

**N-HETEROCYCLIC CARBENE (NHC) CATALYZED SYNTHESIS OF
HYDROXAMIC ACIDS**

This application claims the benefit of, and priority from, U.S. Provisional Patent Application Serial
5 No. 60/907,133, filed March 22, 2007, and U.S. Provisional Patent Application Serial No. 61/006,771, filed January 30, 2008, which are both incorporated herein by reference.

This invention relates to a process for preparing a hydroxamic acid comprising reacting an aldehyde with a
10 nitroso compound in the presence of a *N*-heterocyclic carbene (NHC) catalyst.

BACKGROUND

Hydroxamic acids play a number of roles in a range of biological and biochemical processes and systems.
15 Accordingly, hydroxamic acids have been and continue to be investigated and their chemistry and biochemistry are well documented. Hydroxamic acids have been reported to act in a number of different capacities, including as antibacterial, antifungal and anticancer agents, and as specific enzyme
20 inhibitors. Use of hydroxamic acids as metal ion chelators has been reported. A number of groups have reported on the investigation of hydroxamic acids in human clinical trials as drugs for the treatment of several diseases.

Pathways for synthesizing hydroxamic acids are of
25 interest due to their pharmacological, toxicological and pathological properties. Approaches for synthesizing hydroxamic acids have been reported, including reactions involving the acylation of hydroxylamines. Other pathways for synthesizing hydroxamic acids have been reported,
30 including reactions involving the oxidation of arylacylamides.

Preparation of hydroxamic acids involving the reaction of nitroso compounds has been reported. Nitroso compounds have been reported as exhibiting a high reactivity of the nitroso group. The polarization of the nitrogen-oxygen bond, resembling that of the carbon-oxygen bond in a carbonyl group, results in susceptibility of the nitroso group to the addition of nucleophiles. Preparation of *N*-arylhydroxamic acids involving the reaction of aromatic nitroso compounds with oxoacids in the presence of acidic media has been reported. The conversion of aromatic nitroso compounds into hydroxamic acids using thiamine-dependent enzymes, such as α -ketoglutarate dehydrogenase, pyruvate decarboxylase and transketolase, has been reported (see, for example, Corbett, M. D.; Corbett, B. R.; Doerge, D. R. *J. Chem. Soc. Perkin Trans. I* 1982, 345 and references therein; and Corbett, M. D.; Doerge, D. R.; Corbett, B. R. *J. Chem. Soc. Perkin Trans. I* 1983, 765).

Many groups have reported that organocatalytic reactions provide an efficient means for metal-free carbon-nitrogen (C-N) bond and carbon-carbon (C-C) bond formation.

Examples of organocatalytic C-N bond formation reactions, including *N*-nitroso aldol reaction of enamines selectively forming *N*-hydroxyaminoketones, have been reported (see, for example, Yamamoto, H. and Momiyama N. *J. Am. Chem. Soc.* 2005, 127, 1080; and Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* 2007, 129, 1190).

Many groups have reported that *N*-heterocyclic carbene catalysts can be used for metal-free C-C bond formation via the nucleophilic "Breslow intermediate", or the homoenolate equivalent species. Depending on the electrophile, different types of reactions are possible via both intermediates.

Examples of the former path have been reported, including benzoin condensation, wherein an aryl aldehyde acts as the electrophile, and the Stetter reaction, wherein a Michael acceptor acts as the electrophile. Other examples
5 of this path have been reported, including redox reactions of α -functionalized aldehydes to form the corresponding esters or amides.

Examples of C-C bond forming reactions involving the homoenolate equivalent species have been reported,
10 including lactonization, cyclopentannulation, and azannulation.

Approaches for the preparation of hydroxamic acids using readily available reactants and catalysts are desired.

SUMMARY

15 In one broad aspect of the present invention, there is provided a process for preparing a hydroxamic acid comprising reacting an aldehyde with a nitroso compound in the presence of a NHC catalyst.

20 In another broad aspect of the present invention, there is provided a process for preparing a chiral hydroxamic acid comprising reacting a α -branched aldehyde with a nitroso compound in the presence of an achiral NHC catalyst.

25 In a further broad aspect of the present invention, there is provided a process for preparing a chiral hydroxamic acid comprising reacting a α -branched aldehyde with a nitroso compound in the presence of a chiral NHC catalyst.

In still another aspect of the present invention, there is provided a process for preparing *N*-propionyloxy-*N*-phenylacrylamide.

DETAILED DESCRIPTION

5 I. Process for Preparing Hydroxamic Acid

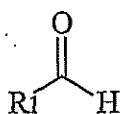
In an embodiment of the present invention, an aldehyde may be reacted with a nitroso compound in the presence of a NHC catalyst to prepare a hydroxamic acid.

A. Aldehyde

10 The aldehyde which may be used in the present invention is not particularly limited. In an embodiment of the present invention, the aldehyde may be, for example, and without limitation, an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, arylalkyl, arylalkenyl, arylalkynyl or
15 heterocyclic aldehyde which may be substituted with one or more substituents which are the same or different.

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

20



(II)

wherein R_1 may be, for example, and without limitation, a hydrogen atom, a C_{1-6} alkyl group which may be substituted with one or more substituents which are the same or
25 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 substituted with one or more

substituents which are the same or different, a C₃₋₈ cycloalkenyl group which may be substituted with one or more substituents which are the same or different, a C₆₋₁₄ aryl group which may be substituted with one or more substituents which are the same or different, a C₆₋₁₄ aryl-C₁₋₆ alkyl group which may be substituted with one or more substituents which are the same or different, a C₆₋₁₄ aryl-C₂₋₆ 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, or 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.

The following definitions of the various groups as described herein are the same for all occurrences of these groups throughout the entire specification unless otherwise indicated.

The C₁₋₆ alkyl group of the alkyl containing groups 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, interrupted by 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, interrupted by 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, interrupted by 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 aryl containing groups 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
5 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
10 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
15 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
20 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
25 one or more heteroatoms which are independently nitrogen, sulfur or oxygen may be, for example, and without limitation, pyrrolidinyl, pyrrolinyl, piperidinyl, piperazinyl, imidazolinyl, pyrazolidinyl, imidazolidinyl, morpholinyl, tetrahydropyranyl, azetidiny, oxetanyl,
30 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 are independently nitrogen, sulfur or oxygen and which group may be substituted, may contain, for example, and without
 5 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 are independently nitrogen, sulfur or oxygen may be, for example, and without limitation, pyrrolyl, pyridinyl,
 10 pyridazinyl, pyrimidinyl, pirazinyl, imidazolyl, thiazolyl or oxazolyl.

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
 15 10-membered non-aromatic heterocyclic and 5- to 14-membered aromatic heterocyclic 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 substituted with, for example, and
 20 without limitation, one to three substituents.

The one or more substituents for each of the above-mentioned groups, which are the same or different, may be, for example, and without limitation, a halogen atom, a hydroxyl group, a thiol group, a nitro group, a nitrile
 25 group, a cyano group; a C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl group which may be substituted; a C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl group which may be substituted; a C₆₋₁₄ aryl group which may be substituted; a C₆₋₁₄ aryl-C₁₋₆ alkyl, C₆₋₁₄ aryl-C₂₋₆ alkenyl or C₆₋₁₄ aryl-C₂₋₆ alkynyl group which may be
 30 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 sulfanyl group, a sulfinyl group which is substituted, a sulfonyl group which is substituted, 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, for example, a C₁₋₆ alkyl group, a C₂₋₆ alkenyl group which may be substituted with C₁₋₆ alkoxy carbonyl, a C₃₋₈ cycloalkyl group, a C₆₋₁₄ aryl group which may be substituted with C₁₋₆ alkoxy, nitro or halogen, a C₆₋₁₄ aryl-C₁₋₆ alkyl group, a C₆₋₁₄ aryl-C₂₋₆ alkenyl group, a C₆₋₁₄ aryl-C₂₋₆ alkenyl group wherein the C₆₋₁₄ aryl may be substituted with one or more substituents which are independently C₁₋₆ alkoxy, nitro or trifluoromethylsulfonyl, or 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 with C₁₋₆ alkyl.

B. Nitroso Compound

The nitroso compound which may be used in the present invention is not particularly limited.

In an embodiment of the present invention, the nitroso compound may be, for example, and without limitation, a compound represented by the formula (III):



wherein R₂ may be, for example, and without limitation, 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, a C₃₋₈ cycloalkenyl group which may be substituted with one or more substituents which are the same or different, a C₆₋₁₄ aryl group which may be substituted with one or more substituents which are the same or different, a C₆₋₁₄ aryl-C₁₋₆ alkyl group which may be substituted with one or more substituents which are the same or different, a C₆₋₁₄ aryl-C₂₋₆ 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 C₁₋₆ alkoxy carbonyl group which may be substituted with one or

more substituents which are the same or different, a C₆₋₁₄ aryloxy carbonyl group which may be substituted with one or more substituents which are the same or different, an amino-C₁₋₆ alkyl group which may be substituted with one or
 5 more substituents which are the same or different, an amino-C₆₋₁₄ aryl group which may be substituted with one or more substituents which are the same or different, an acetyl group or an amido group.

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, C₁₋₆ alkoxy carbonyl, C₆₋₁₄ aryloxy carbonyl, amino-C₁₋₆ alkyl and amino-C₆₋₁₄ aryl groups may be substituted with one or more
 10 substituents which are the same or different. In an embodiment of the present invention, each of the above-mentioned groups may be substituted with, for example, and without limitation, one to three substituents.

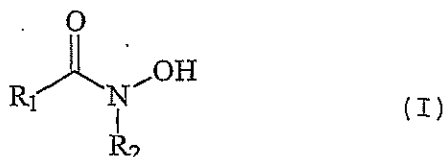
The one or more substituents for each of the above-mentioned groups, which are the same or different, may
 20 be, for example, and without limitation, the same substituents as defined anywhere above for the aldehyde.

In an exemplary embodiment of the present invention, R₂ may be, for example, and without limitation, a phenyl group which may be substituted with one or more
 25 substituents which are the same or different.

In an embodiment of the present invention, R₂ may be, for example, and without limitation, a phenyl group which may be substituted with one or more substituents, which are the same or different, and are a halogen atom, an
 30 amino group which may be substituted by C₁₋₆ alkyl, a C₁₋₆ alkyl group or a hydroxyl group.

C. Hydroxamic Acid

In an embodiment of the present invention, the hydroxamic acid may be, for example, and without limitation, a compound represented by the formula (I):



wherein R_1 and R_2 may be defined as anywhere above.

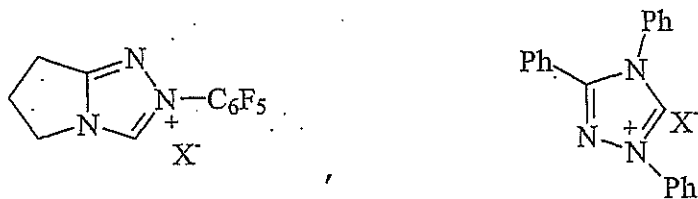
10 D. NHC Catalyst

The NHC catalyst that may be used in 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
15 limitation, a triazolium salt or an imidazolium salt.

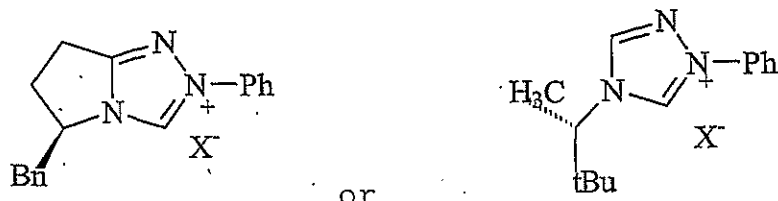
In an embodiment of the present invention, the NHC catalyst may be derived from, for example, and without limitation, a triazolium salt.

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





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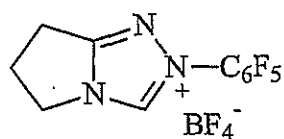


or

wherein X^- may be, for example, and without limitation, BF_4^- , ClO_4^- , Br^- or Cl^- .

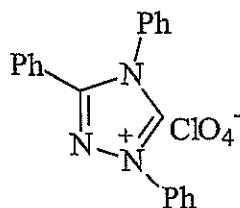
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In an embodiment of the present invention, the NHC catalyst may be derived from, for example, a triazolium salt represented by the formula:



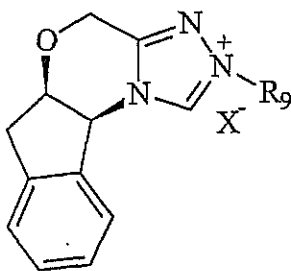
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In an embodiment of the present invention, the NHC catalyst may be derived from, for example, a triazolium salt represented by the formula:



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

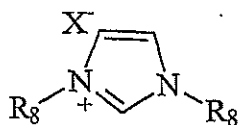


5 wherein R_9 may be, for example, and without limitation, phenyl (Ph) which may be substituted, i-propyl (i Pr), mesityl (Mes) or 2,6-diisopropylphenyl (2,6- i Pr-Ph); and X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- .

10 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:

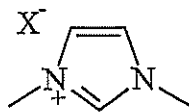
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wherein R_8 may be, for example, and without limitation, phenyl (Ph), i-propyl (i Pr), mesityl (Mes) or 2,6-diisopropylphenyl (2,6- i Pr-Ph); and X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- .

In an embodiment of the present invention, the NHC catalyst may be derived from, for example, an imidazolium salt represented by the formula:

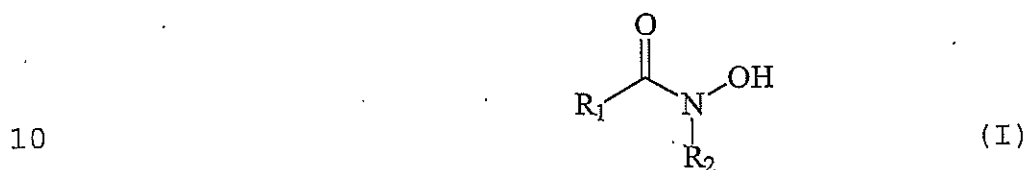
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wherein X^- may be, for example, and without limitation, Br^- , BF_4^- or Cl^- .

E. Preparation of Hydroxamic Acid

5 In an embodiment of the present invention, and without limitation, there is provided a process for preparing a hydroxamic acid represented by the formula (I):



wherein R_1 and R_2 may be defined as anywhere above, which process comprises reacting an aldehyde represented by the formula (II):

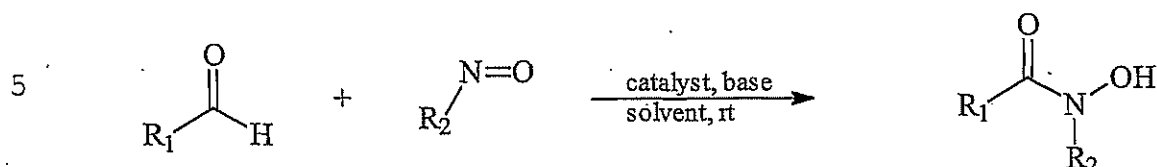


wherein R_1 may be defined as above, with a nitroso compound represented by the formula (III):



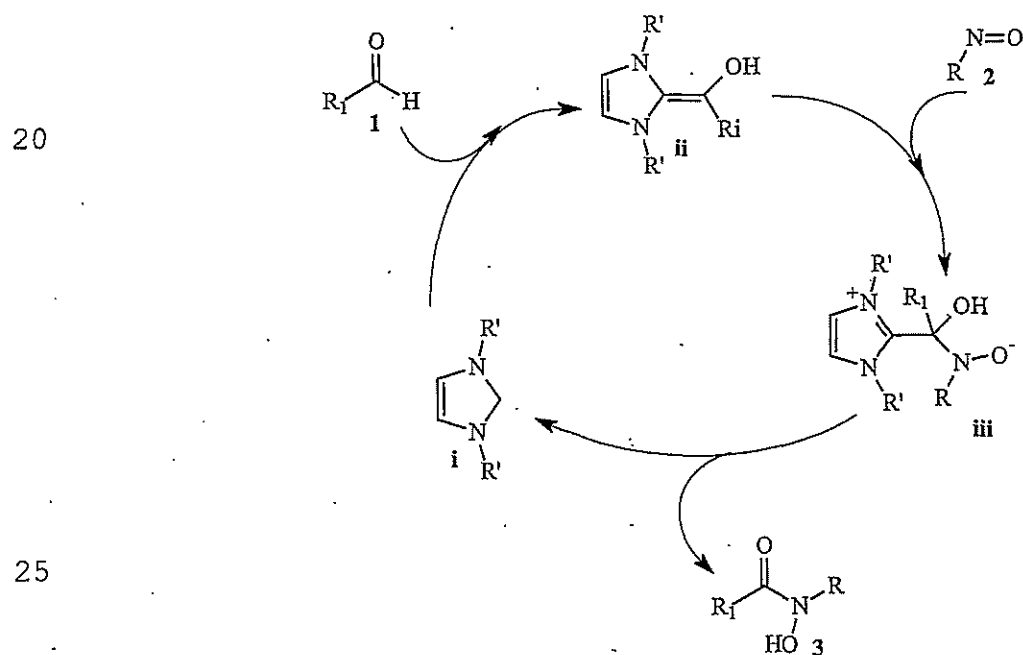
wherein R_2 may be defined as above, in the presence of a NHC catalyst.

An embodiment of the present invention may be represented by, for example, and without limitation, the following scheme:



wherein R_1 and R_2 may be defined as anywhere above.

Without being bound by theory, it is believed that the polarization of the nitrogen-oxygen bond of the nitroso compound, resembling the polarization of the carbon-oxygen bond in a carbonyl group, provides the susceptibility of the nitroso group to additions of nucleophiles. By way of example, and without limitation, as represented in the following scheme, it is believed that the higher reactivity of the nitroso group to nucleophilic attack than its carbonyl group counterpart gives rise to the reaction of the intermediate **ii** with nitrosobenzene **2** forming a hydroxamic acid **3** instead of acyloin.



wherein R_1 is defined as anywhere above, R is phenyl and R' is a hydrocarbon group including those as defined for R_1 above.

The amounts of the aldehyde and nitroso compound
5 which may be used in the present invention are not particularly limited. Suitable amounts of the aldehyde and nitroso compound 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
10 the art would understand that the aldehyde and nitroso compound may be used according to their stoichiometric ratio.

In an embodiment of the present invention, the aldehyde, nitroso compound and NHC catalyst may be, for
15 example, and without limitation, reacted in the presence of a 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 a non-nucleophilic base,
20 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
25 invention, the base may be, 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, and without limitation, carried out in the presence of a suitable solvent. The
30 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, an aprotic solvent. In an embodiment of the present invention, the solvent may be, for example, dichloromethane (CH_2Cl_2) or tetrahydrofuran (THF).

5 The amount of the NHC catalyst which may be used in 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
10 NHC catalyst may be, for example, and without limitation, less than 20 mol%, for example, and without limitation, from 0.125 to 20 mol%, and including any specific value in this range, such as, for example, and without limitation, from 0.5 to 20 mol%.

15 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 24 hours,
20 for example, and without limitation, from 2 minutes to 24 hours, and including any specific time in this range, such as, for example, and without limitation, from 1 to 12 hours.

 The reaction temperature is not particularly limited and suitable reaction temperatures would be
25 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
30 hydroxamic acid may be 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 hydroxamic acid may be isolated and/or purified by chromatographic methods or crystallization.

5 F. Process for Preparing Chiral Hydroxamic Acid

The above process for preparing the hydroxamic acid may be modified as described below in order to prepare a chiral hydroxamic acid using an achiral NHC catalyst.

10 In an embodiment of the present invention, a α -branched aldehyde may be reacted with a nitroso compound in the presence of an achiral NHC catalyst to prepare a chiral hydroxamic acid.

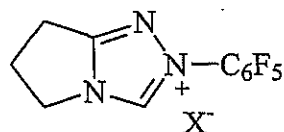
15 In an embodiment of the present invention, a α -branched aldehyde which may have one enantiomer in excess of the other (i.e., in enantiomeric excess or "ee") or which may be enantiomerically pure may be reacted with a nitroso compound in the presence of an achiral NHC catalyst to prepare a chiral hydroxamic acid which may be in enantiomeric excess or which may be enantiomerically pure.

20 In an embodiment of the present invention, an enantiomerically pure α -branched aldehyde may be reacted with a nitroso compound in the presence of an achiral NHC catalyst to prepare an enantiomerically pure chiral hydroxamic acid.

25 The achiral NHC catalyst is not particularly limited and suitable achiral NHC 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 achiral NHC catalyst may be derived from, for example, and without limitation, an achiral triazolium salt.

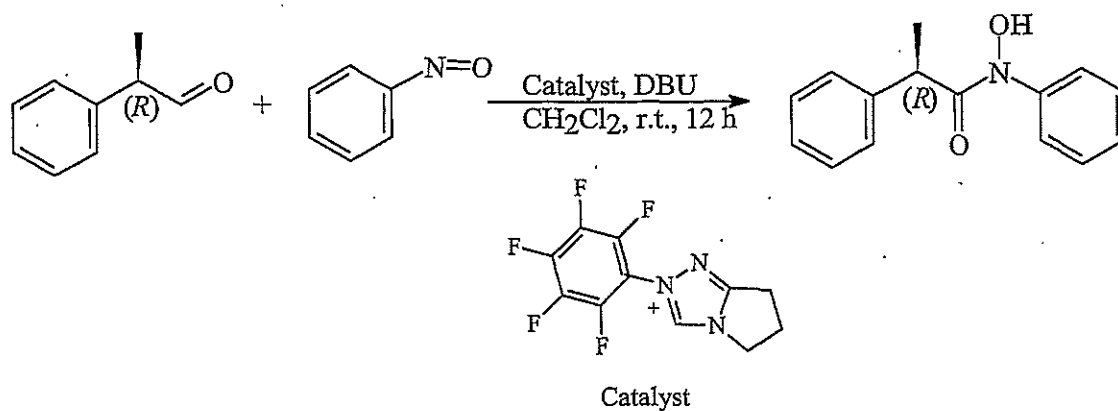
In an embodiment of the present invention, the achiral triazolium salt may be represented by, for example, the formula:



wherein X^- may be, for example, and without limitation, BF_4^- , ClO_4^- , Br^- or Cl^- .

The skilled person will appreciate that the amount of the α -branched aldehyde, the amount of the nitroso compound, the base, the solvent, the amount of the NHC catalyst, the reaction time, the reaction temperature, the isolation methods and the purification methods described above may also be used for preparing the chiral hydroxamic acid as described herein.

An embodiment of the present invention for preparing the chiral hydroxamic acid may be represented by, for example, and without limitation, the following scheme:



The above process for preparing the hydroxamic acid may also be modified as described below in order to prepare a chiral hydroxamic acid using a chiral NHC catalyst.

5 In an embodiment of the present invention, a α -branched aldehyde may be reacted with a nitroso compound in the presence of a chiral NHC catalyst to prepare a chiral hydroxamic acid.

10 In an embodiment of the present invention, a α -branched aldehyde may be reacted with a nitroso compound in the presence of a chiral NHC catalyst to prepare a chiral hydroxamic acid in enantiomeric excess.

15 In an embodiment of the present invention, a α -branched aldehyde racemate may be reacted with a nitroso compound in the presence of a chiral NHC catalyst to prepare a chiral hydroxamic acid in enantiomeric excess.

20 In an embodiment of the present invention, a α -branched aldehyde racemate may be reacted with a nitroso compound in the presence of a chiral NHC catalyst to prepare a chiral hydroxamic acid in enantiomeric excess, wherein a stoichiometric excess of the α -branched aldehyde racemate is reacted.

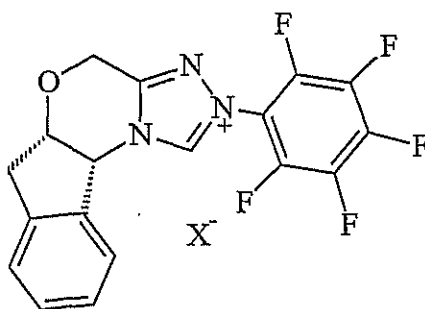
25 In an embodiment of the present invention, a α -branched aldehyde racemate may be reacted with a nitroso compound in the presence of a chiral NHC catalyst to prepare a chiral hydroxamic acid in enantiomeric excess, wherein a stoichiometric excess of the α -branched aldehyde racemate is reacted and the reaction is stopped at less than 100% conversion of the aldehyde.

In an embodiment of the present invention, a α -branched aldehyde racemate may be reacted with a nitroso compound in the presence of a chiral NHC catalyst to prepare a chiral hydroxamic acid in enantiomeric excess, wherein a stoichiometric excess of the α -branched aldehyde racemate is reacted and the reaction is stopped at about 50% conversion of the aldehyde.

The chiral NHC catalyst is not particularly limited and suitable chiral NHC catalysts would be understood to and can be determined by those of ordinary skill in the art.

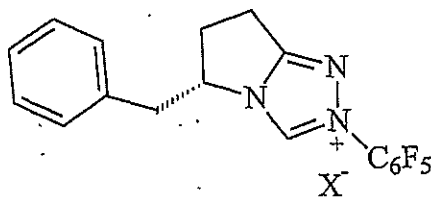
In an embodiment of the present invention, the chiral NHC catalyst may be derived from, for example, and without limitation, a chiral triazolium salt.

In an embodiment of the present invention, the chiral triazolium salt may be represented by, for example, the formula:



wherein X^- may be, for example, and without limitation, BF_4^- , ClO_4^- , Br^- or Cl^- .

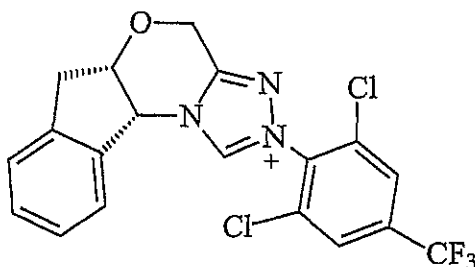
In an embodiment of the present invention, the chiral triazolium salt may be represented by, for example, the formula:



wherein X^- may be, for example, and without limitation, BF_4^- , ClO_4^- , Br^- or Cl^- .

In an embodiment of the present invention, the chiral triazolium salt may be represented by, for example,

5 the formula:



wherein X^- may be, for example, and without limitation, BF_4^- ,
10 ClO_4^- , Br^- or Cl^- .

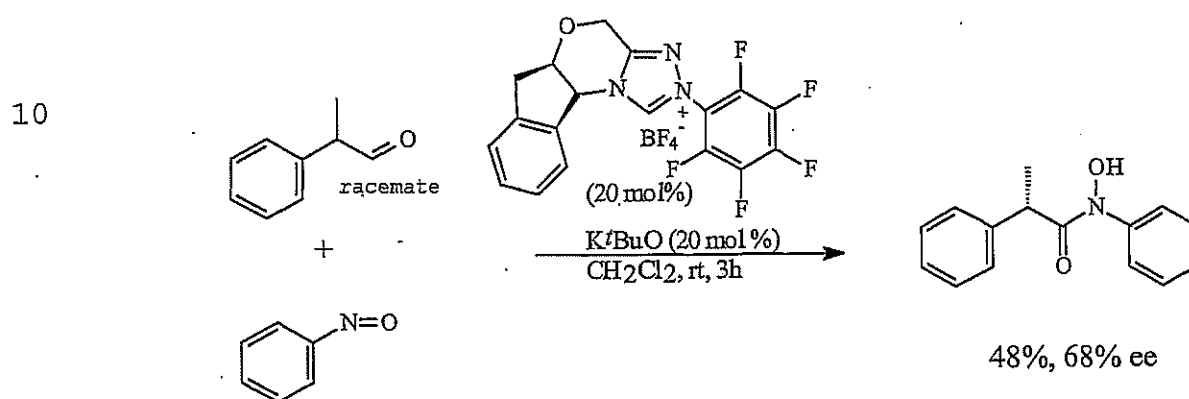
In an embodiment of the present invention using a chiral catalyst, a stoichiometric excess of the α -branched aldehyde may be used. Suitable amounts of the aldehyde would be understood to and can be determined by those of
15 ordinary skill in the art. For example, and without limitation, those of ordinary skill in the art would understand that a ratio of the α -branched aldehyde to the nitroso compound of 2:1 may be used.

In an embodiment of the present invention using a
20 chiral catalyst, for example, and without limitation, the reaction may proceed with less than 100% conversion of the α -branched aldehyde. Suitable amounts of conversion of the α -branched aldehyde would be understood to and can be determined by those of ordinary skill in the art. For
25 example, and without limitation, those of ordinary skill in the art would understand that the reaction may proceed with about 50% conversion of the α -branched aldehyde.

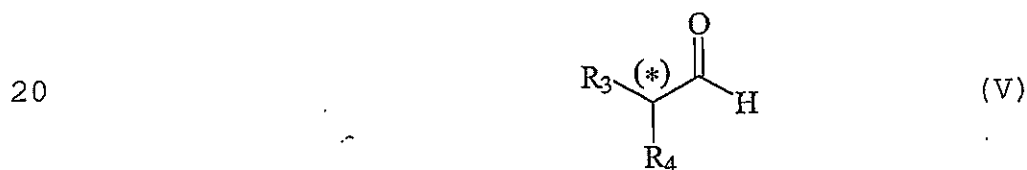
The skilled person will appreciate that the base, the solvent, the amount of the NHC catalyst, the reaction

time, the reaction temperature, the isolation methods and the purification methods described above may also be used for preparing the chiral hydroxamic acid as described herein.

5 An embodiment of the present invention for preparing the chiral hydroxamic acid by kinetically resolving the α -branched aldehyde may be represented by, for example, and without limitation, the following scheme:



15 In an embodiment of the present invention using either an achiral or chiral catalyst, the α -branched aldehyde may be, for example, and without limitation, a compound represented by the formula (V):



wherein:

(*) refers to a chiral center; and

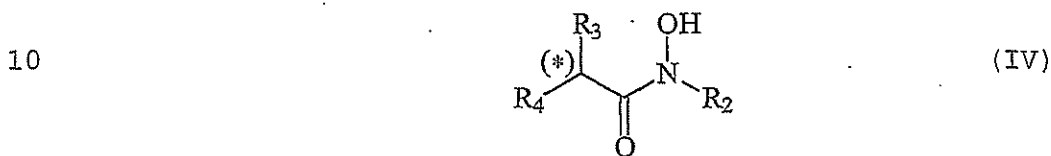
R_3 and R_4 , which are different, may be for example, and without limitation, a halogen atom, a hydroxyl group, a thiol group, a nitro group, a nitrile group, a cyano group;

a C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl group which may be substituted; a C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl group which may be substituted; a C₆₋₁₄ aryl group which may be substituted, a C₆₋₁₄ aryl-C₁₋₆ alkyl group which may be substituted, a C₆₋₁₄ aryl-C₂₋₆ alkenyl group which may be substituted, a C₆₋₁₄ aryl-C₂₋₆ alkynyl 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 sulfanyl group, a sulfinyl group which is substituted, a sulfonyl group which is substituted, a C₁₋₆ alkoxycarbonyl group, a C₁₋₆ alkylsulfonyl group, an oxo group or a C₁₋₆ alkoxyimino group.

In an embodiment of the present invention, R_3 , for example, is a C_{1-6} alkyl group.

In an embodiment of the present invention, R_4 , for example, is a phenyl group.

5 In an embodiment of the present invention using either an achiral or chiral catalyst, the chiral hydroxamic acid may be, for example, and without limitation, a compound represented by the formula (IV):



wherein (*), R_2 , R_3 and R_4 are as defined anywhere above.

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

15 G. Examples

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

20

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
25 CombiFlashTM (ISCO, Inc.).

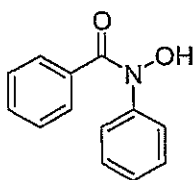
Chemical yields refer to pure isolated substances.

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

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were obtained using a Bruker™ 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), m_c (centered multiplet)); coupling constants (J, Hz); integration; assignment.

Studies using different NHC catalysts were conducted by adding base (5×10^{-3} to 0.02 mmol) under argon to a solution of benzaldehyde (10.6 mg, 0.1 mmol), nitroso compound (10.7 mg, 0.1 mmol) and the catalyst (5×10^{-3} to 0.02 mmol) in solvent (0.5 ml). The reaction mixture was stirred at room temperature for 10 min. The yields were determined by GC.

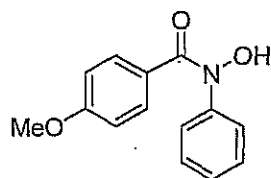
N-hydroxy-*N*-phenylbenzamide



DBU (3.8 mg, 0.025 mmol) was added under argon to a solution of benzaldehyde (106 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (1.82 mg, 0.005 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.05 (br s, 1H, OH),
 7.45–7.36 (m, 3H, Ar-H), 7.33–7.25 (m, 5H, Ar-H), 7.22–7.19
 (m, 2H, Ar-H). ^{13}C (100 MHz, CDCl_3): δ = 164.9 (C_q , CO), 139.1
 (C_q), 131.8 (C_q), 131.1, 129.2, 128.9, 128.3, 128.2, 126.0.
 5 MS (ESI): m/z 197 ($\text{M}^+ - \text{O}$), 105, 77.

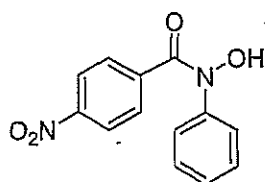
N-hydroxy-4-methoxy-*N*-phenylbenzamide



DBU (7.61 mg, 0.05 mmol) was added under argon to
 10 a solution of 4-methoxybenzaldehyde (136 mg, 1 mmol),
 nitrosobenzene (107 mg, 1 mmol) and catalyst (18.15 mg, 0.05
 mmol) in dichloromethane (5 mL). The reaction mixture was
 stirred at room temperature for 10 min. The solvent was
 removed under vacuum, and the residue was purified by flash
 15 silica gel column chromatography using hexane and ethyl
 acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.07 (br s, 1H, OH), 7.40
 (AB, d, J_{AB} = 8.9 Hz, 2H, Ar-H), 7.35–7.28 (m, 3H, Ar-H),
 7.24–7.22 (m, 2H, Ar-H), 6.76 (AB, d, J_{AB} = 8.9 Hz, 2H, Ar-
 20 H), 3.79 (s, 3H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 165.1 (C_q ,
 CO), 161.7 (C_q), 140.4 (C_q), 131.0, 129.1, 127.9, 125.9,
 124.3 (C_q), 113.4, 55.3. MS (ESI): m/z 227 ($\text{M}^+ - \text{O}$), 135, 107,
 92, 77.

25 *N*-hydroxy-4-nitro-*N*-phenylbenzamide

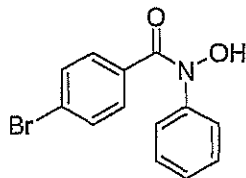


DBU (3.8 mg, 0.025 mmol) was added under argon to a solution of 4-nitrobenzaldehyde (151 mg, 1 mmol), nitroso benzene (107 mg, 1 mmol) and catalyst (1.82 mg, 0.005 mmol) in dichloromethane (5 mL). The reaction mixture was stirred
5 at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

Scale up: DBU (3.8 mg, 0.025 mmol) was added under
10 argon to a solution of 4-nitrobenzaldehyde (3 g, 20 mmol), nitrosobenzene (2.14 g, 20 mmol) and catalyst (9 mg, 0.025 mmol) in dichloromethane (100 mL). The reaction mixture was stirred at room temperature for 2 min. The product precipitated as a yellow solid. The solvent was removed
15 under vacuum, and the solid was washed with hexane and ether to yield a pure product (5g).

^1H (400 MHz, CDCl_3): δ = 8.93 (br s, 1H, OH), 8.13 (AB, d, J_{AB} = 9.1 Hz, 2H, Ar-H), 7.60 (AB, d, J_{AB} = 9.1 Hz, 2H, Ar-H), 7.36-7.34 (m, 3H, Ar-H), 7.24-7.22 (m, 2H, Ar-H).
20 ^{13}C (100 MHz, CDCl_3): δ = 162.7 (C_q , CO), 148.9 (C_q), 138.3, 138.0, 130.0, 129.5, 129.1 (C_q), 126.2, 123.4. MS (ESI): m/z 242 ($\text{M}^+ - \text{O}$), 150, 134, 120, 104, 92, 76.

4-Bromo-*N*-hydroxy-*N*-phenylbenzamide



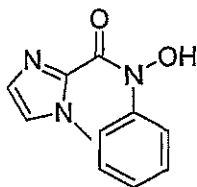
25

DBU (3.8 mg, 0.025 mmol) was added under argon to a solution of 4-bromobenzaldehyde (185 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (1.82 mg, 0.005 mmol) in dichloromethane (5 mL). The reaction mixture was

stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

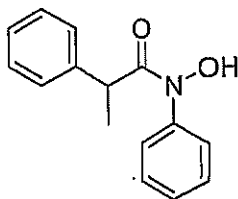
5 ^1H (400 MHz, CDCl_3): δ = 9.00 (br s, 1H, OH), 7.41 (AB, d, J_{AB} = 8.7 Hz, 2H, Ar-H), 7.36–7.31 (m, 3H, Ar-H), 7.29 (AB, d, J_{AB} = 8.7 Hz, 2H, Ar-H), 7.22–7.20 (m, 2H, Ar-H). ^{13}C (100 MHz, CDCl_3): δ = 164.6 (C_q , CO), 139.3 (C_q), 131.5, 130.7 (C_q), 130.5, 129.3, 128.6, 126.1, 125.8 (C_q). MS
10 (ESI): m/z 275 ($\text{M}^+ - \text{O}$), 183, 155, 104, 76.

N-hydroxy-1-methyl-*N*-phenyl-1*H*-imidazole-2-carboxamide



DBU (3.8 mg, 0.025 mmol) was added under argon to
15 a solution of 1-methyl-1*H*-imidazole-2-carbaldehyde (110 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (1.82 mg, 0.005 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was
20 purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 13.64 (br s, 1H, OH), 7.81 (d, J = 7.4 Hz, 2H, Ar-H), 7.42 (td, J = 2.0, 7.4 Hz, 2H, Ar-H), 7.24 (td, J = 1.2, 7.4 Hz, 1H, Ar-H), 7.11 (d, J = 1.1 Hz, 2H, HC=), 7.04 (d, J = 1.1 Hz, 1H, HC=), 4.12 (s, 3H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 153.7 (C_q , CO), 139.7 (C_q), 139.0 (C_q), 128.5, 126.2, 125.8, 125.1, 122.3, 36.2. MS
25 (ESI): m/z 201 ($\text{M}^+ - \text{O}$), 184, 172, 159, 109, 82.

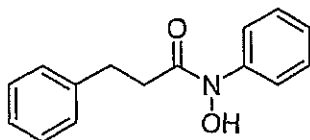
N-hydroxy-*N*,2-diphenylpropanamide

DBU (30 mg, 0.2 mmol) was added under argon to a
 5 solution of 2-phenylpropanal (134 mg, 1 mmol),
 nitrosobenzene (107 mg, 1 mmol) and catalyst (72.8 mg, 0.2
 mmol) in dichloromethane (5 mL). The reaction mixture was
 stirred at room temperature for 10 min. The solvent was
 removed under vacuum, and the residue was purified by flash
 10 silica gel column chromatography using hexane and ethyl
 acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 8.91 (br s, 1H, OH), 7.42-
 7.39 (m, 3H, Ar-H), 7.28-7.21 (m, 5H, Ar-H), 7.15-7.10 (m,
 2H, Ar-H), 3.72 (br s, 1H, CH), 1.50 (br s, J = 7.0 Hz, 3H,
 15 CH_3). ^{13}C (100 MHz, CDCl_3): δ = 169.5 (C_q , CO), 140.7 (C_q),
 138.1 (C_q), 129.5, 129.4, 128.7, 127.7, 127.4, 127.1, 41.9,
 19.8. MS (ESI): m/z 225 ($\text{M}^+ - \text{O}$), 132, 120, 105, 93, 77.

N-Hydroxy-*N*,3-diphenylpropanamide

20

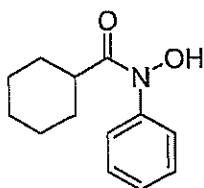


DBU (15 mg, 0.1 mmol) was added under argon to a
 solution of 3-phenylpropanal (134 mg, 1 mmol),
 25 nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1
 mmol) in dichloromethane (5 mL). The reaction mixture was
 stirred at room temperature for 10 min. The solvent was
 removed under vacuum, and the residue was purified by flash

silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.34 (br s, 1H, OH), 7.40-7.10 (m, 10H, Ar-H), 2.97 (t, J = 7.4 Hz, 2H, CH_2), 2.57 (br s, 2H, CH_2). ^{13}C (100 MHz, CDCl_3): δ = 167.7, 140.3, 138.2, 129.3, 128.7, 128.6, 128.4, 126.9, 126.4, 34.2, 31.4. MS (ESI): m/z 225 (M^+-O), 105, 93.

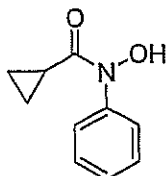
10 *N*-hydroxy-*N*-phenylcyclohexanecarboxamide



DBU (15 mg, 0.1 mmol) was added under argon to a solution of cyclohexanal (112 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

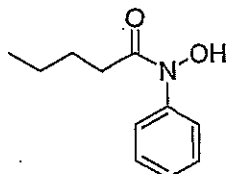
20

^1H (400 MHz, CDCl_3): δ = 9.15 (br s, 1H, OH), 7.48-7.30 (m, 5H, Ar-H), 2.33 (br s, 1H, CH), 1.77-1.67 (m, 4H, CH_2), 1.65-1.55 (m, 3H, CH_2), 1.27-1.15 (m, 1H, CH_2), 1.14-1.01 (m, 2H, CH_2). ^{13}C (100 MHz, CDCl_3): δ = 171.5 (C_q , CO), 138.2 (C_q), 129.4, 129.2, 126.7, 40.2, 29.1, 25.6, 25.5, 25.4. MS (ESI): m/z 203 (M^+-O), 148, 93, 83.

N-hydroxy-*N*-phenylcyclopropanecarboxamide

DBU (15 mg, 0.1 mmol) was added under argon to a solution of cyclopropanal (70 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 8.81 (br s, 1H, OH), 7.50–7.43 (m, 4H, Ar-H), 7.40–7.36 (m, 1H, Ar-H), 1.68 (s, 1H, CH), 1.17–1.13 (dddd, J = 3.0, 3.8, 4.7, 7.8 Hz, 2H, CH_2), 0.85–0.80 (dddd, J = 3.0, 3.8, 4.1, 7.8 Hz, 2H, CH_2). ^{13}C (100 MHz, CDCl_3): δ = 170.6 (C_q , CO), 139.7 (C_q), 129.1, 128.3, 126.2, 11.7, 8.5. MS (ESI): m/z 161 ($\text{M}^+ - \text{O}$), 106, 93, 77.

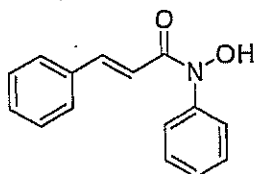
N-hydroxy-*N*-phenylpentanamide

DBU (15 mg, 0.1 mmol) was added under argon to a solution of pentanal (86 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 30 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel

column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.25 (br s, 1H, OH),
 5 7.47-7.43 (m, 2H, Ar-H), 7.41-7.37 (m, 3H, Ar-H), 2.31 (br
 t, J = 7.4 Hz, 2H, CH_2), 1.64 (pentet, J = 7.4 Hz, 2H, CH_2),
 1.29 (sextet, J = 7.4 Hz, 2H, CH_2), 0.85 (t, J = 7.4 Hz, 3H,
 CH_3). ^{13}C (100 MHz, CDCl_3): δ = 169.3 (C_q , CO), 138.8 (C_q),
 129.2, 126.8, 121.4, 32.3, 27.4, 22.3, 13.8. MS (ESI): m/z .
 10 177 (M^+-O), 135, 93.

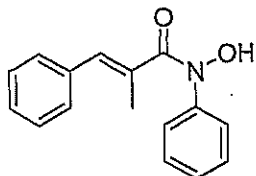
(*E*)-*N*-hydroxy-*N*-phenylcinnamamide



DBU (15 mg, 0.1 mmol) was added under argon to a
 15 solution of (*E*)-cinnamaldehyde (132 mg, 1 mmol),
 nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg,
 0.1 mmol) in dichloromethane (5 mL). The reaction mixture
 was stirred at room temperature for 10 min. The solvent was
 removed under vacuum, and the residue was purified by flash
 20 silica gel column chromatography using hexane and ethyl
 acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.3 (br s, 1H, OH), 7.78
 (d, J = 15.6 Hz, 1H, HC=), 7.51-7.39 (m, 7H, Ar-H),
 25 7.35-7.33 (m, 3H, Ar-H), 6.55 (d, J = 15.6 Hz, 1H, HC=). ^{13}C
 (100 MHz, CDCl_3): δ = 161.8 (C_q , CO), 143.1 (C_q), 137.8,
 134.6, 130.1, 129.3, 129.0, 128.8, 128.0, 126.2, 115.1. MS
 (ESI): m/z 223 (M^+-O), 131, 103, 93, 77.

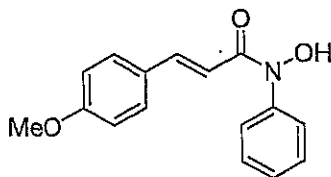
(E)-N-hydroxy-2-methyl-N,3-diphenylacrylamide



DBU (15 mg, 0.1 mmol) was added under argon to a solution of (E)-2-methyl-3-phenylacrylaldehyde (146 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.04 (br s, 1H, OH), 7.43-7.38 (m, 4H, Ar-H), 7.37-7.30 (m, 3H, Ar-H), 7.28-7.24 (m, 1H, Ar-H), 7.16-7.14 (m, 2H, Ar-H), 6.84 (s, 1H, HC=), 1.96 (d, J = 1.5 Hz, 3H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 167.8 (C_q , CO), 140.6 (C_q), 137.7, 136.8, 130.9 (C_q), 130.6, 130.4, 129.7, 129.4, 126.8, 15.8. MS (ESI): m/z 237 (M^+-O), 145, 117, 91.

(E)-N-hydroxy-3-(4-methoxyphenyl)-N-phenylacrylamide



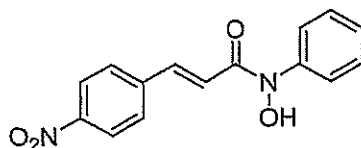
DBU (7.5 mg, 0.05 mmol) was added under argon to a solution of (E)-4-methoxycinnamaldehyde (162 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (18.2 mg, 0.05 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash

silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.18 (br s, 1H, OH), 7.73 (d, J = 15.6 Hz, 1H, HC=), 7.50–7.40 (m, 5H, Ar-H), 7.36 (AB, d, J_{AB} = 8.8 Hz, 2H, Ar-H), 6.85 (AB, d, J_{AB} = 8.8 Hz, 2H, Ar-H), 6.43 (d, J = 15.6 Hz, 1H, HC=), 3.81 (s, 3H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 161.2 (C_q , CO), 142.7 (C_q), 137.8 (C_q), 129.7, 129.1, 128.9, 128.6, 127.4 (C_q), 126.1, 114.2, 112.5, 55.4. MS (ESI): m/z 253 ($\text{M}^+ - \text{O}$), 161, 133, 118.

(*E*)-*N*-hydroxy-3-(4-nitrophenyl)-*N*-phenylacrylamide

15

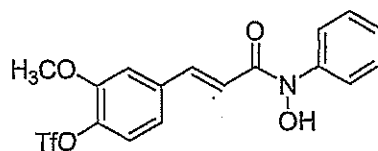


DBU (7.5 mg, 0.05 mmol) was added under argon to a solution of (*E*)-4-nitrocinnamaldehyde (177 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (18.2 mg, 0.05 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.64 (br s, 1H, OH), 8.13 (d, J = 15.3 Hz, 1H, =CH), 7.98 (d, J = 8.1 Hz, 1H, Ar-H), 7.57–7.39 (m, 8H, Ar-H), 6.42 (br s, 1H, =CH). ^{13}C (100 MHz, CDCl_3): δ = 160.6 (C_q , CO), 148.2, 138.3, 133.4, 130.9, 130.0, 129.5, 129.2, 126.6, 124.8, 120.7. MS (ESI): 268 ($\text{M}^+ - \text{O}$), 176, 148.

4-[(*E*)-2-(*N*-hydroxy-*N*-phenylcarbamoyl)vinyl]-2-methoxyphenyl trifluoromethanesulfonate

5

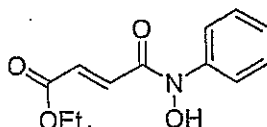


DBU (15 mg, 0.1 mmol) was added under argon to a solution of (*E*)-3-methoxy-4-trifluoromethyl sulfonyloxycinnamaldehyde (310 mg, 1 mmol), nitrosobenzene 10 (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the 15 eluents.

^1H (400 MHz, CDCl_3): δ = 9.24 (br s, 1H, OH), 7.72 (d, J = 15.5 Hz, 1H, =CH), 7.53–7.44 (m, 5H, Ar-H), 7.18 (d, J = 8.6 Hz, 1H, Ar-H), 7.03 (d, J = 8.6 Hz, 1H, Ar-H), 7.02 20 (s, 1H, Ar-H), 6.53 (br s, 1H, =CH), 3.91 (s, 3H, OMe). ^{13}C (100 MHz, CDCl_3): δ = 160.7 (C_q , CO), 151.6, 141.2, 139.4, 135.9, 129.2, 129.4, 126.3, 122.8, 120.3, 120.1, 117.1, 113.9, 112.5, 56.2. HRMS (ESI), calcd for $\text{C}_{17}\text{H}_{14}\text{O}_5\text{NF}_3\text{S}$ ($\text{M}^+ - \text{O}$) 401.0545, found 401.0549

25

(*E*)-Ethyl 3-(*N*-hydroxy-*N*-phenylcarbamoyl)acrylate



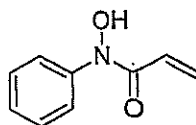
30

DBU (7.5 mg, 0.05 mmol) was added under argon to a solution of (*E*)-ethyl 3-formylacrylate (128 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (18.2 mg,

0.05 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.68 (br s, 1H, OH), 7.44–7.34 (br m, 5H, Ar-H), 6.97–6.90 (br m, 2H, Ar-H), 4.20 (q, J = 7.2 Hz, 2H, CH_2), 1.27 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 165.2, 159.3, 137.1, 131.9, 131.0, 129.6, 128.9, 126.5, 61.3, 14.1. HRMS (ESI), calcd for $\text{C}_{12}\text{H}_{13}\text{O}_3\text{N}$ (M^+-O) 219.0895, found 219.0894.

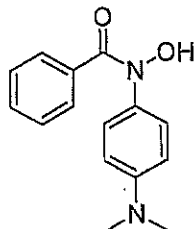
N-hydroxy-*N*-phenylacrylamide



DBU (15 mg, 0.1 mmol) was added under argon to a solution of acrolein (56 mg, 1 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 9.15 (br s, 1H, OH), 7.49–7.40 (m, 5H, Ar-H), 6.50 (dd, J = 1.6, 16.9 Hz, 1H, =CH), 6.28 (br dd, J = 10.3, 16.9 Hz, 1H, =CH), 5.73 (dd, J = 1.6, 10.3 Hz, 1H, =CH). ^{13}C (100 MHz, CDCl_3): δ = 161.2 (C_q , CO), 137.8 (C_q), 129.4, 129.1 (=CH₂), 128.9, 126.3, 125.1 (C-Ar). MS (ESI): m/z 147 (M^+-O), 119, 93, 77.

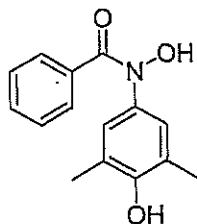
N-(4-(dimethylamino)phenyl)-*N*-hydroxybenzamide



DBU (15 mg, 0.1 mmol) was added under argon to a
 5 solution of benzaldehyde (106 mg, 1 mmol), *N,N*-dimethyl-4-
 nitrosobenzenamine (150 mg, 1 mmol) and catalyst (36.4 mg,
 0.1 mmol) in dichloromethane (5 mL). The reaction mixture
 was stirred at room temperature for 60 min. The solvent was
 removed under vacuum, and the residue was purified by flash
 10 silica gel column chromatography using hexane and ethyl
 acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 7.86 (d, AB, J_{AB} = 7.2 Hz,
 2H), 7.65 (br s, 1H, OH), 7.55–7.46 (m, 5H, Ar-H), 6.75 (d,
 15 AB, J_{AB} = 8.8 Hz, 2H), 2.95 (s, 6H, CH_3). ^{13}C (100 MHz, CDCl_3):
 δ = 165.5 (C_q , CO), 148.2 (C_q), 135.3 (C_q), 131.5, 128.7,
 127.7 (C_q), 126.9, 122.0, 113.1, 40.9. MS (ESI): m/z 240
 (M^+-O), 135, 121, 105, 77.

20 *N*-hydroxy-*N*-(4-hydroxy-3,5-dimethylphenyl)benzamide



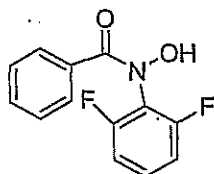
DBU (15 mg, 0.1 mmol) was added under argon to a
 solution of benzaldehyde (106 mg, 1 mmol), 2,6-dimethyl-4-
 nitrosophenol (151 mg, 1 mmol) and catalyst (36.4 mg, 0.1
 25 mmol) in dichloromethane (5 mL). The reaction mixture was
 stirred at room temperature for 60 min. The solvent was

removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

5 ^1H (400 MHz, CDCl_3): δ = 7.43–7.42 (m, 2H, Ar-H), 7.36 (br s, 1H, OH), 7.34–7.32 (m, 3H, Ar-H), 7.26 (s, 2H, Ar-H), 2.26 (s, 6H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 165.6 (C_q , CO), 149.4 (C_q), 135.1 (C_q), 131.7, 130.1 (C_q), 128.8, 126.9, 123.7, 121.2, 16.1. MS (ESI): m/z 241 ($\text{M}^+ - \text{O}$), 138, 105, 77.

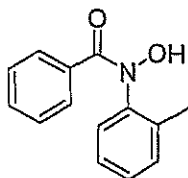
10

N-(2,6-difluorophenyl)-*N*-hydroxybenzamide



DBU (15 mg, 0.1 mmol) was added under argon to a
15 solution of benzaldehyde (106 mg, 1 mmol), 1,3-difluoro-2-nitrosobenzene (143 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 60 min. The solvent was removed under vacuum, and the residue was purified by flash
20 silica gel column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 8.80 (br s, 1H, OH), 7.55–7.51 (m, 2H, Ar-H), 7.43–7.29 (m, 4H, Ar-H), 6.94–6.90 (m, 2H, Ar-H). ^{13}C (100 MHz, CDCl_3): δ = 169.7 (C_q , CO), 160.1, 157.5 (C_q), 131.7, 128.3, 128.0 (C-Ar), 118.3 (C_q), 112.3, 112.1 (C-Ar). MS (ESI): m/z 233 ($\text{M}^+ - \text{O}$), 105, 77.

N-hydroxy-*N*-*o*-tolylbenzamide

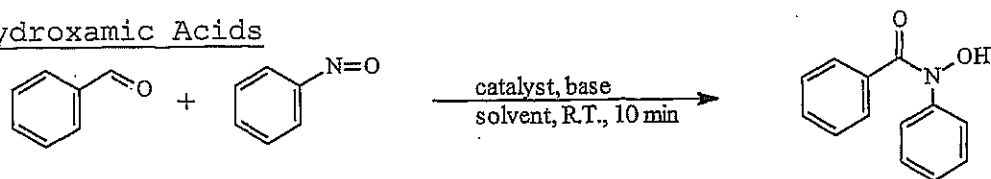
DBU (15 mg, 0.1 mmol) was added under argon to a solution of benzaldehyde (106 mg, 1 mmol), 1-methyl-2-nitrosobenzene (121 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 60 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

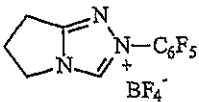
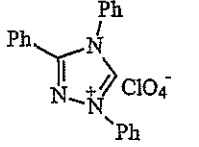
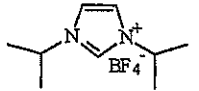
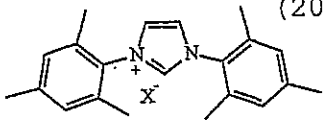
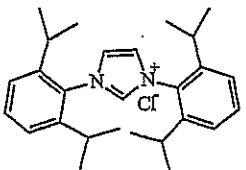
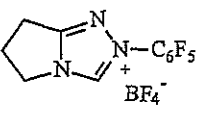
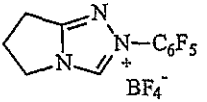
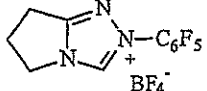
^1H (400 MHz, CDCl_3): δ = 9.45 (br s, 1H, OH), 7.40–7.32 (m, 3H, Ar-H), 7.28–7.20 (m, 4H, Ar-H), 7.15–7.12 (m, 2H, Ar-H), 2.32 (s, 3H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 165.6 (C_q , CO), 138.1 (C_q), 136.9 (C_q), 131.4 (C_q), 131.3, 131.1, 130.0, 129.3, 128.6, 128.1, 126.9, 17.7. MS (ESI): m/z 211 (M^+-O), 105, 77.

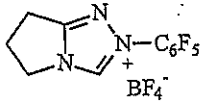
In studies using different imidazolium and triazolium salts, it was observed that sterically less hindered triazolium salts provided higher yields of the product (Table 1).

Reaction with catalyst concentrations as low as 0.125 mol % was observed.

Table 1. Reaction Conditions for the Preparation of Hydroxamic Acids



entry	catalyst (mol%)	solvent	Base (mol%)	GC yield, %
1	(20) 	CH ₂ Cl ₂	DBU	99
2	(20) 	CH ₂ Cl ₂	KO ^t Bu	50
3	(20) 	CH ₂ Cl ₂	KO ^t Bu	Trace
4	(20) 	CH ₂ Cl ₂	KO ^t Bu	55
5	(20) 	CH ₂ Cl ₂	KO ^t Bu	Trace
6	(20) 	CH ₂ Cl ₂	KO ^t Bu	95
7	(20) 	THF	KO ^t Bu	85
8	(5) 	CH ₂ Cl ₂	DBU	99

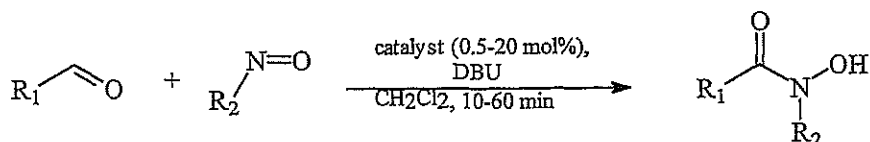
9		(0.5)	CH ₂ Cl ₂	DBU	99
10	none		CH ₂ Cl ₂	DBU	0

Benzaldehyde and nitrosobenzene were observed to react in the presence of the NHC catalyst generated from the triazolium salt and DBU, forming *N*-hydroxy-*N*-phenylbenzamide in yields above 75%. No formation of benzoin was observed under these conditions (Table 2).

Yields above 75% of the corresponding hydroxamic acids for a variety of aryl, alkyl, alkenyl, and heterocyclic aldehydes were observed (Table 2).

Yields above 75% of the corresponding hydroxamic acids for a variety of nitroso compounds were observed (Table 2). Yields above 75% are considered excellent yields.

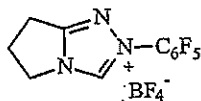
Table 2. Preparation of Hydroxamic Acids with Various Aldehydes or Nitroso Compounds



entry	R ₁	R ₂	isolated yield, %
1	C ₆ H ₅	C ₆ H ₅	96
2	4-OMeC ₆ H ₅	C ₆ H ₅	99
3	4-NO ₂ C ₆ H ₅	C ₆ H ₅	99
4	4-BrC ₆ H ₅	C ₆ H ₅	95
5	1-methyl-1H-imidazol-2-	C ₆ H ₅	98
6	C ₆ H ₅ CH(CH ₃)	C ₆ H ₅	89
7	C ₆ H ₅ CH ₂ CH ₂	C ₆ H ₅	78

8	C ₆ H ₁₁	C ₆ H ₅	97
9	C ₃ H ₅	C ₆ H ₅	99
10	n-C ₄ H ₉	C ₆ H ₅	99
11	C ₆ H ₅ CH=CH	C ₆ H ₅	95
12	C ₆ H ₅ CH=C(CH ₃)	C ₆ H ₅	96
13	4-OMeC ₆ H ₄ CH=CH	C ₆ H ₅	87
14	4-NO ₂ C ₆ H ₄ CH=CH	C ₆ H ₅	99
15	3-OMe-4-OTfC ₆ H ₄ CH=CH	C ₆ H ₅	80
16	EtOOC-CH=CH	C ₆ H ₅	99
17	CH ₂ =CH	C ₆ H ₅	99
18	C ₆ H ₅	4-(Me) ₂ NC ₆ H ₅	93
19	C ₆ H ₅	3,5-Me-4-(OH)C ₆ H ₅	55
20	C ₆ H ₅	2,6-F ₂ C ₆ H ₅	82
21	C ₆ H ₅	2-MeC ₆ H ₅	77

catalyst:



- 5 Azoxybenzene was observed as a side-product. By modifying the reaction conditions according to routine experiments, the amount of azoxybenzene can be minimized.

Procedure for NHC-catalyzed synthesis of chiral hydroxamic

10 acids

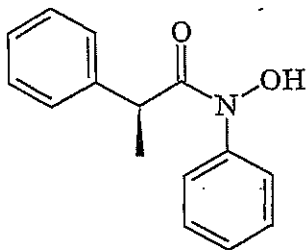
- DBU (7.5 mg, 0.05 mmol) was added under argon to a solution of aldehyde (0.50 mmol), nitroso compound (0.51 mmol) and the catalyst (0.05 mmol) in dichloromethane (2 mL). The reaction mixture was stirred at room temperature
- 15 for 3 h. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the eluents.

Procedure for NHC-catalyzed kinetic resolution of α -branched aldehyde

KBu^tO (7.5 mg, 0.05 mmol) was added under argon to a solution of aldehyde (1 mmol), nitroso compound
 5 (0.50 mmol) and the catalyst (0.05 mmol) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 3 h. The solvent was removed under vacuum, and the residue was purified by flash silica gel column chromatography using hexane and ethyl acetate as the
 10 eluents. The ee value was determined by chiral HPLC using OD-RH column (47% AcN/Water). The GC yields were determined by using dodecane as an internal standard.

N-hydroxy-N,2-diphenylpropanamide

15



¹H (400 MHz, CDCl₃): δ = 8.91 (br s, 1H, OH), 7.42–
 20 7.39 (m, 3H, Ar-H), 7.28–7.21 (m, 5H, Ar-H), 7.15–7.10 (m, 2H, Ar-H), 3.72 (br s, 1H, CH), 1.50 (br s, J =7.0 Hz, 3H, CH₃). ¹³C (100 MHz, CDCl₃): δ = 169.5 (C_q, CO), 140.7 (C_q), 138.1 (C_q), 129.5, 129.4, 128.7, 127.7, 127.4, 127.1, 41.9, 19.8. MS (ESI): m/z 225, 132, 120, 105, 93, 77.

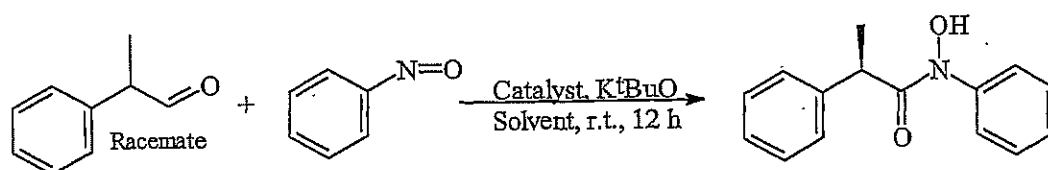
25 The α -branched aldehyde and nitroso compound were observed to react in the presence of the NHC catalyst generated from the triazolium salt and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), forming the R-

enantiomer of the corresponding chiral hydroxamic acid in 90% yields.

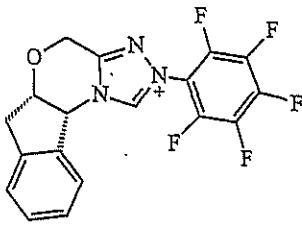
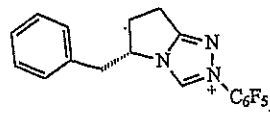
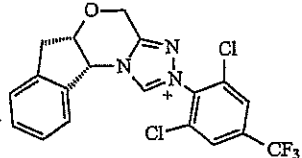
The kinetic resolution of the α -branched aldehyde racemate was investigated by using different chiral triazolium salts. Yields of up to 50% of the corresponding chiral hydroxamic acids and moderate to good ee values (30–75%) were observed (Table 3).

Table 3. NHC-catalyzed Kinetic Resolution of α -Branched Aldehyde

10



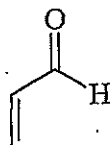
Entry	Catalyst	Solvent	Yield	%ee
1		CH ₂ Cl ₂	50 ^a	75
2		THF	44 ^b	43
3		THF + Toluene (1:9)	50 ^b	45

4		CH ₃ CN	40 ^b	55
5		CH ₂ Cl ₂	50 ^b	30
6		CH ₂ Cl ₂	45 ^b	30

^aIsolated yield. ^bGC yield

II. Process for Preparing N-Propionyloxyacrylamide Derivative

In an embodiment of the present invention, an
5 aldehyde represented by the formula:

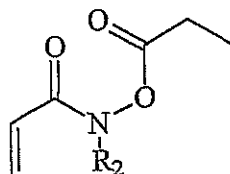


may be reacted in stoichiometric excess with a nitroso
10 compound represented by the formula (III):



wherein R_2 may be defined as anywhere above, in the presence of a NHC catalyst to prepare a *N*-propionyloxyacrylamide derivative represented by the formula:

5

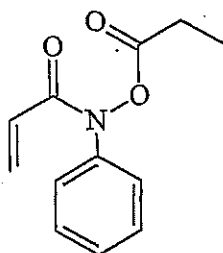


wherein R_2 may be defined as anywhere above.

In an embodiment of the present invention, the nitroso compound may be, for example, and without
10 limitation, nitrosobenzene.

In an embodiment of the present invention, *N*-propionyloxy-*N*-phenylacrylamide represented by the following formula:

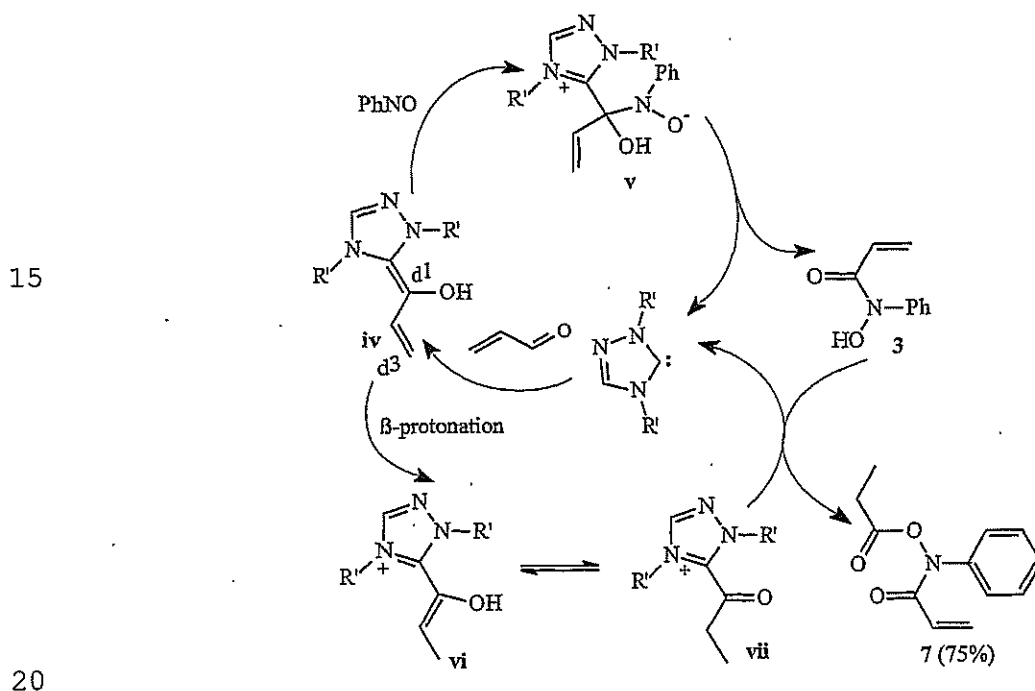
15



may be prepared.

Suitable amounts of the aldehyde would be understood to and can be determined by those of ordinary
20 skill in the art. In an embodiment of the present invention, for example, and without limitation, the aldehyde may be reacted according to four times its stoichiometric ratio with the nitroso compound. In an embodiment of the present invention, for example, the aldehyde may be reacted
25 according to three times its stoichiometric ratio with the nitroso compound.

Without being bound by theory, it is believed that in this aspect of the present invention, two catalytic cycles seem to operate. By way of example, and without limitation, as represented in the following scheme, it is
 5 believed that one catalytic cycle forms a hydroxamic acid **3** by the reaction of a d¹ nucleophile with the nitroso compound, and a second catalytic cycle forms *N*-propionyloxy-*N*-phenylacrylamide through protonation of a d³ nucleophile, which forms an activated ester **vii** which then reacts with
 10 the hydroxamate nucleophile forming the product **7** and the carbene catalyst.



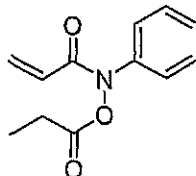
wherein R' is a hydrocarbon group including those as defined for R₁ above.

The skilled person will appreciate that the base, the solvent, the amount of the NHC catalyst, the reaction
 25 time, the reaction temperature, the isolation methods and the purification methods described above, which may be used for preparing the hydroxamic acid, may also be used for

preparing the *N*-propionyloxyacrylamide derivative as described herein.

N-Propionyloxy-*N*-phenylacrylamide

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DBU (15 mg, 0.1 mmol) was added under argon to a
 10 solution of acrolein (168 mg, 3 mmol), nitrosobenzene (107 mg, 1 mmol) and catalyst (36.4 mg, 0.1 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 10 min. The solvent was removed under vacuum, and the residue was purified by flash silica gel
 15 column chromatography using hexane and ethyl acetate as the eluents.

^1H (400 MHz, CDCl_3): δ = 7.49-7.37 (m, 5H, Ar-H), 6.50 (d, J = 16.6 Hz, 1H, =CH), 6.19 (br dd, J = 10.5, 16.6 Hz, 1H, =CH), 5.70 (d, J = 10.5 Hz, 1H, =CH), 2.51 (q, J = 7.5 Hz, 2H, CH_2), 1.22 (t, J = 7.5 Hz, 1H, CH_3). ^{13}C (100 MHz, CDCl_3): δ = 171.4, 162.2, 138.8, 129.7, 129.4, 129.3, 127.5, 126.6, 25.0, 8.7.

The present invention includes isomers such as
 25 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
 30 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
5 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.

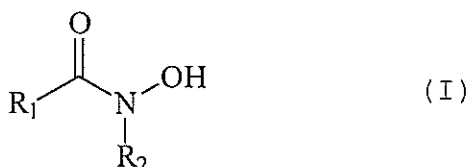
10 Unless defined otherwise all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

All publications, patents and patent applications
15 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
20 specification is not an admission that the publication, patent or patent application is prior art.

CLAIMS:

1. A process for preparing a hydroxamic acid comprising reacting an aldehyde with a nitroso compound comprising an optionally substituted aryl substituent in the presence of a *N*-heterocyclic carbene (NHC) catalyst.

2. The process according to claim 1 for preparing a hydroxamic acid represented by the formula (I):



wherein:

R_1 is a hydrogen atom, 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 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 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 C_{6-14} aryl- C_{2-6} alkynyl group which may be substituted with one or more substituents which may be 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, or a 5- to 14-membered aromatic heterocyclic group containing one or more
 5 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; and

R_2 is a C_{6-14} aryl group which may be substituted with one or more substituents which are the same or different,

10 which process comprises reacting an aldehyde represented by the formula (II):



wherein R_1 is as defined above, with a nitroso compound
 15 represented by the formula (III):

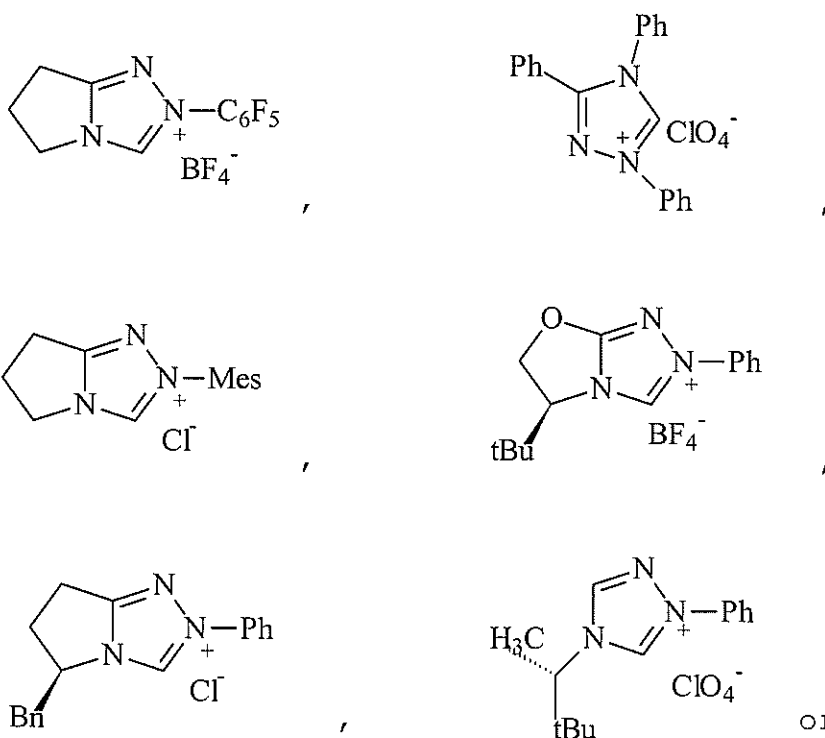


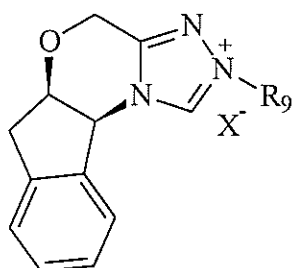
wherein R_2 is as defined above, in the presence of a *N*-
 20 heterocyclic carbene (NHC) catalyst.

3. The process according to claim 2, wherein R_1 is a C_{1-6} alkyl group, a C_{2-6} alkenyl group which may be substituted with C_{1-6} alkoxy, a C_{3-8} cycloalkyl group, a C_{6-14} aryl group which may be substituted with C_{1-6} alkoxy,
 25 nitro or halogen, a C_{6-14} aryl- C_{1-6} alkyl group, a C_{6-14} aryl- C_{2-6} alkenyl group, a C_{6-14} aryl- C_{2-6} alkenyl group wherein the C_{6-14} aryl may be substituted with one or more substituents which are independently C_{1-6} alkoxy, nitro or

trifluoromethylsulfonyl, or 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 with C₁₋₆ alkyl

- 5 4. The process according to claim 2 or 3, wherein R₂ is a phenyl group which may be substituted with one or more substituents, which are the same or different, and are a halogen atom, an amino group which may be substituted by C₁₋₆ alkyl, a C₁₋₆ alkyl group or a hydroxyl group.
- 10 5. The process according to any one of claims 1 to 4, wherein the NHC catalyst is derived from a triazolium salt or an imidazolium salt.
6. The process according to any one of claims 1 to 5, wherein the NHC catalyst is derived from a triazolium salt
- 15 represented by the formula:

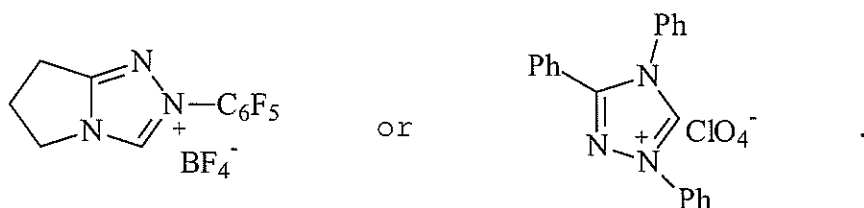




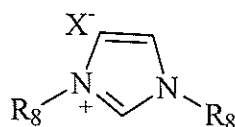
5 wherein R_9 is phenyl (Ph) which may be substituted, i-propyl (i Pr), mesityl (Mes) or 2,6-diisopropylphenyl (2,6- i Pr-Ph); and X^- is Br^- , BF_4^- or Cl^- .

7. The process according to claim 6, wherein the triazolium salt is represented by the formula:

10



8. The process according to any one of claims 1 to 5, wherein the NHC catalyst is derived from an imidazolium salt
15 represented by the formula:



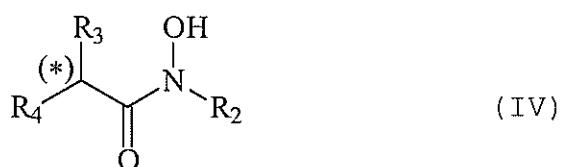
wherein R_8 is phenyl (Ph), i-propyl (i Pr), mesityl (Mes) or
20 2,6-diisopropylphenyl (2,6- i Pr-Ph), and X^- is Br^- , BF_4^- or Cl^- .

9. A process for preparing a chiral hydroxamic acid comprising reacting a α -branched aldehyde with a nitroso compound comprising an optionally substituted aryl
25 substituent in the presence of an achiral *N*-heterocyclic carbene (NHC) catalyst.

10. The process according to claim 9, wherein the chiral hydroxamic acid prepared is enantiomerically pure.

11. The process according to claim 9 or 10, wherein the α -branched aldehyde is enantiomerically pure.

5 12. The process according to any one of claims 9 to 11
for preparing a chiral hydroxamic acid represented by the
formula (IV):



10

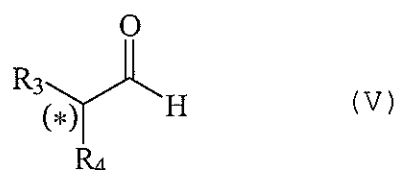
wherein:

(*) refers to a chiral center;

R_2 is as defined in claim 2; and

R₃ and R₄, which are different, is each 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; a C₃₋₈ cycloalkyl or C₃₋₈ cycloalkenyl group which may be substituted; a C₆₋₁₄ aryl group which may be substituted, a C₆₋₁₄ aryl-C₁₋₆ alkyl group which may be substituted, a C₆₋₁₄ aryl-C₂₋₆ alkenyl group which may be substituted, a C₆₋₁₄ aryl-C₂₋₆ alkynyl 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 sulfanyl group, a sulfinyl group which is substituted, a sulfonyl group which is substituted, a C₁₋₆ alkoxy carbonyl group, a C₁₋₆ alkylsulfonyl group, an oxo group or a C₁₋₆ alkoxyimino group,
- which process comprises reacting a α -branched aldehyde represented by the formula (V):



- wherein R₃ and R₄ are as defined above, with a nitroso compound represented by the formula (III):

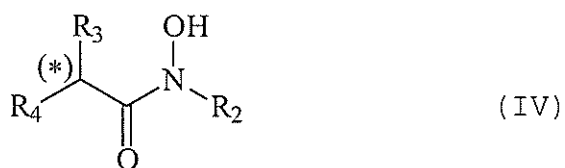


14. The process according to claim 12 or 13, wherein R₄ is a phenyl group.

16. The process according to claim 15, wherein the chiral hydroxamic acid is prepared in enantiomeric excess.

18. The process according to any one of claims 15 to 17, wherein a stoichiometric excess of the α -branched aldehyde is reacted.

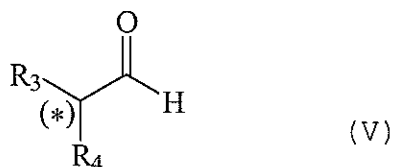
20. The process according to any one of claims 15 to 19 for preparing a chiral hydroxamic acid represented by the formula (IV):



wherein R_2 is as defined in claim 2 and (*), R_3 and R_4 are as defined in claim 12,

which process comprises reacting a α -branched aldehyde represented by the formula (V):

5



wherein R_3 and R_4 are as defined in claim 12, with a nitroso compound represented by the formula (III):

10

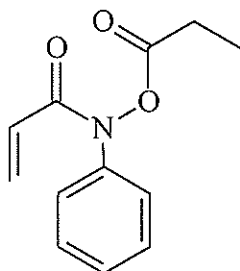


wherein R_2 is as defined in claim 2, in the presence of a chiral *N*-heterocyclic carbene (NHC) catalyst.

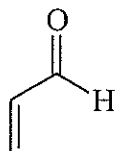
15 21. The process according to claim 20, wherein R_3 is a C_{1-6} alkyl group.

22. The process according to claim 20 or 21, wherein R_4 is a phenyl group.

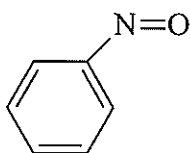
23. A process for preparing *N*-propionyloxy-
20 *N*-phenylacrylamide represented by the formula:



comprising reacting an aldehyde represented by the formula:

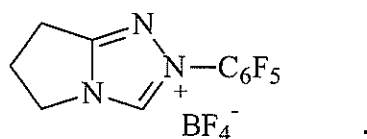


5 with a nitroso compound represented by the formula:



in the presence of a *N*-heterocyclic carbene (NHC) catalyst,
10 wherein a stoichiometric excess of the aldehyde is reacted.

24. The process according to claim 23, wherein the NHC catalyst is represented by the formula:



15 25. The process according to any one of claims 1 to 24, wherein the reaction is carried out in the presence of a base.

26. The process according to claim 25, wherein the base is 1,8-diazabicyclo[5.4.0]undec-7-ene or potassium
20 *tert*-butoxide.

27. The process according to any one of claims 1 to 26, wherein the reaction is carried out in the presence of a solvent.

28. The process according to claim 27, wherein the
25 solvent is dichloromethane or tetrahydrofuran.