ alkoxy carbonyl group which may be substituted with one or more substituents which are the same or different; and

R₂ is a hydrogen atom, a C₁₋₆ alkyl group which may be substituted with one or more substituents which are the same or different, a C₂₋₆ alkenyl group which may be substituted with one or more substituents which are the same or different, a C₂₋₆ alkynyl group which may be substituted with one or more substituents which are the same or different, a C₃₋₈ cycloalkyl group which may be substituted with one or more substituents which are the same or different or a C₃₋₈ cycloalkenyl group which may be substituted with one or more substituents which are the same or different,

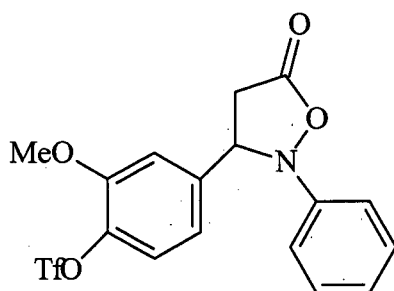
which process comprises reacting an α,β -unsaturated aldehyde represented by the formula (II):



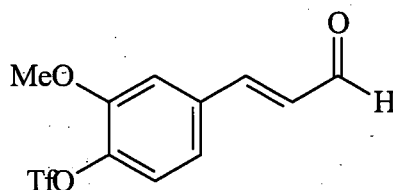
wherein each of R₁ and R₂ is as defined above, with nitrosobenzene in the presence of a NHC catalyst.

In an exemplary embodiment of the present invention, R_2 is hydrogen.

In a further aspect of the present invention, there is provided a process for preparing a
5 *N*-phenylisoxalidin-5-one derivative represented by the formula:



10 comprising reacting an α,β -unsaturated aldehyde represented by the formula:

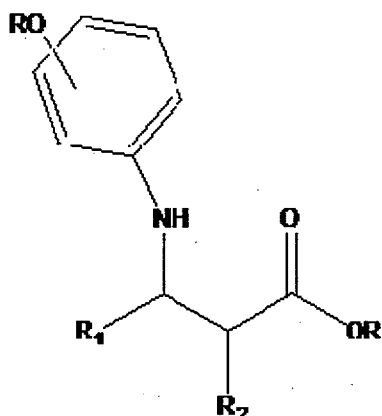


15 with nitrosobenzene in the presence of a NHC catalyst.

In another broad aspect of the present invention, there is provided a process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative comprising reacting
20 an α,β -unsaturated aldehyde with nitrosobenzene in the presence of a *N*-heterocyclic carbene (NHC) catalyst to form a *N*-phenylisoxazolidin-5-one derivative and then treating the *N*-phenylisoxazolidin-5-one derivative with an alcohol in the presence of an acid catalyst.

25 In an embodiment of the present invention, there is provided a process for preparing an *N*-alkoxyphenyl

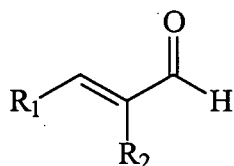
protected β -amino acid ester derivative represented by the formula (IV):



(IV)

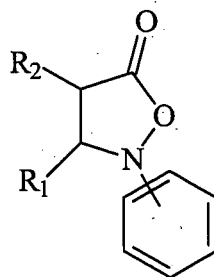
5 wherein each of R_1 and R_2 is as defined above and R_8 is a C_{1-6} alkyl group, which process comprises:

(a) reacting an α,β -unsaturated aldehyde represented by the formula (II):



(II)

wherein each of R_1 and R_2 is as defined above, with nitrosobenzene in the presence of a NHC catalyst to form a *N*-phenylisoxazolidin-5-one derivative represented by the formula (I):



(I)

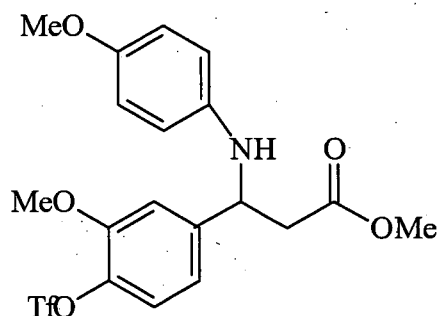
wherein each of R_1 and R_2 is as defined above; and

(b) then treating the *N*-phenylisoxazolidin-5-one derivative with an alcohol represented by the formula R_8OH wherein R_8 is as defined above, in the presence of an acid catalyst.

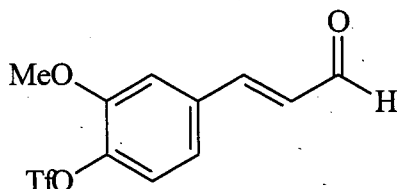
In an exemplary embodiment of the present invention, the alcohol is methanol.

In an exemplary embodiment of the present invention, the *N*-alkoxyphenyl protected β -amino acid ester derivative is an *N*-*p*-alkoxyphenyl protected β -amino acid ester derivative.

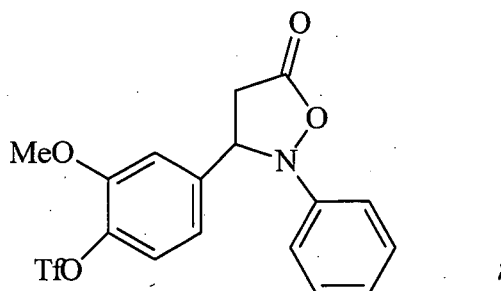
In still another aspect of the present invention, there is provided a process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula:



comprising reacting an α,β -unsaturated aldehyde represented by the formula:



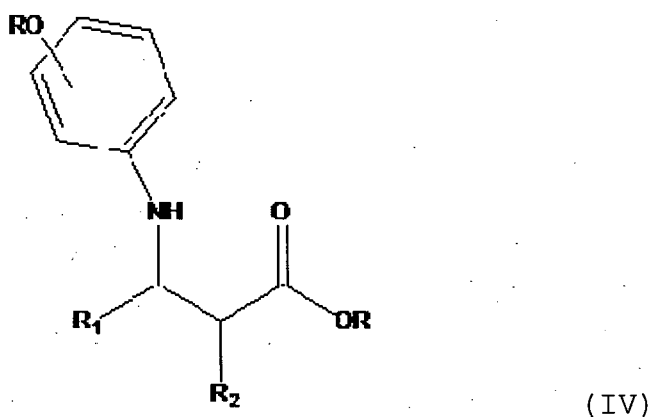
with nitrosobenzene in the presence of a NHC catalyst to form a *N*-phenylisoxazolidin-5-one derivative represented by the formula:



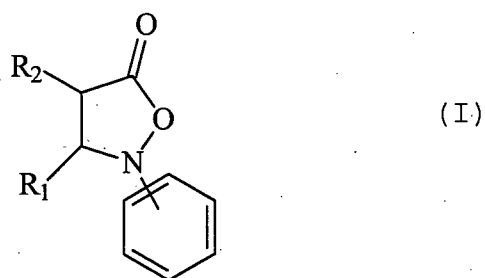
5 and then treating the *N*-phenylisoxazolidin-5-one derivative with methanol in the presence of an acid catalyst.

In a further broad aspect of the present invention, there is provided a process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative
 10 comprising treating a *N*-phenylisoxazolidin-5-one derivative with an alcohol in the presence of an acid catalyst.

In an embodiment of the present invention, there is provided a process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the
 15 formula (IV):



wherein each of R_1 , R_2 and R_3 is as defined above, which
 20 process comprises treating a *N*-phenylisoxazolidin-5-one derivative represented by the formula (I):

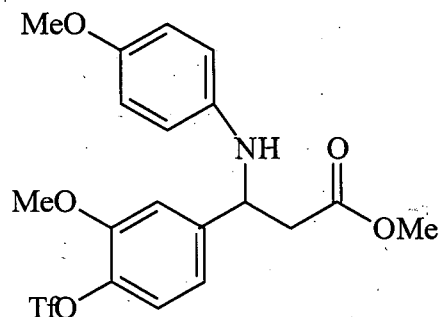


wherein each of R_1 and R_2 is as defined above, with an alcohol represented by the formula R_8OH wherein R_8 is as defined above, in the presence of an acid catalyst.

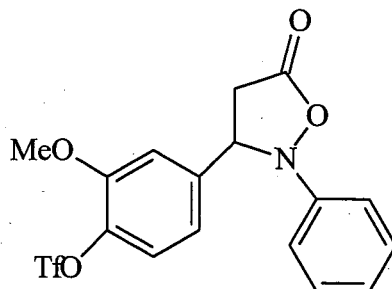
In an exemplary embodiment of the present invention, the alcohol is methanol.

In an exemplary embodiment of the present invention, the *N*-alkoxyphenyl protected β -amino acid ester derivative is an *N*-*p*-alkoxyphenyl protected β -amino acid ester derivative.

In still a further aspect of the present invention, there is provided a process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula:



comprising treating a *N*-phenylisoxalidin-5-one derivative represented by the formula:



with methanol in the presence of an acid catalyst.

DETAILED DESCRIPTION

I. Process for Preparing N-Phenylisoxazolidin-5-one Derivative

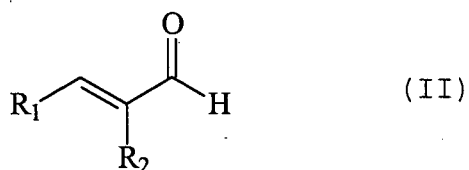
In an embodiment of the process of the present invention to prepare a N-phenylisoxazolidin-5-one derivative, an α,β -unsaturated aldehyde may be reacted with nitrosobenzene in the presence of a NHC catalyst.

A. α,β -Unsaturated Aldehyde

The α,β -unsaturated aldehyde that may be used in the present invention is not particularly limited.

In an embodiment of the present invention, the α,β -unsaturated aldehyde may be, for example, and without limitation, an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, heterocyclic or alkoxycarbonyl α,β -unsaturated aldehyde which may be substituted with one or more substituents which are the same or different.

In an embodiment of the present invention, the α,β -unsaturated aldehyde may be represented by, for example, and without limitation, a compound of the formula (II):



wherein:

- 5 R_1 is a hydrogen atom, a halogen atom, a nitrile group, a C_{1-6} alkyl group which may be substituted with one or more substituents which are the same or different, a C_{2-6} alkenyl group which may be substituted with one or more substituents which are the same or different, a C_{2-6} alkynyl group which
- 10 may be substituted with one or more substituents which are the same or different, a C_{3-8} cycloalkyl group which may be substituted with one or more substituents which are the same or different, a C_{3-8} cycloalkenyl group which may be substituted with one or more substituents which are the same
- 15 or different, a C_{6-14} aryl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl- C_{1-6} alkyl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl- C_{2-6} alkenyl group which may be substituted with one or
- 20 more substituents which are the same or different, a C_{6-14} aryl- C_{2-6} alkynyl group which may be substituted with one or more substituents which are the same or different, a 4- to 10-membered non-aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or
- 25 oxygen and which group may be substituted with one or more substituents which are the same or different, a 5- to 14-membered aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen and which group may be substituted with one or more
- 30 substituents which are the same or different or a C_{1-6} alkoxy carbonyl group which may be substituted with one or more substituents which are the same or different; and

R₂ is a hydrogen atom, a C₁₋₆ alkyl group which may be substituted with one or more substituents which are the same or different, a C₂₋₆ alkenyl group which may be substituted with one or more substituents which are the same or different, a C₂₋₆ alkynyl group which may be substituted with one or more substituents which are the same or different, a C₃₋₈ cycloalkyl group which may be substituted with one or more substituents which are the same or different or a C₃₋₈ cycloalkenyl group which may be substituted with one or more substituents which are the same or different.

The C₁₋₆ alkyl group of the C₁₋₆ alkyl group which may be substituted, may be, for example, and without limitation, any straight or branched alkyl, for example, methyl, ethyl, n-propyl, i-propyl, sec-propyl, n-butyl, i-butyl, sec-butyl, t-butyl, n-pentyl, i-pentyl, sec-pentyl, t-pentyl, n-hexyl, i-hexyl, 1,2-dimethylpropyl, 2-ethylpropyl, 1-methyl-2-ethylpropyl, 1-ethyl-2-methylpropyl, 1,1,2-trimethylpropyl, 1,1,2-triethylpropyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 2-ethylbutyl, 1,3-dimethylbutyl, 2-methylpentyl or 3-methylpentyl. The C₁₋₆ alkyl group may be, for example, and without limitation, optionally interrupted with one or more heteroatoms which are independently nitrogen, sulfur or oxygen.

The C₂₋₆ alkenyl group of the C₂₋₆ alkenyl group which may be substituted, may be, for example, and without limitation, any straight or branched alkenyl, for example, vinyl, allyl, isopropenyl, 1-propene-2-yl, 1-butene-1-yl, 1-butene-2-yl, 1-butene-3-yl, 2-butene-1-yl or 2-butene-2-yl. The C₂₋₆ alkenyl group may be, for example, and without limitation, optionally interrupted with one or more heteroatoms which are independently nitrogen, sulfur or oxygen.

The C₂₋₆ alkynyl group of the C₂₋₆ alkynyl group which may be substituted, may be, for example, and without limitation, any straight or branched alkynyl, for example, ethynyl, propynyl, butynyl, pentynyl or hexynyl. The C₂₋₆ alkynyl group may be, for example, and without limitation, optionally interrupted with one or more heteroatoms which are independently nitrogen, sulfur or oxygen.

The C₃₋₈ cycloalkyl group of the C₃₋₈ cycloalkyl group which may be substituted, may be, for example, and without limitation, cyclopropanyl, cyclobutanyl, cyclopentanyl, cyclohexanyl or cycloheptanyl.

The C₃₋₈ cycloalkenyl group of the C₃₋₈ cycloalkenyl group which may be substituted, may be, for example, and without limitation, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl or cycloheptenyl.

The C₆₋₁₄ aryl group of the C₆₋₁₄ aryl group which may be substituted, may be, for example, and without limitation, phenyl, pentalenyl, indenyl, naphthyl, azulenyl, heptalenyl, benzocyclooctenyl or phenanthrenyl.

The C₆₋₁₄ aryl-C₁₋₆ alkyl group of the C₆₋₁₄ aryl-C₁₋₆ alkyl group which may be substituted, may be, for example, and without limitation, a C₁₋₆ alkyl group as defined anywhere above having a C₆₋₁₄ aryl group as defined anywhere above as a substituent.

The C₆₋₁₄ aryl-C₂₋₆ alkenyl group of the C₆₋₁₄ aryl-C₂₋₆ alkenyl group which may be substituted, may be, for example, and without limitation, a C₂₋₆ alkenyl group as defined anywhere above having a C₆₋₁₄ aryl group as defined anywhere above as a substituent.

The C₆₋₁₄ aryl-C₂₋₆ alkynyl group of the C₆₋₁₄ aryl-C₂₋₆ alkynyl group which may be substituted, may be, for example, and without limitation, a C₂₋₆ alkynyl group as defined anywhere above having a C₆₋₁₄ aryl group as defined
5 anywhere above as a substituent.

The 4- to 10-membered non-aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen of the 4- to 10-membered non-aromatic heterocyclic group containing one
10 or more heteroatoms which are independently nitrogen, sulfur or oxygen and which group may be substituted, may contain, for example, and without limitation, from 1 to 4 heteroatoms which are independently nitrogen, sulfur or oxygen. The 4- to 10-membered non-aromatic heterocyclic group containing
15 one or more heteroatoms which are independently nitrogen, sulfur or oxygen may be, for example, and without limitation, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, imidazolinyl, pyrazolidinyl, imidazolydinyl, morpholinyl, tetrahydropyranyl, azetidiny, oxetanyl,
20 oxathiolanyl, phthalimide or succinimide.

The 5- to 14-membered aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen of the 5- to 14-membered aromatic heterocyclic group containing one or more heteroatoms which
25 are independently nitrogen, sulfur or oxygen and which group may be substituted, may contain, for example, and without limitation, from 1 to 4 heteroatoms which are independently nitrogen, sulfur or oxygen. The 5- to 14-membered aromatic heterocyclic group containing one or more heteroatoms which
30 are independently nitrogen, sulfur or oxygen may be, for example, and without limitation, pyrrolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, imidazolyl, thiazolyl or oxazolyl.

The C₁₋₆ alkoxy carbonyl group of the C₁₋₆ alkoxy carbonyl group which may be substituted, may be, for example, and without limitation, methoxy carbonyl, ethoxy carbonyl, n-propoxy carbonyl, i-propoxy carbonyl, 5 sec-propoxy carbonyl, n-butoxy carbonyl, i-butoxy carbonyl, 1,2-dimethylpropoxy carbonyl or 2-ethylpropoxy carbonyl.

Each of the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₄ aryl, C₆₋₁₄ aryl-C₁₋₆ alkyl, C₆₋₁₄ aryl-C₂₋₆ alkenyl, C₆₋₁₄ aryl-C₂₋₆ alkynyl, 4- to 10 10-membered non-aromatic heterocyclic, 5- to 14-membered aromatic heterocyclic and C₁₋₆ alkoxy carbonyl groups may be substituted with one or more substituents which are the same or different. In an embodiment of the present invention, each of the above-mentioned groups may be, for example, and 15 without limitation, substituted with one to three substituents which are the same or different.

The one or more substituents which are the same or different for each of the above-mentioned groups may be, for example, and without limitation, a halogen atom, a hydroxyl 20 group, a thiol group, a nitro group, a nitrile group, a cyano group, a C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl group which may be substituted with a halogen atom, a C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl group which may be substituted, a C₆₋₁₄ aryl group which may be substituted, a 4- 25 to 10-membered non-aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently nitrogen, oxygen or sulfur and which group may be substituted, a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently nitrogen, oxygen or 30 sulfur and which group may be substituted, a C₁₋₆ alkoxy group which may be substituted, a C₃₋₈ cycloalkoxy group which may be substituted, a C₁₋₆ alkylthio, C₂₋₆ alkenylthio or C₂₋₆ alkynylthio group which may be substituted, a C₃₋₈

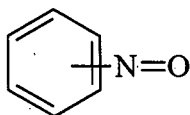
cycloalkylthio or C₃₋₈ cycloalkenylthio group which may be substituted, a C₆₋₁₄ aryloxy group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-oxy group which may be substituted, a 5- to 14-membered aromatic
 5 heterocycle-oxy group which may be substituted, a C₆₋₁₄ arylthio group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-thio group which may be substituted, a 5- to 14-membered aromatic heterocycle-thio group which may be substituted, an amino group which may be
 10 substituted, an azide group, a guanidino group, a carbamide group, a formyl group, a C₁₋₆ imido group, a carbonyl group which is substituted, a carbonyl-oxy group which is substituted, a carboxy group, a carbamoyl group which may be substituted, a C₁₋₄ alkylenedioxy group, a sulfinyl group
 15 which is substituted, a sulfonyl which is substituted with a trifluoromethyl group, a C₁₋₆ alkoxy carbonyl group, a C₁₋₆ alkylsulfonyl group, an oxo group or a C₁₋₆ alkoxyimino group.

In an embodiment of the present invention, R₁ is,
 20 for example, a C₁₋₆ alkoxy carbonyl group or a C₆₋₁₄ aryl group which may be substituted with 1 to 3 substituents which are independently nitro, trifluoromethyl, trifluoromethylsulfonyl, methoxy or methoxycarbonyl.

In an exemplary embodiment of the present
 25 invention, R₂ is a hydrogen atom.

B. Nitrosobenzene

Nitrosobenzene may be represented by the formula (III):



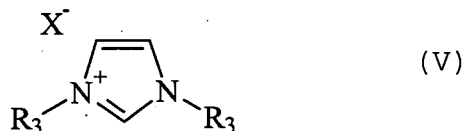
(III)

C. NHC Catalyst

The NHC catalyst of the present invention is not particularly limited.

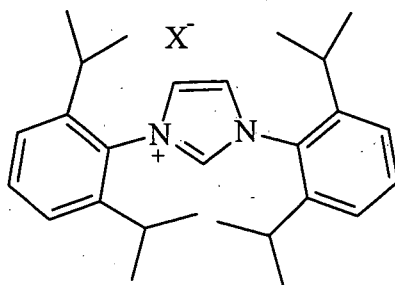
In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt.

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula (V):



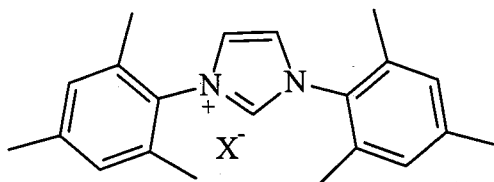
wherein R₃ may be, for example, and without limitation, phenyl (Ph), i-propyl (ⁱPr), mesityl (Mes) or 2,6-diisopropylphenyl (2,6-ⁱPr-Ph); and X⁻ may be, for example, and without limitation, Br⁻, BF₄⁻ or Cl⁻.

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:



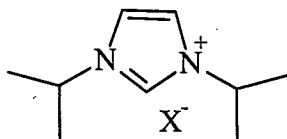
wherein X⁻ may be, for example, and without limitation, Br⁻, BF₄⁻ or Cl⁻. In an embodiment, X⁻ is, for example, Cl⁻.

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:



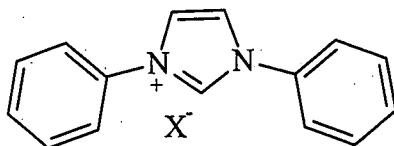
wherein X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- . In an embodiment, X^- is, for example, Cl^- .

10 In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:



15 wherein X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- . In an embodiment, X^- is, for example, BF_4^- .

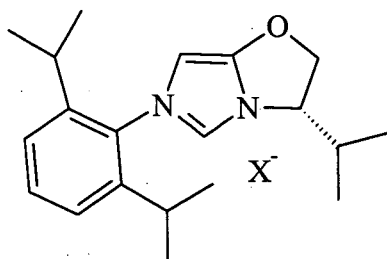
In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:



wherein X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- . In an embodiment, X^- is, for example, Br^- .

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:

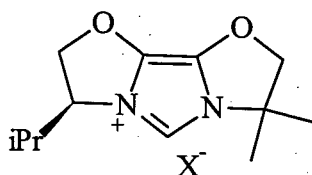
5



wherein X^- may be, for example, and without limitation, trifluoromethylsulfonate (OTf^-), Br^- , BF_4^- or Cl^- . In an embodiment, X^- is, for example, OTf^- .

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:

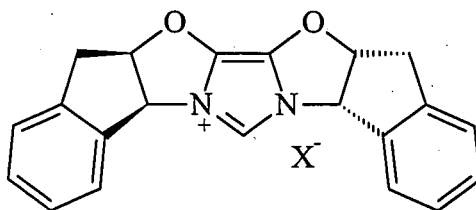
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wherein X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- .

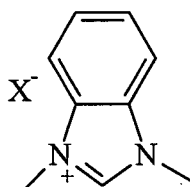
In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:

20



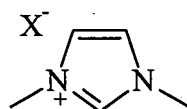
wherein X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- .

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without
5 limitation, an imidazolium salt represented by the formula:



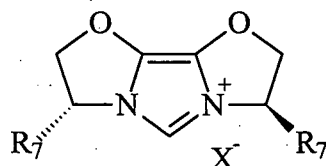
wherein X^- may be, for example, and without limitation, Br^- ,
10 BF_4^- or Cl^- .

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:



wherein X^- may be, for example, and without limitation, Br^- ,
15 BF_4^- or Cl^- .

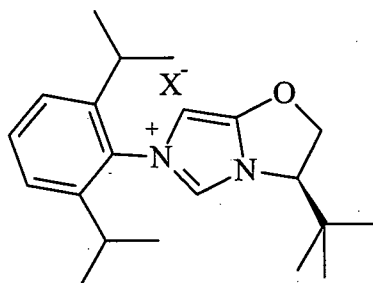
In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without
20 limitation, an imidazolium salt represented by the formula:



wherein R_7 may be, for example, and without limitation, iPr
25 and $t-Bu$; and X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- .

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula:

5

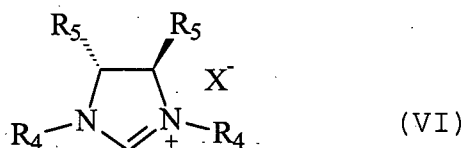


wherein X^- may be, for example, and without limitation, trifluoromethylsulfonate (OTf^-), Br^- , BF_4^- or Cl^- . In an embodiment, X^- is, for example, OTf^- .

10

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula (VI):

15



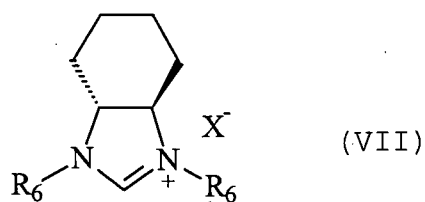
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wherein R_4 may be, for example, and without limitation, 2,6- i Pr-Ph; R_5 may be, for example, and without limitation, hydrogen or Ph; and X^- may be, for example, and without limitation, Cl^- .

25

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, an imidazolium salt represented by the formula (VII):

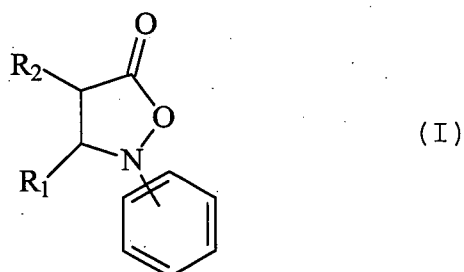
22



5 wherein R_6 may be, for example, and without limitation, 2,6- i Pr-Ph and X^- may be, for example, and without limitation, Cl^- .

D. N-Phenylisoxazolidin-5-one Derivative

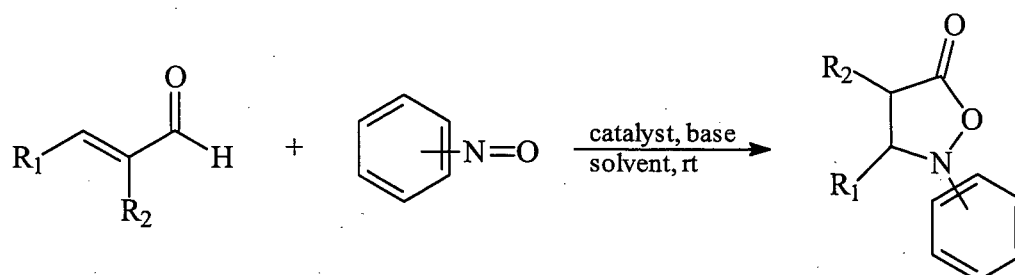
10 In an embodiment, the N-phenylisoxazolidin-5-one derivative that may be prepared in the present invention, may be represented by, for example, and without limitation, a compound of the formula (I):



15 wherein each of R_1 and R_2 is as defined anywhere above.

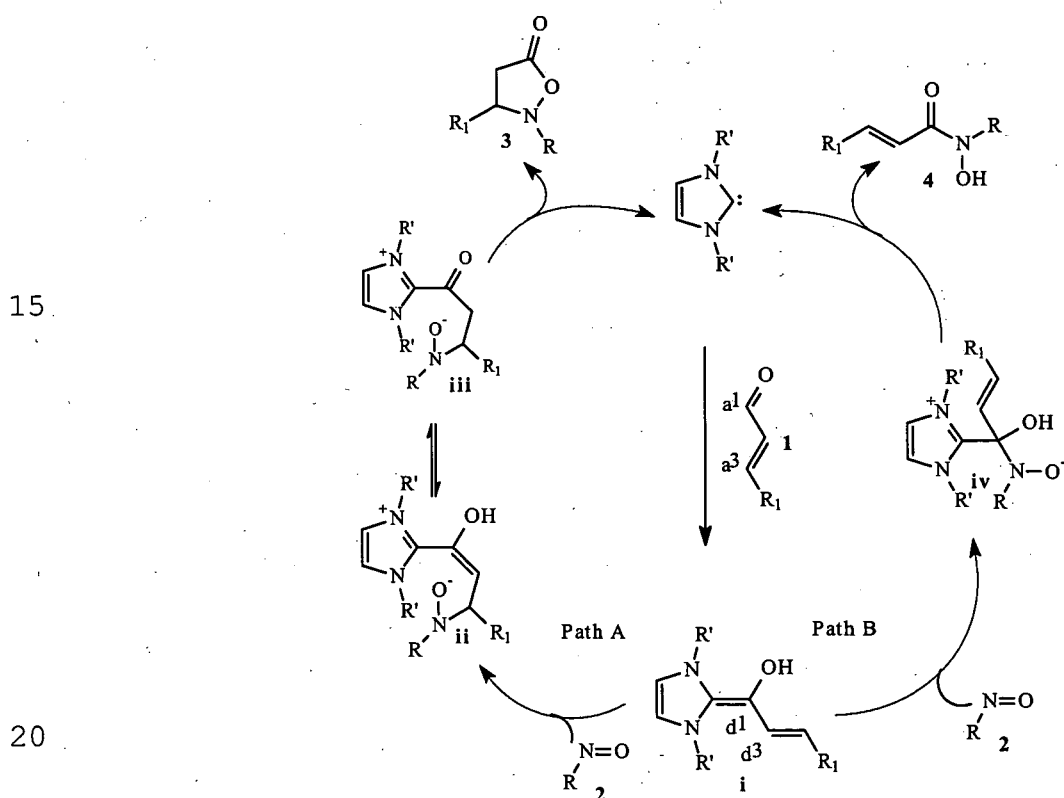
E. Preparation of N-Phenylisoxazolidin-5-one Derivative

20 An embodiment of the process for preparing the N-phenylisoxazolidin-5-one derivative of the present invention may be represented by, for example, and without limitation, the following scheme:



wherein each of R_1 and R_2 is as defined anywhere above.

Without being bound by theory, as represented in the following scheme by way of example, and without limitation, it is believed that the nitroso compound can act as an electrophile, forming C-N bonds leading to amides or β -amino acid derivatives.



wherein in the scheme R is phenyl, R₁ is as defined anywhere above and R' is a hydrocarbon group, including those groups defined for R₁ as above.

It is believed that coupling of the nitroso compound **2** with the homoenolate equivalent **i** (d^3 nucleophile) forms intermediate nitroxide species **ii** and **iii** (Path A). The nitroxide species **iii** can then attack the carbonyl group of the activated carboxylate intramolecularly, leading to formation of the isoxazolidin-5-one **3**, returning the carbene catalyst back for further turnovers. Potential competing reactions are believed to be the reaction of the d^1 nucleophile **i** with the nitroso compound **2** to form the *N*-hydroxycinnamamide **4** (Path B) and the self-condensation of the enal.

In an embodiment of the present invention, the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst may be, for example, reacted in the presence of a suitable base. The base is not particularly limited and suitable bases would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the base may be, for example, and without limitation, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), potassium *tert*-butoxide (KO^tBu), sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium tetramethylpiperidine or sodium *tert*-butoxide. In an embodiment of the present invention, the base is, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene or potassium *tert*-butoxide.

In an embodiment of the present invention, the reaction may be, for example, carried out in the presence of a suitable solvent. The solvent is not particularly limited and suitable solvents would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the solvent may be, for example, and without limitation, dichloromethane (CH_2Cl_2) or tetrahydrofuran (THF).

The amounts of the α,β -unsaturated aldehyde and nitrosobenzene that may be used in the present invention are not particularly limited. Suitable amounts of the α,β -unsaturated aldehyde and nitrosobenzene would be understood to and can be determined by those of ordinary skill in the art. For example, and without limitation, those of ordinary skill in the art would understand that the α,β -unsaturated aldehyde and nitrosobenzene may be reacted according to their stoichiometric ratio.

10 The amount of the NHC catalyst that may be used in the present invention is not particularly limited. Suitable amounts of the NHC catalyst would be understood to and could be determined by those of ordinary skill in the art. In an embodiment of the present invention, the amount of the NHC catalyst may be, for example, and without limitation, less than 20 mol%, for example, and without limitation from 10 to 20 mol%, and including any specific value within this range.

20 The reaction time is not particularly limited and suitable reaction times would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the reaction time may be, for example, and without limitation, less than 12 hours, for example, and without limitation, from 1 to 12 hours, and including any specific time within this range, such as, for example, and without limitation, from 1 to 6 hours or from 1 to 3 hours.

30 The reaction temperature is not particularly limited and suitable reaction temperatures would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the reaction temperature may be, for example, and without limitation, room temperature.

In an embodiment of the present invention, the *N*-phenylisoxazolidin-5-one derivative may be, for example, isolated and/or purified. Suitable isolation and/or purification methods would be understood to and can be determined by those of ordinary skill in the art. For example, and without limitation, those of ordinary skill in the art would understand that the *N*-phenylisoxazolidin-5-one derivative may be isolated and/or purified by chromatographic methods.

Non-limiting examples of one process of the present invention are described in more detail herein.

F. Examples

A number of the *N*-phenylisoxazolidin-5-one derivatives were not isolated due to potential decarboxylation and further hydrolysis. Formation of the derivatives was monitored separately by ^1H nuclear magnetic resonance (NMR) studies.

In general, for the ^1H NMR studies, the base (0.10 mmol) was added under argon to a solution of α,β -unsaturated aldehyde (0.10 mmol), nitrosobenzene (0.11 mmol) and the catalyst (0.02 mmol) in the corresponding deuterated solvent (2 mL). The reaction mixture was stirred at room temperature for 1-3 h. The ^1H NMR spectra were recorded directly.

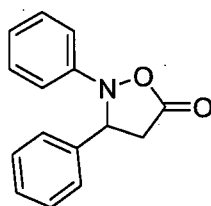
3-(4-Nitrophenyl)-2-phenylisoxazolidin-5-one was isolated and further studied by ^{13}C NMR.

^1H and ^{13}C NMR spectra were obtained using a BrukerTM AV-400 (400 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data were reported in

the following order: chemical shift in ppm (δ) (multiplicity were indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); coupling constants (J , Hz); integration; assignment.

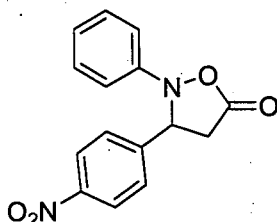
5 The following compounds were prepared and studied in accordance with the above method.

2,3-Diphenylisoxazolidin-5-one



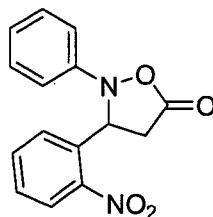
^1H NMR (400 MHz, CDCl_3): δ 7.40–7.00 (m, 10H, Ar-H),
10 4.77 (dd, J = 7.6, 9.6 Hz, 1H, CH), 3.13 (dd, J = 7.6, 17.3
Hz, 1H, CH_2), 2.94 (dd, J = 9.6, 17.3 Hz, 1H, CH_2). MS (ESI):
 m/z 239 (M^+), 196, 131, 120, 104.

3-(4-Nitrophenyl)-2-phenylisoxazolidin-5-one



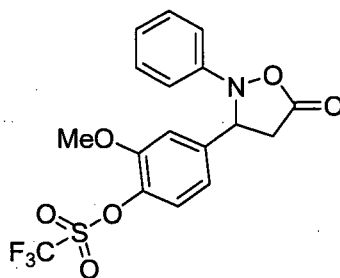
15 ^1H NMR (400 MHz, CDCl_3): δ 8.24 (AB, d, J_{AB} = 8.8 Hz, 2H,
Ar-H), 7.62 (AB, d, J_{AB} = 8.8 Hz, 2H, Ar-H), 7.19–7.05 (m,
4H, Ar-H), 6.98–6.95 (m, 1H, Ar-H), 5.14 (dt, J = 2.5, 6.0
Hz, 1H, CH), 3.12 (dd, J = 6.0, 12.9 Hz, 1H, CH_2), 2.81 (dd,
 J = 6.0, 12.9 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 167.8
20 (Cq, CO), 149.3, 144.9, 135.2 (Cq), 126.6, 124.3, 124.2,
122.8, 120.7 (C-Ar), 62.5 (CH), 38.8 (CH_2).

3-(2-Nitrophenyl)-2-phenylisoxazolidin-5-one



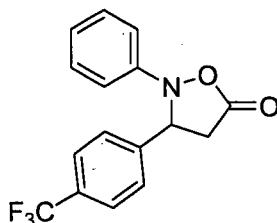
^1H NMR (400 MHz, CDCl_3): δ 8.00–6.90 (m, 9H, Ar-H), 5.54 (dd, $J = 5.8, 8.7$ Hz, 1H, CH), 3.49 (dd, $J = 8.7, 17.9$ Hz, 1H, CH_2), 2.68 (dd, $J = 5.8, 17.9$ Hz, 1H, CH_2). m/z 284 (M^+), 266, 249, 224, 176, 130, 120, 108, 91, 79.

2-Methoxy-4-(5-oxo-2-phenylisoxazolidin-3-yl)phenyl trifluoromethanesulfonate



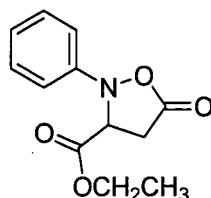
10. ^1H NMR (400 MHz, CDCl_3): δ 7.70–7.00 (m, 8H, Ar-H), 4.84 (t, $J = 8.0$ Hz, 1H, CH), 3.84 (s, 3H, OCH_3), 3.20 (dd, $J = 8.0, 17.3$ Hz, 1H, CH_2), 2.92 (dd, $J = 8.9, 17.3$ Hz, 1H, CH_2).

3-(4-(Trifluoromethyl)phenyl)-2-phenylisoxazolidin-5-one



15. ^1H NMR (400 MHz, CDCl_3): δ 7.59–7.00 (m, 9H, Ar-H), 4.87 (t, $J = 8.1$ Hz, 1H, CH), 3.19 (dd, $J = 8.1, 17.3$ Hz, 1H, CH_2), 2.90 (dd, $J = 9.0, 17.3$ Hz, 1H, CH_2). MS (ESI): m/z 307 (M^+), 264, 199, 120, 109.

Ethyl 5-oxo-2-phenylisoxazolidine-3-carboxylate

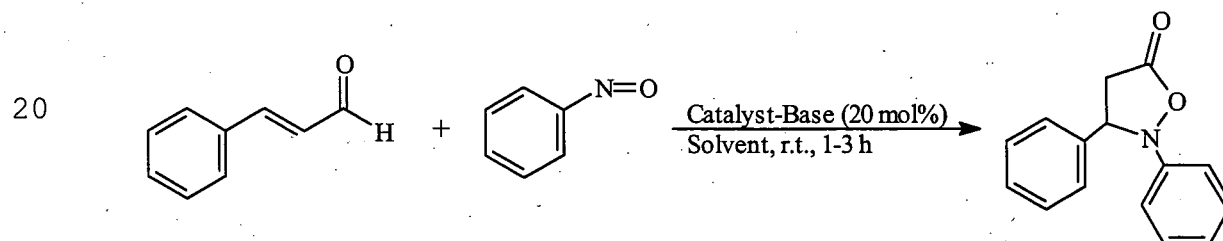


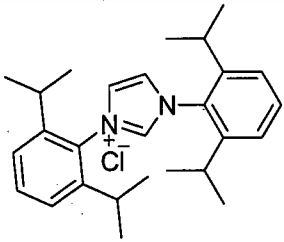
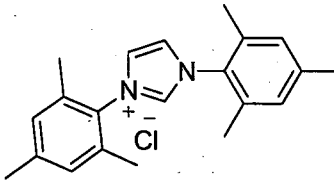
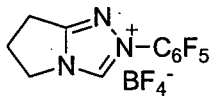
¹H NMR (400 MHz, CDCl₃): δ 7.50-7.00 (m, 5H, Ar-H), 4.62 (dd, *J* = 4.9, 7.5 Hz, 1H, CH), 4.26 (q, *J* = 7.0 Hz, 2H, OCH₂), 3.11 (m_c, 2H, CH₂), 1.29 (t, *J* = 7.0 Hz, 3H, CH₃). MS (ESI): *m/z* 235 (M⁺), 207, 162, 134, 120, 99.

Cinnamaldehyde and nitrosobenzene were observed to react in the presence of the NHC catalysts, forming 2,3-diphenylisoxazolidin-5-one. In studies using different imidazolium and triazolium salts, it was observed that more sterically hindered imidazolium catalysts provided higher yields of the product (Table 1).

Azoxybenzene side-product was observed. By modifying reactions conditions in accordance with routine experiments, the amount of azoxybenzene can be minimized.

Table 1. Reaction Conditions for NHC-catalyzed Synthesis of N-Phenylisoxazolidin-5-one Derivatives



entry	Catalyst	Solvent	base	yield, % ^a
1	 (IPrCl)	THF	KO ^t Bu	80
2	 (IMesCl)	THF	KO ^t Bu	60
3 ^b	 $\text{N}^+\text{-C}_6\text{F}_5$ BF_4^-	THF	KO ^t Bu	—
4	IprCl	CH ₂ Cl ₂	KO ^t Bu	82
5	IprCl	Benzene	KO ^t Bu	50
6	IprCl	CH ₂ Cl ₂	DBU ^c	48

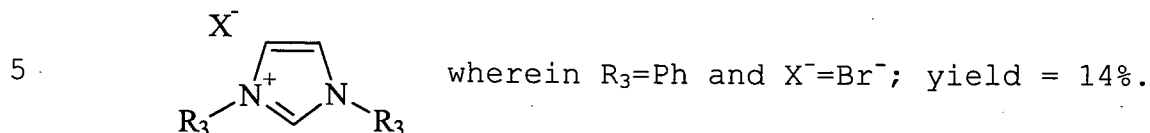
^a Yields determined by ¹H NMR.

^b Exclusive formation of N-hydroxy-N-phenylcinnamamide was observed.

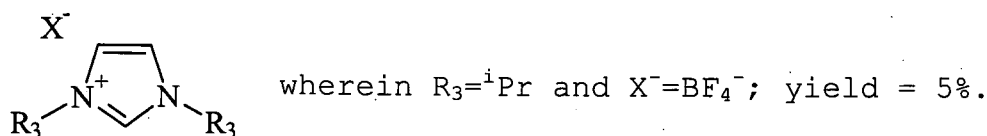
^c DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Experiments were also conducted using the following catalysts, all in the presence of THF and KO^tBu , and forming 2,3-diphenylisoxazolidin-5-one in the following yields (%):

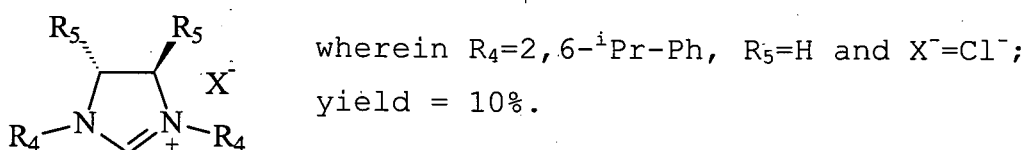
i)



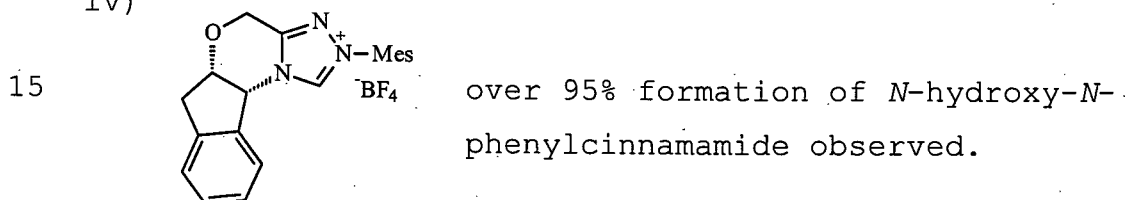
ii)



10 iii)



iv)



II. Process for Preparing *N*-Alkoxyphenyl Protected β -Amino Acid Ester Derivative

20 In an embodiment of the present invention, an α,β -unsaturated aldehyde may be reacted with nitrosobenzene in the presence of a NHC catalyst to form a *N*-phenylisoxalidin-5-one derivative, and then the *N*-phenylisoxalidin-5-one derivative may be treated with an alcohol in the presence of an acid catalyst to form an

25 *N*-alkoxyphenyl protected β -amino acid ester derivative.

In an embodiment of the present invention, a *N*-phenylisoxalidin-5-one derivative may be treated with an alcohol in the presence of an acid catalyst to form an *N*-alkoxyphenyl protected β -amino acid ester derivative.

5 In an embodiment of the present invention, the *N*-alkoxyphenyl protected β -amino acid ester derivative may be deprotected.

A. α,β -Unsaturated Aldehyde, Nitrosobenzene,
N-Phenylisoxalidin-5-one Derivative and NHC Catalyst

10 The skilled person will appreciate that the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst as described above, which may be used for preparing the *N*-phenylisoxalidin-5-one derivative, may also be used for preparing the *N*-alkoxyphenyl protected β -amino acid
15 ester derivative as described herein.

B. Alcohol

Suitable alcohols would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the alcohol may be, for
20 example, and without limitation, methanol, ethanol, propanol, butanol or pentanol.

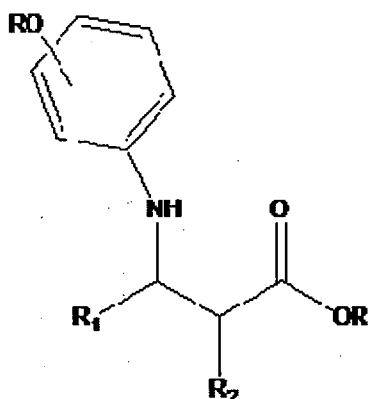
In an embodiment of the present invention, the alcohol may be represented by, for example, and without limitation, the formula R_8OH wherein R_8 may be, for example,
25 and without limitation, a C_{1-6} alkyl group, including those groups defined for R_1 and R_2 above. In an embodiment of the present invention, R_8 may be, for example, methyl.

C. Acid Catalyst

The acid catalyst that may be used in the present invention is not particularly limited. Suitable acid catalysts would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the acid catalyst may be, for example, and without limitation, perchloric acid.

D. N-Alkoxyphenyl Protected β -Amino Acid Ester Derivative

In an embodiment of the present invention, the N-alkoxyphenyl protected β -amino acid ester derivative may be represented by, for example, and without limitation, a compound of the formula (IV):



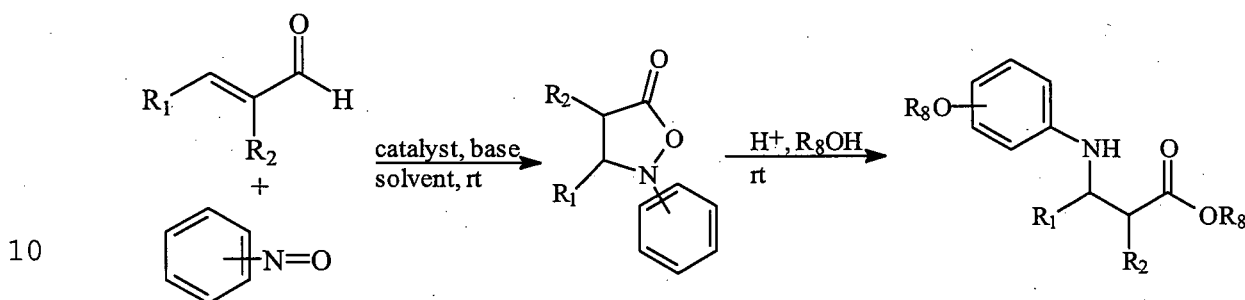
wherein each of R_1 , R_2 and R_3 is as defined anywhere above.

In an exemplary embodiment of the present invention, the N-alkoxyphenyl protected β -amino acid ester derivative may be, for example, a N-p-alkoxyphenyl protected β -amino acid ester derivative.

In an embodiment of the present invention, the N-alkoxyphenyl protected β -amino acid ester derivative may be, for example, a N-p-methoxyphenyl protected β -amino acid ester derivative.

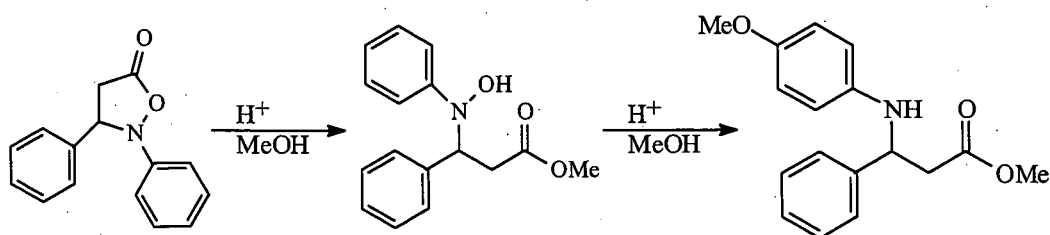
E. Preparation of *N*-Alkoxyphenyl Protected β -Amino Acid Ester Derivative

An embodiment of the process of the present invention for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative may be represented by, for example,
 5 acid ester derivative may be represented by, for example, and without limitation, the following scheme:



wherein each of R_1 , R_2 and R_8 is as defined anywhere above.

An embodiment of the acid-catalyzed esterification, followed by the Bamberger-like rearrangement of the *N*-phenylisoxazolidin-5-one derivative for preparing the *N*-alkoxyphenyl protected β -amino acid ester derivative may be represented by, for example, and without limitation, the following scheme showing the acid-catalyzed ring opening and Bamberger-like rearrangement of 2,3-diphenylisoxazolidin-5-one.
 20 diphenylisoxazolidin-5-one.

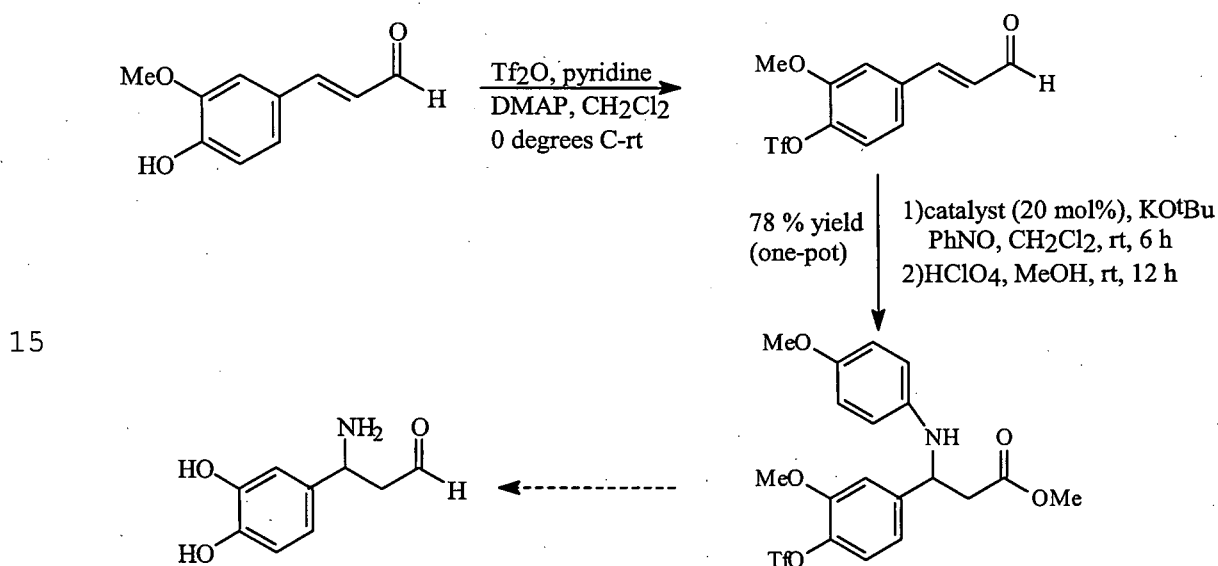


25 In an embodiment of the present invention, the process for preparing the *N*-alkoxyphenyl protected β -amino

acid ester derivative may be, for example, and without limitation, a one-pot process.

In an embodiment of the present invention, the *N*-alkoxyphenyl protected β -amino acid ester derivative may be, for example, deprotected under mild oxidative conditions.

The process of the present invention may be used, for example, and without limitation, for the preparation of the natural product β -dihydroxyphenylalanine (β -DOPA), and may be represented by, for example, the following scheme:



In an embodiment of the present invention, the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst may be, for example, reacted in the presence of a suitable base. The base is not particularly limited and suitable bases would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the base may be, for example, and without limitation, 1,8-diazabicyclo[5.4.0]undec-7-ene, potassium *tert*-butoxide, sodium bis(trimethylsilyl)amide,

potassium bis(trimethylsilyl) amide, lithium tetramethylpiperidine or sodium *tert*-butoxide. In an embodiment of the present invention, the base is, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene or potassium
5 *tert*-butoxide.

In an embodiment of the present invention, the reaction of the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst may be, for example, carried out in the presence of a suitable solvent. The solvent is not
10 particularly limited and suitable solvents would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the solvent may be, for example, and without limitation, dichloromethane or tetrahydrofuran.

15 The amounts of the α,β -unsaturated aldehyde and nitrosobenzene that may be used in the present invention are not particularly limited. Suitable amounts of the α,β -unsaturated aldehyde and nitrosobenzene would be understood to and can be determined by those of ordinary
20 skill in the art. For example, and without limitation, those of ordinary skill in the art would understand that the α,β -unsaturated aldehyde and nitrosobenzene may be reacted according to their stoichiometric ratio.

The amount of the NHC catalyst that may be used in
25 the present invention is not particularly limited. Suitable amounts of the NHC catalyst would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the amount of the NHC catalyst may be, for example, and without limitation, less
30 than 20 mol%, for example, and without limitation from 10 to 20 mol%, and including any specific value within this range.

The reaction time for the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst is not particularly limited and suitable reaction times would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the reaction time may be, for example, and without limitation, less than 12 hours, for example, and without limitation, from 1 to 12 hours, and including any specific time within this range, such as, for example, and without limitation, from 1 to 6 hours or from 1 to 3 hours.

The reaction temperature for the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst is not particularly limited and suitable reaction temperatures would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the reaction temperature may be, for example, and without limitation, room temperature.

The amount of the acid catalyst that may be used in the present invention is not particularly limited and suitable amounts of the acid catalyst would be understood to and can be determined by those of ordinary skill in the art.

The amounts of the *N*-phenylisoxalidin-5-one derivative and the alcohol that may be used are not particularly limited. Suitable amounts of the *N*-phenylisoxalidin-5-one derivative and the alcohol would be understood to and can be determined by those of ordinary skill in the art. For example, and without limitation, those of ordinary skill in the art would understand that a stoichiometric excess of the alcohol may be used.

The reaction time for the *N*-phenylisoxalidin-5-one derivative and the alcohol is not particularly limited and suitable reaction times for this step would be understood to

and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the reaction time may be, for example, and without limitation, less than 24 hours, for example, and without limitation, from 1 to 24 hours, and including any specific time within this range, such as, for example, and without limitation, from 1 to 12 hours.

The reaction temperature for the *N*-phenylisoxalidin-5-one derivative and the alcohol is not particularly limited and suitable reaction temperatures would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the reaction temperature may be, for example, and without limitation, room temperature.

In an embodiment of the present invention, the *N*-alkoxyphenyl protected β -amino acid ester derivative may be, for example, isolated and/or purified. Suitable isolation and/or purification methods would be understood to and can be determined by those of ordinary skill in the art. For example, and without limitation, those of ordinary skill in the art would understand that the *N*-alkoxyphenyl protected β -amino acid ester derivative may be isolated and/or purified by chromatographic methods.

The conditions for deprotecting the *N*-alkoxyphenyl protected β -amino acid ester derivative are not particularly limited and suitable conditions would be understood to and can be determined by those of ordinary skill in the art. In an embodiment of the present invention, the *N*-alkoxyphenyl protected β -amino acid ester derivative may be deprotected, for example, and without limitation, under mild oxidative conditions.

Non-limiting examples of one process of the present invention are described in more detail herein.

F. EXAMPLES

All reactions were performed in oven-dried (140°C) or flame-dried glassware under an inert atmosphere of dry N₂ or argon. All solvents were anhydrous and purchased from Aldrich or Fluka.

KO^tBu (0.1 mmol) was added under argon to a solution of α,β -unsaturated aldehyde (0.5 mmol), nitrosobenzene (0.51 mmol) and the catalyst (0.1 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature for 1-3 h. The solvent was removed under vacuum, and the residue was diluted with methanol (5 mL), followed by addition of perchloric acid (3-5 drops). The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was diluted with CH₂Cl₂ (5 mL) and saturated aqueous NaHCO₃ (10 mL). The aqueous layer was extracted with CH₂Cl₂ (10 mL × 2). The combined organic layer was washed with saturated aqueous NaHCO₃ (10 mL) and then brine (10 mL), dried (MgSO₄), and concentrated. The pure product was obtained through flash silica gel column chromatography of the residue using hexane and ethyl acetate as the eluents.

In general, reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel coated glass plates (60F-254) with UV light to visualize the course of reaction. Flash column chromatography was performed using CombiFlashTM (ISCO, Inc.).

Chemical yields refer to pure isolated substances.

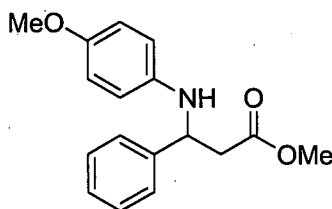
Gas chromatography-mass spectrometry (GC-MS) was conducted using ShimadzuTM GC-2010 coupled with GCMS-QP2010.

¹H and ¹³C nuclear magnetic resonance spectra were obtained using a BrukerTM AV-400 (400 MHz) spectrometer.

5 Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data were reported in the following order: chemical shift in ppm (δ) (multiplicity were indicated by br (broadened), s (singlet), d (doublet), t (triplet), q (quartet),
10 m (multiplet)); coupling constants (*J*, Hz); integration; assignment.

The following compounds were prepared in accordance with the above method.

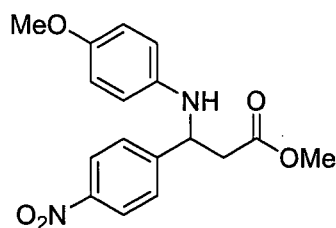
Methyl 3-(4-methoxyphenylamino)-3-phenylpropanoate



15

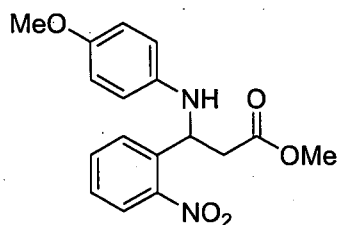
¹H NMR (400 MHz; CDCl₃): δ 7.39–7.25 (m, 5H, Ar-H), 6.71 (AB, d, *J*_{AB} = 8.4 Hz, 2H, Ar-H), 6.56 (AB, d, *J*_{AB} = 8.4 Hz, 2H, Ar-H), 4.77 (t, *J* = 6.4 Hz, 1H, CH), 4.32 (br s, 1H, NH), 3.71 (s, 3H, CH₃), 3.66 (s, 3H, CH₃), 2.84 (d, *J* = 6.4 Hz, 2H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 171.7 (Cq, CO), 152.6, 142.0, 140.3 (Cq), 128.8, 127.5, 126.4 (C-Ar), 115.6, 114.7 (C-Ar), 56.2, 55.7 (OCH₃), 51.9 (CH), 42.5 (CH₂).
20

Methyl 3-(4-methoxyphenylamino)-3-(4-nitrophenyl)propanoate



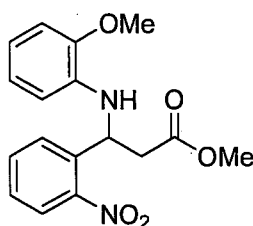
^1H NMR (400 MHz, CDCl_3): δ 8.18 (AB, d, $J_{AB} = 8.6$ Hz, 2H, Ar-H), 7.57 (AB, d, $J_{AB} = 8.6$ Hz, 2H, Ar-H), 6.70 (AB, d, $J_{AB} = 8.8$ Hz, 2H, Ar-H), 6.48 (AB, d, $J_{AB} = 8.8$ Hz, 2H, Ar-H), 4.87 (dd, $J = 4.6, 6.8$ Hz, 1H, CH), 4.30 (br s, 1H, NH), 3.70 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 2.83 (dd, $J = 7.9, 15.3$ Hz, 2H, CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 171.1 (Cq, CO), 152.7, 150.2, 147.3, 140.1 (Cq), 127.4, 124.1 (C-Ar), 115.2, 114.8 (C-Ar), 55.6, 55.3 (OCH_3), 52.1 (CH), 42.1 (CH_2). MS (ESI): m/z 330 (M^+), 257, 211, 122, 108.

Methyl 3-(4-methoxyphenylamino)-3-(2-nitrophenyl)propanoate



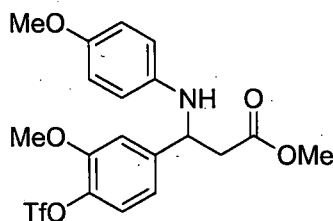
^1H NMR (400 MHz, CDCl_3): δ 7.97 (dd, $J = 1.2, 8.0$ Hz, 1H, Ar-H), 7.73 (dd, $J = 1.2, 8.0$ Hz, 1H, Ar-H), 7.56 (dt, $J = 1.2, 8.0$ Hz, 1H, Ar-H), 7.41 (dt, $J = 1.2, 8.0$ Hz, 1H, Ar-H), 6.68 (AB, d, $J_{AB} = 8.8$ Hz, 2H, Ar-H), 6.45 (AB, d, $J_{AB} = 8.8$ Hz, 2H, Ar-H), 5.40 (dd, $J = 4.3, 7.9$ Hz, 1H, CH), 4.30 (br s, 1H, NH), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 3.04 (dd, $J = 4.3, 15.3$ Hz, 1H, CH_2), 2.81 (dd, $J = 7.9, 15.3$ Hz, 1H, CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 171.4 (Cq, CO), 152.6, 148.9, 140.0, 137.7 (Cq), 133.6, 128.6, 128.4, 125.0 (C-Ar), 116.4, 114.8 (C-Ar), 55.6, 52.0 (OCH_3), 51.4 (CH), 41.2 (CH_2). MS (ESI): m/z 330 (M^+), 296, 257, 237, 122, 108.

Methyl 3-(2-methoxyphenylamino)-3-(2-nitrophenyl)propanoate



^1H NMR (400 MHz, CDCl_3): δ 7.98 (dd, $J = 1.1, 8.0$ Hz, 1H, Ar-H), 7.69 (dd, $J = 1.1, 8.0$ Hz, 1H, Ar-H), 7.54 (dt, $J = 1.1,$
 5 8.0 Hz, 1H, Ar-H), 7.40 (dt, $J = 1.1, 8.0$ Hz, 1H, Ar-H), 6.77 (dd, $J = 1.9, 7.6$ Hz, 1H, Ar-H), 6.67 (dq, $J = 2.0, 7.6$
 Hz, 2H, Ar-H), 6.25 (dd, $J = 1.9, 7.6$ Hz, 1H, Ar-H), 5.53
 (br dd, $J = 4.3, 7.9$ Hz, 1H, CH), 5.39 (br d, $J = 6.4$ Hz,
 1H, NH), 3.90 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.08 (dd,
 10 $J = 4.3, 15.3$ Hz, 1H, CH_2), 2.86 (dd, $J = 7.9, 15.3$ Hz, 1H,
 CH_2). ^{13}C NMR (100 MHz, CDCl_3): δ 171.1 (Cq, CO), 148.8,
 146.9, 137.8, 135.7 (Cq), 133.7, 128.4, 128.3, 125.0, 121.1,
 117.5, 110.8, 109.6 (C-Ar), 55.6, 52.0 (OCH_3), 50.3 (CH),
 41.5 (CH_2). MS (ESI): m/z 330 (M^+), 257, 207, 123, 108.

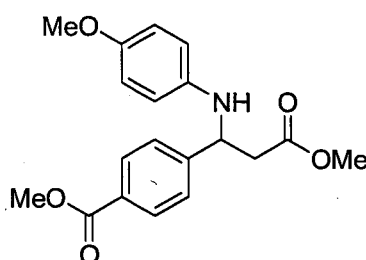
15 4-(2-Methoxycarbonyl)-1-(4-methoxyphenylamino)ethyl-2-methoxyphenyl trifluoromethane sulfonate



^1H NMR (400 MHz, CDCl_3): δ 7.18 (d, $J = 8.4$ Hz, 1H, Ar-H),
 7.09 (d, $J = 2.0$ Hz, 1H, Ar-H), 6.99 (dd, $J = 2.0, 8.4$ Hz,
 20 1H, Ar-H), 6.73 (AB, d, $J_{AB} = 8.8$ Hz, 2H, Ar-H), 6.51 (AB, d,
 $J_{AB} = 8.8$ Hz, 2H, Ar-H), 4.73 (dd, $J = 5.8, 7.6$ Hz, 1H, CH),
 4.32 (br s, 1H, NH), 3.89 (s, 3H, CH_3), 3.72 (s, 3H, CH_3),
 3.68 (s, 3H, CH_3), 2.79 (ddd, $J = 5.6, 5.8, 7.6$ Hz, 2H, CH_2).
 ^{13}C NMR (100 MHz, CDCl_3): δ 171.4 (Cq, CO), 152.6, 151.6

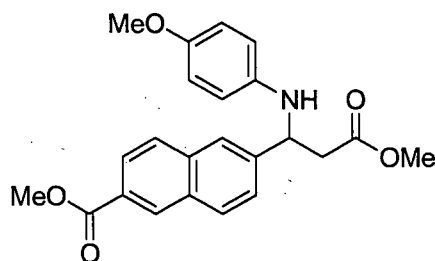
(Cq), 144.4, 140.5, 137.7 (C-Ar), 117.3 (q, $J_{CF} = 270.4$ Hz, Cq, CF₃), 122.6, 117.1, 115.2, 114.8 (C-Ar), 111.0 (Cq), 56.2, 55.6 (OCH₃), 52.0 (CH), 42.5 (CH₂). MS (ESI): m/z 463 (M⁺), 390, 299, 256, 122.

5 Methyl 4-(2-methoxycarbonyl)-1-(4-methoxyphenylamino)ethylbenzoate



¹H NMR (400 MHz, CDCl₃): δ 8.00 (AB, $J_{AB} = 8.2$ Hz, 2H, Ar-H), 7.45 (AB, $J_{AB} = 8.2$ Hz, 2H, Ar-H), 6.69 (AB, d, $J_{AB} = 8.4$ Hz, 2H, Ar-H), 6.50 (AB, d, $J_{AB} = 8.4$ Hz, 2H, Ar-H), 4.81 (t, $J = 6.7$ Hz, 1H, CH), 4.25 (br s, 1H, NH), 3.90 (s, 3H, CH₃), 3.69 (s, 3H, CH₃), 3.65 (s, 3H, CH₃), 2.80 (dd, $J = 5.7, 7.6$ Hz, 2H, CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 171.4, 166.8 (Cq, CO), 152.5, 147.8, 140.5, 130.1, 129.4 (Cq), 126.4, 115.2, 114.8 (C-Ar), 55.7, 55.6, 52.1 (CH), 52.0 (OCH₃), 42.3 (CH₂). MS (ESI): m/z 343 (M⁺), 270, 122, 108.

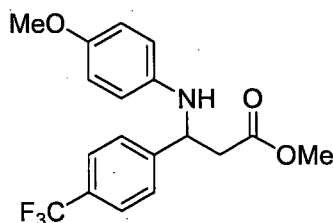
Methyl 6-(2-methoxycarbonyl)-1-(4-methoxyphenylamino)ethyl)naphthalene-2-carboxylate



¹H NMR (400 MHz, CDCl₃): δ 8.58 (s, 1H, Ar-H), 8.05 (dd, $J = 1.7, 8.5$ Hz, 1H, Ar-H), 7.93 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.88 (s, 1H, Ar-H), 7.84 (d, $J = 8.5$ Hz, 1H, Ar-H), 7.57 (dd, $J =$

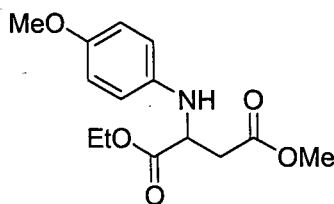
1.7, 8.5 Hz, 1H, Ar-H), 6.69 (AB, d, $J_{AB} = 8.4$ Hz, 2H, Ar-H),
 6.57 (AB, d, $J_{AB} = 8.4$ Hz, 2H, Ar-H), 4.94 (dd, $J = 5.7, 7.6$
 Hz, 1H, CH), 4.30 (br s, 1H, NH), 3.98 (s, 3H, CH₃), 3.68 (s,
 3H, CH₃), 3.67 (s, 3H, CH₃), 2.84 (dd, $J = 5.7, 7.6$ Hz, 2H,
 5 CH₂). ¹³C NMR (100 MHz, CDCl₃): δ 171.5, 167.2 (Cq, CO),
 152.4, 142.7, 140.7, 135.6, 132.0 (Cq), 130.8, 130.1, 128.2
 (C-Ar), 127.3 (Cq), 125.6, 125.2, 125.0 (C-Ar), 115.2, 114.8
 (C-Ar), 56.0, 55.7, 52.0 (OCH₃), 52.3 (CH), 42.5 (CH₂).

Methyl 3-(4-methoxyphenylamino)-3-(4-
 10 trifluoromethyl)phenyl)propanoate



¹H NMR (400 MHz, CDCl₃): δ 7.59 (AB, $J_{AB} = 8.4$ Hz, 2H, Ar-H),
 7.51 (AB, $J_{AB} = 8.4$ Hz, 2H, Ar-H), 6.72 (AB, d, $J_{AB} = 8.4$ Hz,
 2H, Ar-H), 6.51 (AB, d, $J_{AB} = 8.4$ Hz, 2H, Ar-H), 4.81 (t, $J =$
 15 6.7 Hz, 1H, CH), 4.20 (br s, 1H, NH), 3.71 (s, 3H, CH₃), 3.68
 (s, 3H, CH₃), 2.82 (dd, $J = 5.6, 7.2$ Hz, 2H, CH₂). ¹³C NMR
 (100 MHz, CDCl₃): δ 171.3 (Cq, CO), 152.6, 146.6, 140.4 (Cq),
 129.7 (q, $J = 32.0$ Hz, Cq), 126.7 (C-Ar), 125.8 (q, $J = 3.8$
 Hz, C-Ar), 125.6 (q, $J_{CF} = 270.4$ Hz, Cq, CF₃), 115.2, 114.8
 20 (C-Ar), 55.6, 55.5 (OCH₃), 52.0 (CH), 42.4 (CH₂). MS (ESI):
 m/z 353 (M⁺), 280, 122, 108.

1-Ethyl 4-methyl 2-(4-methoxyphenylamino)succinate

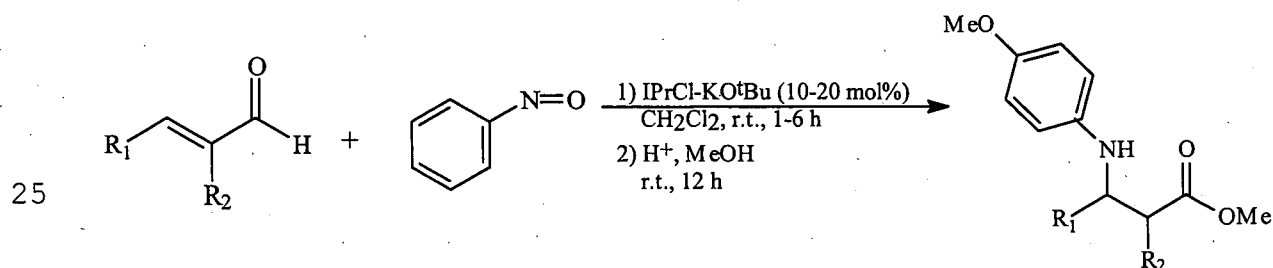


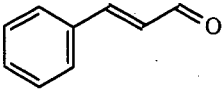
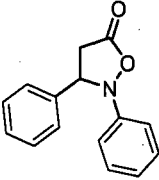
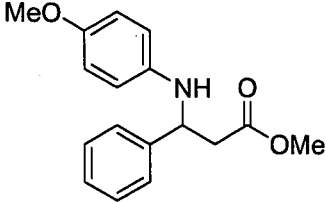
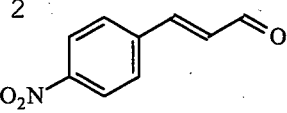
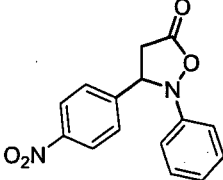
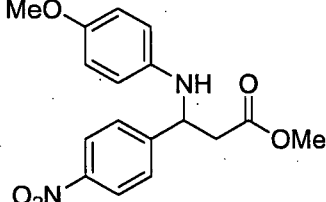
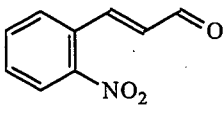
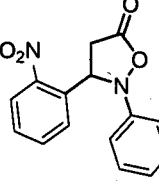
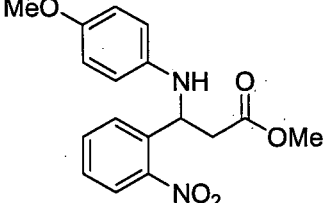
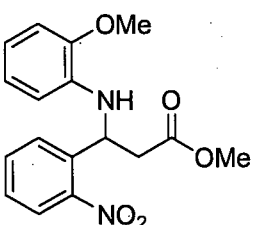
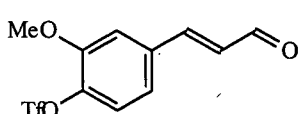
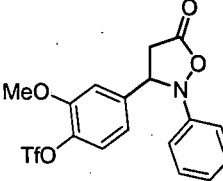
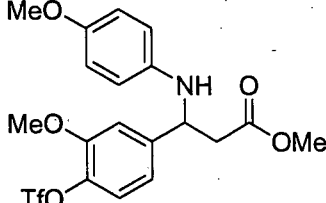
^1H NMR (400 MHz, CDCl_3): δ 6.78 (AB, d, $J_{AB} = 8.9$ Hz, 2H, Ar-H), 6.67 (AB, d, $J_{AB} = 8.9$ Hz, 2H, Ar-H), 4.36 (t, $J = 6.0$ Hz, 1H, CH), 4.20 (dq, $J = 2.5, 7.1$ Hz, 2H, CH_2), 3.75 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 2.85 (d, $J = 6.0$ Hz, 2H, CH_2), 2.0 (br s, 1H, NH), 1.85 (t, $J = 7.1$ Hz, 3H, CH_3). ^{13}C NMR (100 MHz, CDCl_3): δ 172.5, 171.1 (Cq, CO), 153.2, 140.1 (Cq), 115.9, 114.8 (C-Ar), 61.6 (OCH_2), 55.7, 54.9 (OCH_3), 52.0 (CH), 37.4 (CH_2), 14.1 (CH_3). MS (ESI): m/z 281 (M^+), 208, 148, 134.

A variety of aryl- and alkyl-substituted α,β -unsaturated aldehydes were observed to form the corresponding isoxazolidin-5-one derivatives and β -amino acid ester derivatives. In general, it was observed that aryl- and alkyl-substituted α,β -unsaturated aldehydes with an electron-withdrawing group provided higher yields. It is worth noting that substrates with different functional groups, including ether, ester, nitro, and sulfonate groups, can be used. (Table 2)

Traces of *N*-*p*-hydroxyphenyl β -amino acid ester were observed in some cases.

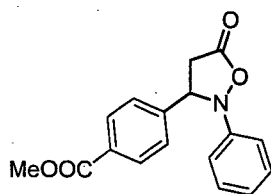
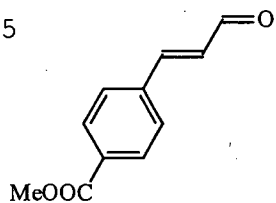
Table 2. NHC-catalyzed Synthesis of *N*-Phenylisoxazolidin-5-one Derivatives and Corresponding β -Amino Acid Esters



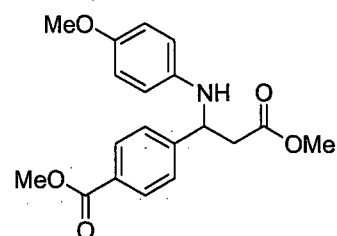
isoxazolidin-5-one				
entry	aldehyde	(yield, % ^a)	β -aminoester	yield, % ^b
1		 (82)		75
2		 (98)		92 ^c
3		 (84)		75
				5
4		 (84)		78

(81)

5

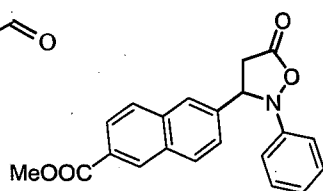
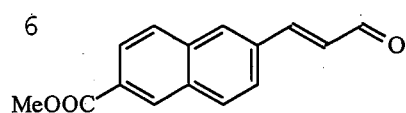


(88)

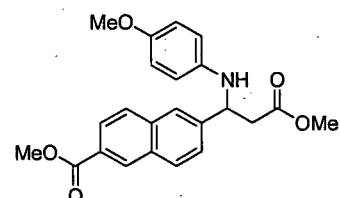


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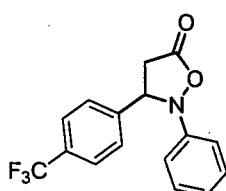
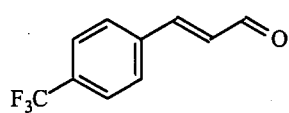


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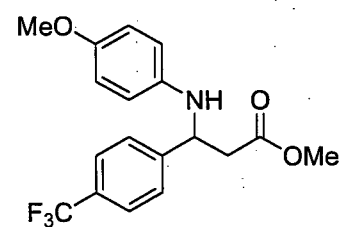


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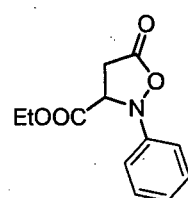
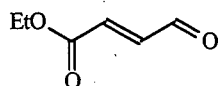


(90)

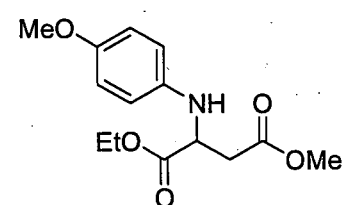


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8



(96)



91

^a Yield determined by ¹H NMR and GC-MS analyses.

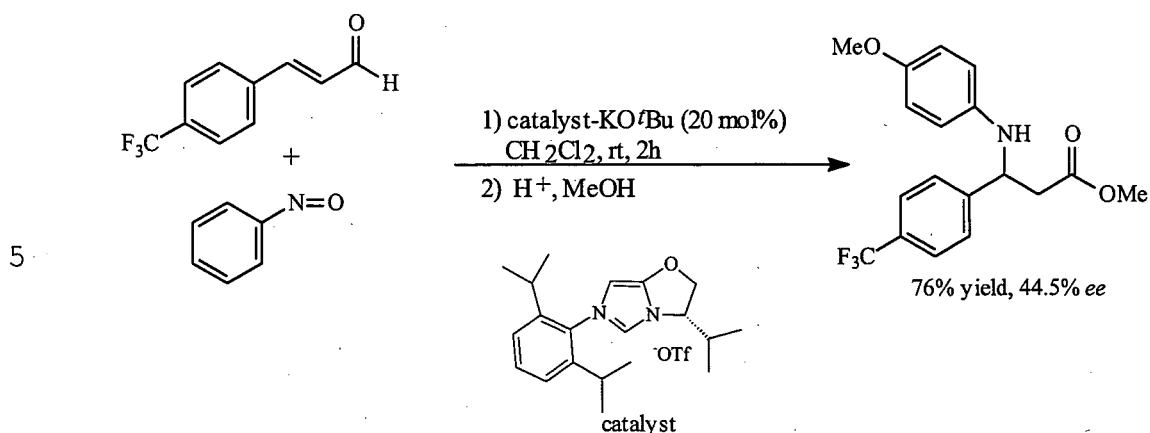
^b Isolated yield of the β -amino acid ester with respect to the aldehyde.

^c 10 mol% catalyst was used.

Experiments were also conducted by reacting the following
5 α,β -unsaturated aldehydes represented by the formula (II) as defined above, all with nitrosobenzene in the presence of the IPrCl catalyst (10-20 mol%), KO^tBu and CH₂Cl₂ (r.t., 1-6 h) forming the corresponding *N*-phenylisoxazolidin-5-one derivatives in the following yields a (% , determined by ¹H
10 NMR), and then treating the *N*-phenylisoxazolidin-5-one derivatives with MeOH in the presence of an acid catalyst (r.t., 12 h) forming the corresponding β -amino acid ester derivatives in the following yields b (%):

- i) R₁=3-Br-4-OTfPh and R₂=H; yield a = 83%; yield b = 79%.
- 15 ii) R₁=4-CNPh and R₂=H; yield a = 95%; yield b = 40%.
- iii) R₁=C₆F₅ and R₂=H; yield a = 85%; yield b = 72%.
- iv) R₁=3,5-F₂Ph and R₂=H; yield a = 88%; yield b = 78%.
- v) R₁=C₄H₉ and R₂=H; yield a = 40%; yield b = 30%.

Enantiomeric selectivity was observed in one study
20 using a NHC catalyst derived from a chiral imidazolium salt, which is represented by way of example, and without limitation, by the following scheme:



The reaction of the homoenolate with nitrosobenzene may be directed to 1,4- or 1,2-addition by modifying steric and/or electronic properties of the NHC catalyst according to routine experiments.

The present invention includes isomers such as geometrical isomers, optical isomers based on asymmetric carbon, stereoisomers and tautomers and is not limited by the description of the formula illustrated for the sake of convenience.

Although the foregoing invention has been described in some detail by way of illustration and example, and with regard to one or more embodiments, for the purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes, variations and modifications may be made thereto without departing from the spirit or scope of the invention as described in the appended claims.

It must be noted that as used in the specification and the appended claims, the singular forms of "a", "an" and

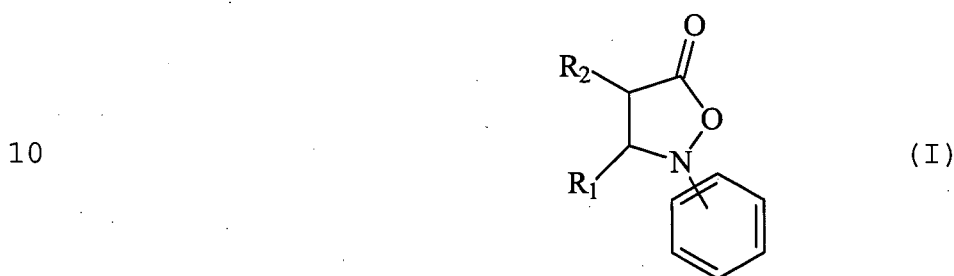
"the" include plural reference unless the context clearly indicates otherwise.

Unless defined otherwise all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

All publications, patents and patent applications cited in this specification are incorporated herein by reference as if each individual publication, patent or patent application were specifically and individually indicated to be incorporated by reference. The citation of any publication, patent or patent application in this specification is not an admission that the publication, patent or patent application is prior art.

CLAIMS:

1. A process for preparing a *N*-phenylisoxazolidin-5-one derivative comprising reacting an α,β -unsaturated aldehyde with nitrosobenzene in the presence of a
- 5 *N*-heterocyclic carbene (NHC) catalyst.
2. The process according to claim 1 for preparing a *N*-phenylisoxazolidin-5-one derivative represented by the formula (I):



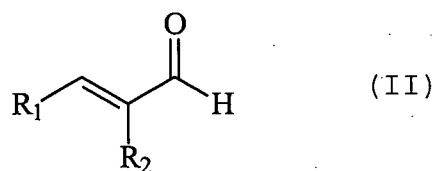
wherein:

- R_1 is a hydrogen atom, a halogen atom, a nitrile group, a C_{1-6} alkyl group which may be substituted with one or more
- 15 substituents which are the same or different, a C_{2-6} alkenyl group which may be substituted with one or more substituents which are the same or different, a C_{2-6} alkynyl group which may be substituted with one or more substituents which are the same or different, a C_{3-8} cycloalkyl group which may be
- 20 substituted with one or more substituents which are the same or different, a C_{3-8} cycloalkenyl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl group which may be substituted with one or more substituents which are the same or different, a
- 25 C_{6-14} aryl- C_{1-6} alkyl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl- C_{2-6} alkenyl group which may be substituted with one or more substituents which are the same or different, a C_{6-14} aryl- C_{2-6} alkynyl group which may be substituted with one or
- 30 more substituents which are the same or different, a 4- to

10-membered non-aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen and which group may be substituted with one or more substituents which are the same or different, a 5- to 5 14-membered aromatic heterocyclic group containing one or more heteroatoms which are independently nitrogen, sulfur or oxygen and which group may be substituted with one or more substituents which are the same or different or a C₁₋₆ alkoxy carbonyl group which may be substituted with one or 10 more substituents which are the same or different; and

R₂ is a hydrogen atom, a C₁₋₆ alkyl group which may be substituted with one or more substituents which are the same or different, a C₂₋₆ alkenyl group which may be substituted with one or more substituents which are the same or 15 different, a C₂₋₆ alkynyl group which may be substituted with one or more substituents which are the same or different, a C₃₋₈ cycloalkyl group which may be substituted with one or more substituents which are the same or different or a C₃₋₈ cycloalkenyl group which may be substituted with one or more 20 substituents which are the same or different,

which process comprises reacting an α,β -unsaturated aldehyde represented by the formula (II):



25

wherein each of R₁ and R₂ is as defined above, with nitrosobenzene in the presence of a NHC catalyst.

3. The process according to claim 2, wherein in the formulae (I) and (II), each of the C₁₋₆ alkyl, C₂₋₆ alkenyl, 30 C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₄ aryl,

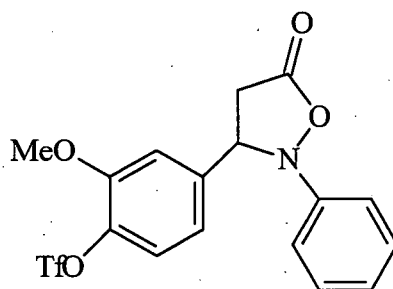
C₆₋₁₄ aryl-C₁₋₆ alkyl, C₆₋₁₄ aryl-C₂₋₆ alkenyl, C₆₋₁₄ aryl-C₂₋₆ alkynyl, 4- to 10-membered non-aromatic heterocyclic, 5- to 14-membered aromatic heterocyclic and C₁₋₆ alkoxy carbonyl groups may be substituted with 1 to 3 substituents which are
5 independently a halogen atom, a hydroxyl group, a thiol group, a nitro group, a nitrile group, a cyano group, a C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl group which may be substituted with a halogen atom, a C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl group which may be substituted, a C₆₋₁₄ aryl
10 group which may be substituted, a 4- to 10-membered non-aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently nitrogen, oxygen or sulfur and which group may be substituted, a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 heteroatoms which are
15 independently nitrogen, oxygen or sulfur and which group may be substituted, a C₁₋₆ alkoxy group which may be substituted, a C₃₋₈ cycloalkoxy group which may be substituted, a C₁₋₆ alkylthio, C₂₋₆ alkenylthio or C₂₋₆ alkynylthio group which may be substituted, a C₃₋₈ cycloalkylthio or C₃₋₈
20 cycloalkenylthio group which may be substituted, a C₆₋₁₄ aryloxy group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-oxy group which may be substituted, a 5- to 14-membered aromatic heterocycle-oxy group which may be substituted, a C₆₋₁₄ arylthio group which may be
25 substituted, a 4- to 10-membered non-aromatic heterocycle-thio group which may be substituted, a 5- to 14-membered aromatic heterocycle-thio group which may be substituted, an amino group which may be substituted, an azide group, a guanidino group, a carbamide group, a formyl group, a C₁₋₆
30 imido group, a carbonyl group which is substituted, a carbonyl-oxy group which is substituted, a carboxy group, a carbamoyl group which may be substituted, a C₁₋₄ alkylenedioxy group, a sulfinyl group which is substituted, a sulfonyl which is substituted with a trifluoromethyl

group, a C₁₋₆ alkoxy carbonyl group, a C₁₋₆ alkylsulfonyl group, an oxo group or a C₁₋₆ alkoxyimino group.

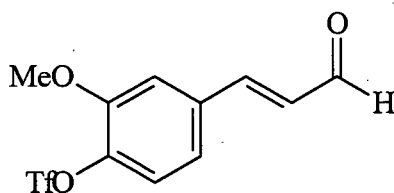
4. The process according to claim 2 or 3, wherein in the formulae (I) and (II), R₁ is a C₁₋₆ alkoxy carbonyl group or a C₆₋₁₄ aryl group which may be substituted with 1 to 3 substituents which are independently nitro, trifluoromethyl, trifluoromethylsulfonyl, methoxy or methoxycarbonyl.

5. The process according to any one of claims 2 to 4, wherein the formulae (I) and (II), R₂ is a hydrogen atom.

10 6. A process for preparing a *N*-phenylisoxalidin-5-one derivative represented by the formula:



15 comprising reacting an α,β -unsaturated aldehyde represented by the formula:

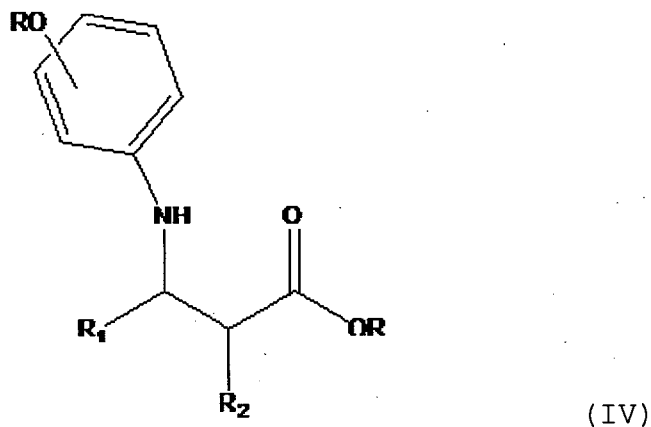


20 with nitrosobenzene in the presence of a NHC catalyst.

7. A process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative comprising reacting an α,β -unsaturated aldehyde with nitrosobenzene in the presence of a *N*-heterocyclic carbene (NHC) catalyst to form a *N*-phenylisoxazolidin-5-one derivative and then treating

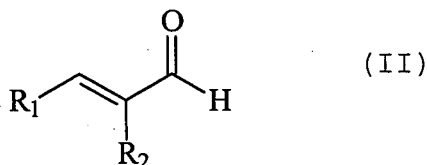
the *N*-phenylisoxazolidin-5-one derivative with an alcohol in the presence of an acid catalyst.

8. The process according to claim 7 for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula (IV):

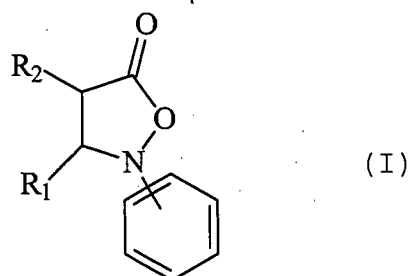


wherein each of R_1 and R_2 is as defined in claim 2 and R_8 is a C_{1-6} alkyl group, which process comprises:

- 10 (a) reacting an α,β -unsaturated aldehyde represented by the formula (II):



- wherein each of R_1 and R_2 is as defined in claim 2, with
15 nitrosobenzene in the presence of a NHC catalyst to form a *N*-phenylisoxazolidin-5-one derivative represented by the formula (I):



wherein each of R₁ and R₂ is as defined in claim 2; and

(b) then treating the *N*-phenylisoxazolidin-5-one derivative with an alcohol represented by the formula R₈OH wherein R₈ is as defined above, in the presence of an acid catalyst.

9. The process according to claim 7 or 8 further comprising deprotecting under mild oxidative conditions a nitrogen-protecting group from the *N*-alkoxyphenyl protected β -amino acid ester derivative.

10. The process according to claim 8 or 9, wherein for each of R₁ and R₂ in the formulae (I), (II) and (IV), each of the C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, C₃₋₈ cycloalkenyl, C₆₋₁₄ aryl, C₆₋₁₄ aryl-C₁₋₆ alkyl, C₆₋₁₄ aryl-C₂₋₆ alkenyl, C₆₋₁₄ aryl-C₂₋₆ alkynyl, 4- to 10-membered non-aromatic heterocyclic, 5- to 14-membered aromatic heterocyclic and C₁₋₆ alkoxy carbonyl groups may be substituted with 1 to 3 substituents which are independently a halogen atom, a hydroxyl group, a thiol group, a nitro group, a nitrile group, a cyano group, a C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl group which may be substituted with a halogen atom, a C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl group which may be substituted, a C₆₋₁₄ aryl group which may be substituted, a 4- to 10-membered non-aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently nitrogen, oxygen or sulfur and which group may be substituted, a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently nitrogen, oxygen or sulfur and which group may be substituted, a C₁₋₆ alkoxy group which may be substituted, a C₃₋₈ cycloalkoxy group which may be substituted, a C₁₋₆ alkylthio, C₂₋₆ alkenylthio or C₂₋₆ alkynylthio group which may be substituted, a C₃₋₈ cycloalkylthio or C₃₋₈

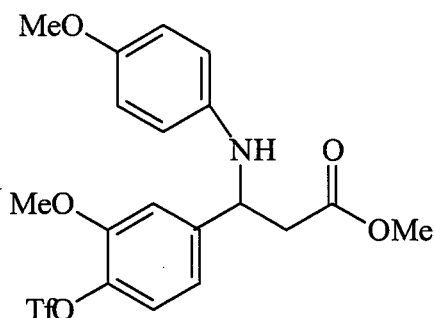
cycloalkenylthio group which may be substituted, a C₆₋₁₄ aryloxy group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-oxy group which may be substituted, a 5- to 14-membered aromatic heterocycle-oxy group which may be substituted, a C₆₋₁₄ arylthio group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-thio group which may be substituted, a 5- to 14-membered aromatic heterocycle-thio group which may be substituted, an amino group which may be substituted, an azide group, a guanidino group, a carbamide group, a formyl group, a C₁₋₆ imido group, a carbonyl group which is substituted, a carbonyl-oxy group which is substituted, a carboxy group, a carbamoyl group which may be substituted, a C₁₋₄ alkylendioxy group, a sulfinyl group which is substituted, a sulfonyl which is substituted with a trifluoromethyl group, a C₁₋₆ alkoxy carbonyl group, a C₁₋₆ alkylsulfonyl group, an oxo group or a C₁₋₆ alkoxyimino group.

11. The process according to any one of claims 8 to 10, wherein in the formulae (I), (II) and (IV), R₁ is a C₁₋₆ alkoxy carbonyl group or a C₆₋₁₄ aryl group which may be substituted with 1 to 3 substituents which are independently nitro, trifluoromethyl, trifluoromethylsulfonyl, methoxy or methoxy carbonyl.

12. The process according to any one of claims 8 to 11, wherein R₂ is a hydrogen atom.

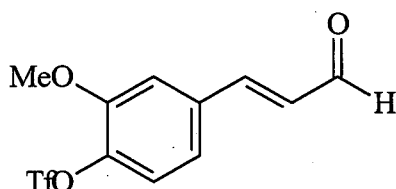
13. A process for preparing an N-alkoxyphenyl protected β -amino acid ester derivative represented by the formula:

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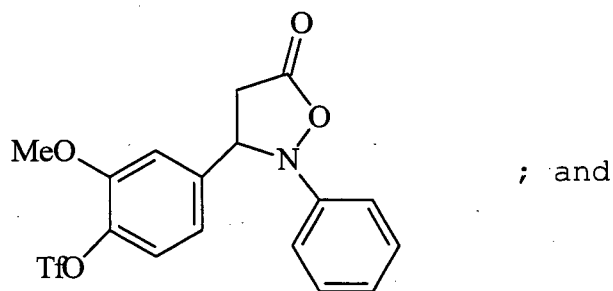
comprising reacting an α,β -unsaturated aldehyde represented by the formula:

10



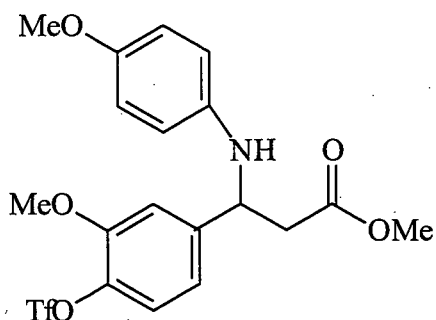
with nitrosobenzene in the presence of a NHC catalyst to form a *N*-phenylisoxalidin-5-one derivative represented by the formula:

15



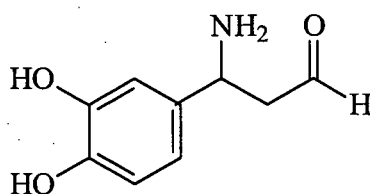
then treating the *N*-phenylisoxalidin-5-one derivative with methanol in the presence of an acid catalyst.

20 14. The process according to claim 13 further comprising deprotecting under mild oxidative conditions the nitrogen protecting group of the *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula:



5

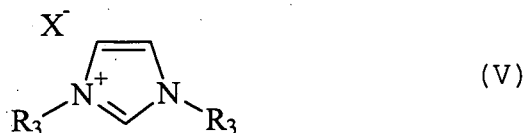
to form the compound represented by the formula:



10 15. The process according to any one of claims 7 to 14, wherein the acid catalyst is perchloric acid.

16. The process according to any one of claims 1 to 15, wherein the NHC catalyst is derived from an imidazolium salt.

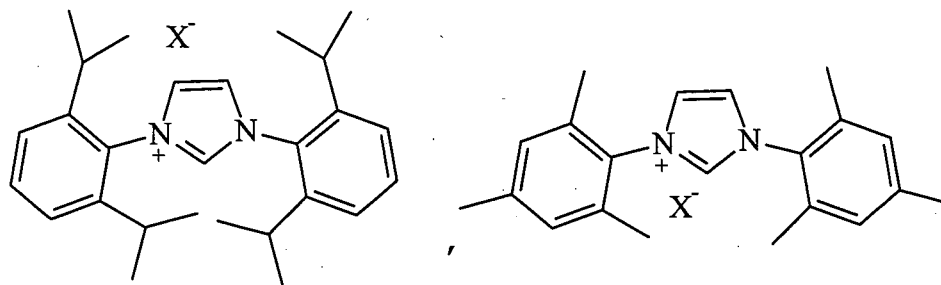
15 17. The process according to claim 16, wherein the imidazolium salt is represented by the formula (V):



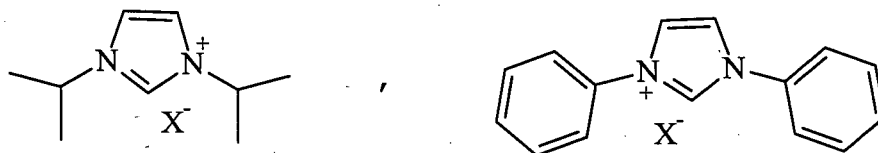
20 wherein R_3 is Ph, i Pr, Mes or 2,6- i Pr-Ph; and X^- is Br^- , BF_4^- or Cl^- .

18. The process according to claim 16, wherein the imidazolium salt is represented by the formula:

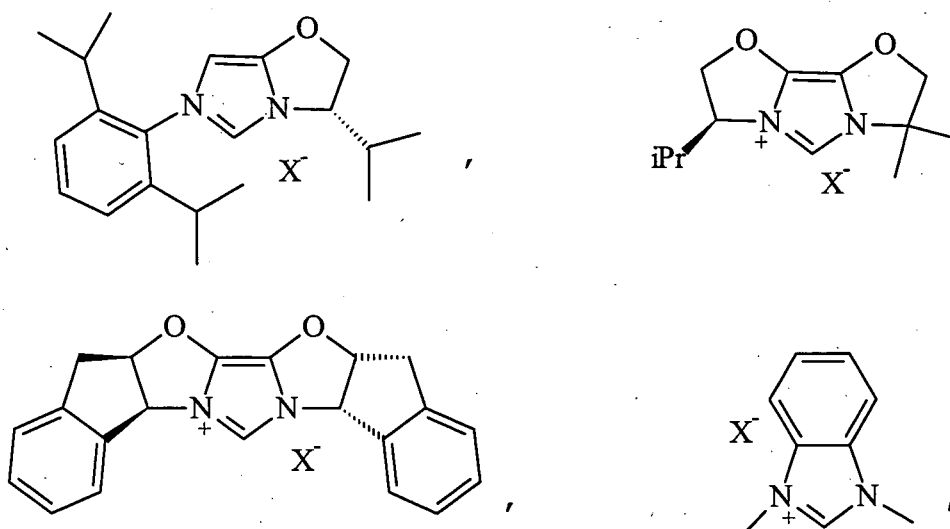
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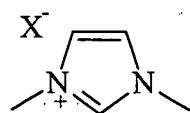
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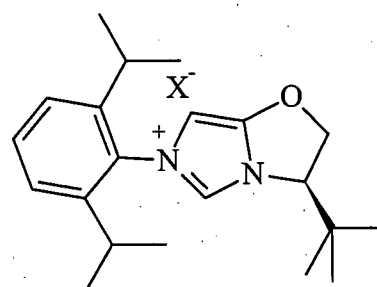
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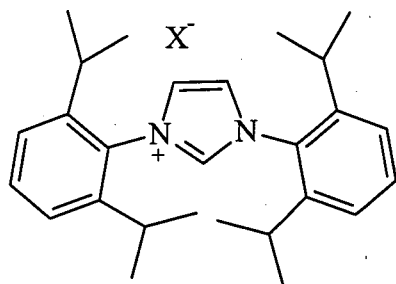
or



wherein X^- is Br^- , BF_4^- , Cl^- or OTf^- .

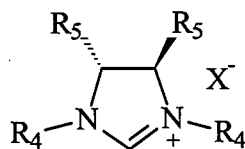
19. The process according to claim 16, wherein the imidazolium salt is represented by the formula:

5



wherein X^- is Cl^- .

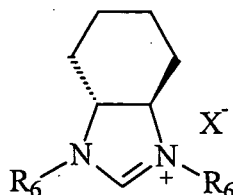
10 20. The process according to claim 16, wherein the imidazolium salt is represented by the formula (VI):



(VI)

15 wherein R_4 is 2,6- i Pr-Ph; R_5 is hydrogen or Ph; and X^- is Cl^- .

21. The process according to claim 16, wherein the imidazolium salt is represented by the formula (VII):

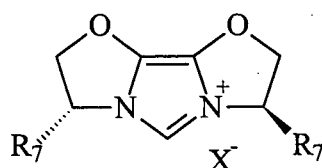


(VII)

20

wherein R_6 is 2,6- i Pr-Ph and X^- is Cl^- .

22. The process according to claim 16, wherein the imidazolium salt represented by the formula:



wherein R_7 is i -Pr or t -Bu; and X^- is Br^- , BF_4^- or Cl^- .

5 23. The process according to any one of claims 1 to 22, wherein the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst are reacted in the presence of a base.

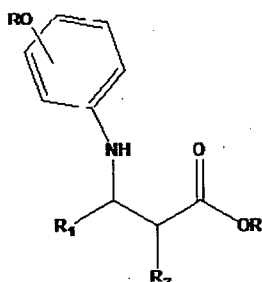
24. The process according to claim 23, wherein the
base is 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or
10 potassium *tert*-butoxide (KO^tBu).

25. The process according to any one of claims 1 to 24, wherein the α,β -unsaturated aldehyde, nitrosobenzene and the NHC catalyst are reacted in the presence of a solvent.

26. The process according to claim 25, wherein the
15 solvent is dichloromethane or tetrahydrofuran.

27. A process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative comprising treating a *N*-phenylisoxazolidin-5-one derivative with an alcohol in the presence of an acid catalyst.

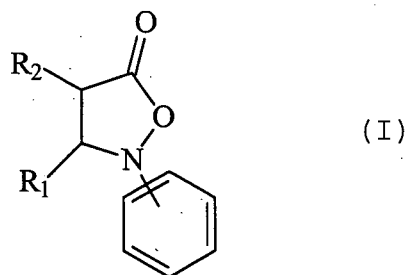
20 28. The process according to claim 27 for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula (IV):



(IV)

wherein each of R_1 and R_2 is as defined in claim 2 and R_8 is a C_{1-6} alkyl group, which process comprises treating a *N*-phenylisoxazolidin-5-one derivative represented by the formula (I):

5



wherein each of R_1 and R_2 is as defined in claim 2, with an alcohol represented by the formula R_8OH wherein R_8 is as defined above, in the presence of an acid catalyst.

29. The process according to claim 27 or 28 further comprising deprotecting under mild oxidative conditions a nitrogen-protecting group from the *N*-alkoxyphenyl protected β -amino acid ester derivative.

30. The process according to claim 28 or 29, wherein for each of R_1 and R_2 in the formulae (I) and (IV), each of the C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl, C_{6-14} aryl, C_{6-14} aryl- C_{1-6} alkyl, C_{6-14} aryl- C_{2-6} alkenyl, C_{6-14} aryl- C_{2-6} alkynyl, 4- to 10-membered non-aromatic heterocyclic, 5- to 14-membered aromatic heterocyclic and C_{1-6} alkoxy carbonyl groups may be substituted with 1 to 3 substituents which are independently a halogen atom, a hydroxyl group, a thiol group, a nitro group, a nitrile group, a cyano group, a C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl group which may be substituted with a halogen atom, a C_{3-8} cycloalkyl or C_{3-8} cycloalkenyl group which may be substituted, a C_{6-14} aryl group which may be substituted, a 4- to 10-membered non-aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently

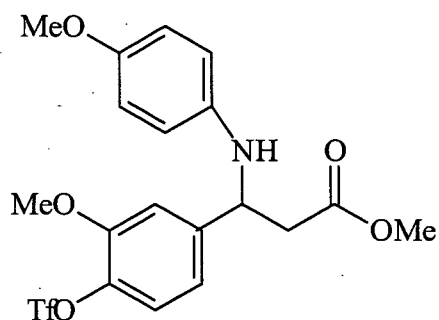
nitrogen, oxygen or sulfur and which group may be substituted, a 5- to 14-membered aromatic heterocyclic group containing 1 to 4 heteroatoms which are independently nitrogen, oxygen or sulfur and which group may be substituted, a C₁₋₆ alkoxy group which may be substituted, a C₃₋₈ cycloalkoxy group which may be substituted, a C₁₋₆ alkylthio, C₂₋₆ alkenylthio or C₂₋₆ alkynylthio group which may be substituted, a C₃₋₈ cycloalkylthio or C₃₋₈ cycloalkenylthio group which may be substituted, a C₆₋₁₄ aryloxy group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-oxy group which may be substituted, a 5- to 14-membered aromatic heterocycle-oxy group which may be substituted, a C₆₋₁₄ arylthio group which may be substituted, a 4- to 10-membered non-aromatic heterocycle-thio group which may be substituted, a 5- to 14-membered aromatic heterocycle-thio group which may be substituted, an amino group which may be substituted, an azide group, a guanidino group, a carbamide group, a formyl group, a C₁₋₆ imido group, a carbonyl group which is substituted, a carbonyl-oxy group which is substituted, a carboxy group, a carbamoyl group which may be substituted, a C₁₋₄ alkylenedioxy group, a sulfinyl group which is substituted, a sulfonyl which is substituted with a trifluoromethyl group, a C₁₋₆ alkoxy carbonyl group, a C₁₋₆ alkylsulfonyl group, an oxo group or a C₁₋₆ alkoxyimino group.

31. The process according to any one of claims 28 to 30, wherein in the formulae (I) and (IV), R₁ is a C₁₋₆ alkoxy carbonyl group or a C₆₋₁₄ aryl group which may be substituted with 1 to 3 substituents which are independently nitro, trifluoromethyl, trifluoromethylsulfonyl, methoxy or methoxycarbonyl.

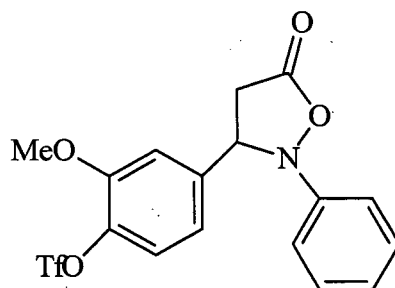
32. The process according to any one of claims 28 to 31, wherein R₂ is a hydrogen atom.

33. A process for preparing an *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula:

5



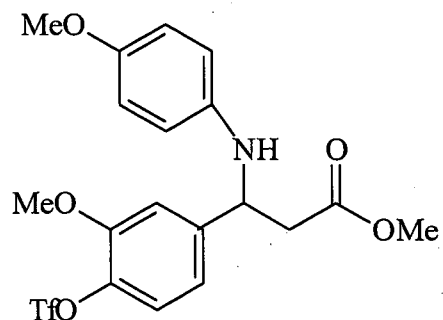
comprising treating a *N*-phenylisoxalidin-5-one derivative
10 represented by the formula:



15 with methanol in the presence of an acid catalyst.

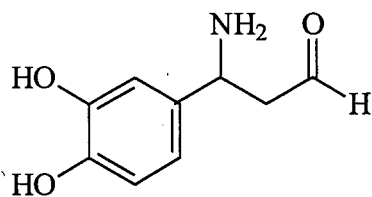
34. The process according to claim 33 further comprising deprotecting under mild oxidative conditions the nitrogen protecting group of the *N*-alkoxyphenyl protected β -amino acid ester derivative represented by the formula:

20



to form the compound represented by the formula:

66



35. The process according to any one of claims 27 to
5 34, wherein the acid catalyst is perchloric acid.

36. The process according to claim 7 or 27, wherein
the alcohol is methanol.

37. The process according to claim 8, 9, 10, 11, 12,
28, 29, 30, 31 or 32, wherein R₈ is methyl.