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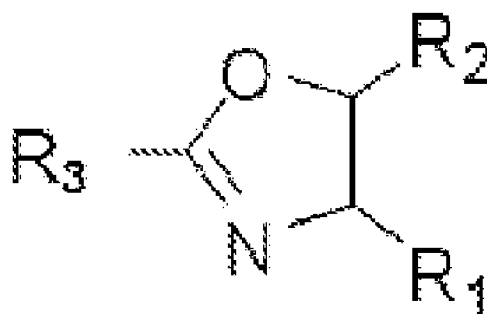
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(54) Title: SYNTHESIS OF OXAZOLINE COMPOUNDS



(I)

(57) **Abstract:** The present invention provides an improved process for preparing an oxazoline compound of the formula: (I) wherein R_1 and R_2 are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or R_1 and R_2 combined together with the carbon atoms to which they are attached form an optionally substituted fused 6-member aromatic ring provided that R_1 and R_2 are attached to carbon atoms adjacent to each other; and R_3 is hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or an enantiomer thereof; or an enantiomeric mixture thereof; comprising the step of contacting an acylamino alcohol compound to a suitable amount of fluoroalkanesulfonyl fluoride compound and organic basic reagent. By using a fluoroalkanesulfonyl fluoride compound with an organic basic reagent, the present invention efficiently converts acylamino alcohol compounds into highly chemoselective oxazoline compounds with a remarkable variety of substrates, mild conditions and relatively short reaction time.

SYNTHESIS OF OXAZOLINE COMPOUNDS

Field of the Invention

The invention is directed to a novel process for preparing oxazoline
5 compounds.

Background of the Invention

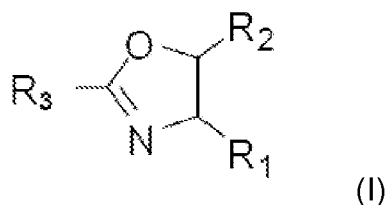
Oxazoline compounds are five-membered nitrogen heterocycles that are of
great interest to organic chemistry. Present in some biologically active natural
10 products, optically active oxazolines have been proven to be useful as effective
auxiliaries and ligands for selected asymmetric syntheses. Oxazolines have been
used as monomers in ring opening polymerizations and have been used as
protecting groups for carboxyl moieties in organic synthesis. Oxazolines are
valuable intermediates in organic synthesis.

15 Several methods have been developed for the synthesis of oxazoline
compounds. The most common synthesis method is by dehydrative cyclization of N-
acylamino alcohols. Acid-insensitive substrates such as molybdenum oxide,
BF₃·Et₂O and TsOH as Lewis or Brønsted acid catalysts have been used for this
cyclization reaction, as reported by A. Sakakura et al., Org. Lett., 7, 1971-1974 (2005)
20 and P. Chaudhry et al., J. Comb. Chem., 9, 473-476 (2007). Alternatively,
electrophilic reagents such as SOCl₂, TsCl, PPh₃/CCl₄, Vilsmeier Reagent, DAST, or
Deoxo-Fluorand Burgess reagent have been used to activate the hydroxyl group of
the amino alcohols, as reported by P. Wuts et al., J. Org. Chem., 65, 9223-9225
(2000) and P. Lafargue et al., Heterocycles, 41, 947-958 (1995). However, these
25 synthesis methods are disadvantageous since they are not applicable to various
structural types and often require long reaction time under harsh reaction conditions.

Thus, the development of a process to prepare oxazoline compounds at a rapid rate and high yield is an important challenge. It is desirable to provide a process for preparing oxazolines that is simple to operate and produces highly chemoselective compounds at high yield. It is also desirable to provide a process
5 for preparing oxazolines which requires a short reaction time and mild conditions. This desired process is generally applicable to a wide variety of substrates.

Summary of the Invention

The present invention provides an improved process for preparing an
10 oxazoline compound of the formula:



wherein

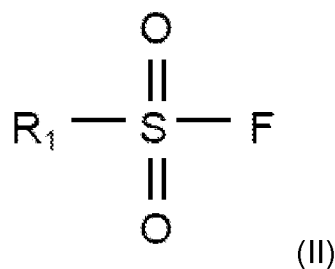
R₁ and R₂ are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or
15 optionally substituted polycyclic aryl; or

R₁ and R₂ combined together with the carbon atoms to which they are attached form an optionally substituted fused 6-member aromatic ring provided that R₁ and R₂ are attached to carbon atoms adjacent to each other; and

R₃ is hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl,
20 optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl.

The invention provides an improved process for preparing an oxazoline compound from its corresponding acylamino alcohol compound using a

fluoroalkanesulfonyl fluoride compound to effect cyclization. The process comprises the step of contacting an acylamino alcohol compound to an oxazoline compound in the presence of a suitable organic basic reagent and a compound of the formula:



5

wherein R₁ is a fluorinated alkyl or aryl; or an isomer thereof; or an isomeric mixture thereof.

The process of the present invention provides a simple process to prepare oxazoline compounds in excellent yields and selectivities. By using a
10 fluoroalkanesulfonyl fluoride compound as a reagent, the present invention has the advantages of providing a process to efficiently convert acylamino alcohol compounds into oxazoline compounds with a remarkable variety of substrates, high chemoselectivity, mild conditions and relatively short reaction time. The present invention has the further advantage of providing a process for preparing oxazoline
15 compounds whose stereoisomeric configuration can be easily determined beforehand simply by the selection of the appropriate starting materials.

Other objects, features, advantages and aspects of the present invention will become apparent to those skilled in the art from the following description and appended claims. It should be understood, however, that the following description,
20 appended claims, and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only. Various changes and

modifications within the spirit and scope of the disclosed invention will become readily apparent to those skilled in the art from reading the following.

Detailed Description of the Invention

5 Listed below are definitions of various terms used to describe the compounds of the present invention. These definitions apply to the terms as they are used throughout the specification unless they are otherwise limited in specific instances either individually or part of a larger group.

 The term “optionally substituted alkyl” refers to unsubstituted or substituted
10 straight or branched-chain hydrocarbon groups having 1-20 carbon atoms, preferably 1-7 carbon atoms. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, *n*-butyl, *t*-butyl, isobutyl, pentyl, neopentyl, hexyl, isohexyl, heptyl, octyl and the like. Substituted alkyl groups include, but are not limited to, alkyl groups substituted by one or more of the following groups: halo, cyano,
15 hydroxyl, acyl, alkoxy, carboxyl, amino, alkylamino, dialkylamino, cycloalkyl, alkenyl, or heterocyclyl.

 The term “lower alkyl” refers to those optionally substituted alkyl groups as described above having 1-7 carbon atoms.

 The term “alkoxy” refers to optionally substituted alkyl-O-.

20 The term “alkenyl” refers to any of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon double bond at the point of attachment.

 The term “alkynyl” refers to any of the above alkyl groups having at least two carbon atoms and further containing a carbon to carbon triple bond at the point of
25 attachment.

 The term “halogen” or “halo” refers to fluorine, chlorine, bromine and iodine.

The term "cycloalkyl" refers to optionally substituted monocyclic aliphatic hydrocarbon groups of 3-6 carbon atoms, which may be substituted by one or more substituents, such as optionally substituted alkyl, aryl, halo, cyano, hydroxyl, carboxyl, and amino.

5 Exemplary monocyclic hydrocarbon groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The terms "alkylamino" and "dialkylamino" refer to alkyl-NH- and (alkyl)₂N-, respectively.

The term "aryl" refers to a carbocyclic moiety containing at least one
10 benzenoid-type ring, with the aryl groups preferably containing from 6 to 15 carbon atoms, for example, phenyl, naphthyl, indenyl or indanyl, which may optionally be substituted by 1-4 substituents, such as optionally substituted alkyl, aryl, cyano, carboxyl, amino, halo or alkoxy.

The term "polycyclic aryl" refers to an optionally substituted, fully saturated
15 or unsaturated, aromatic or non-aromatic cyclic group, for example, which is a 4- to 7-membered monocyclic, 7- to 12- membered bicyclic, or 10- to 15-membered tricyclic ring system. Substituted polycyclic aryl groups refer to polycyclic groups substituted with 1, 2 or 3 substituents selected from the group consisting of: optionally substituted alkyl, halo, cyano, hydroxyl, carboxyl, and amino.

20 The term "aralkyl" refers to an aryl group bonded directly through an alkyl group, such as benzyl or phenethyl.

The term "heterocyclyl" or "heterocyclo" refers to an optionally substituted, fully saturated or unsaturated, aromatic or non-aromatic cyclic group, for example, which is a 4- to 7-membered monocyclic, 7- to 12- membered bicyclic, or 10- to 15-
25 membered tricyclic ring system, which has at least one heteroatom in at least one

carbon atom containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2 or 3 heteroatoms selected from nitrogen atoms, oxygen atoms and sulfur atoms, where the nitrogen and sulfur heteroatoms may also optionally be oxidized. The heterocyclic group may be attached at a heteroatom or a carbon atom.

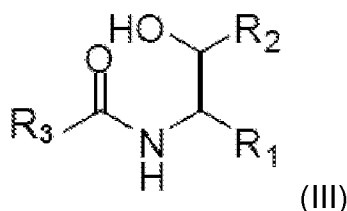
The terms "heterocyclyl" includes substituted heterocyclic groups. Substituted heterocyclic groups refer to heterocyclic groups substituted with 1, 2 or 3 substituents selected from the group consisting of: optionally substituted alkyl, halo, cyano, hydroxyl, and amino.

The term "fluorinated alkyl" refers to a fluorinated alkyl group having from 1 to about 10 carbon atoms; substituted or fluorinated ether groups (e.g., $\text{HC}_2\text{F}_4\text{OC}_2\text{F}_4$ -, $\text{IC}_2\text{F}_4\text{OC}_2\text{F}_4$ -, $\text{ClC}_2\text{F}_4\text{OC}_2\text{F}_4$ -); or substituted or fluorinated ester groups (e.g., MeOOCCF_2 -).

The term "fluorinated aryl" refers to a fluorinated cycloalkyl group having from about 4 to 8 carbon atoms.

As described herein above, the present invention relates to a method for preparing oxazoline compounds of formula (I) with a suitable organic basic reagent and a fluoroalkanesulfonyl fluoride compound of formula (II). The process of the present invention is particularly useful to prepare high yields of a chemospecific oxazoline compound. The process of the present invention is particularly useful to prepare an oxazoline compound with a remarkable variety of substrates, mild conditions and relatively short reaction time.

The acylamino alcohols suitable for use with the process of the invention include compounds of the formula:



wherein

R₁ and R₂ are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl or alkenyl or alkynyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or

R₁ and R₂ combined together with the carbon atoms to which they are attached form an optionally substituted fused 6-member aromatic ring provided that R₁ and R₂ are attached to carbon atoms adjacent to each other; and

R₃ is hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl.

The acylamino alcohols useful in the present invention include N-acylamino alcohols, wherein R₂ in the compound of formula (III) is hydrogen, or an N-acyl-1,2-disubstituted amino alcohol

The acylamino alcohols useful in the present invention are known compounds that are industrially produced and available commercially. Representative methods of preparing N-acylamino alcohols are described in European Patent Application 0075868. However, other methods of preparing N-acylamino alcohols that are well-known to one skilled in the art may be used. The preparative teachings of these references are incorporated herein by reference.

Sulfonyl fluoride compounds suitable for use in the process of the invention are fluorinated saturated aliphatic or alicyclic sulfonyl fluorides. A useful class of such fluoroalkanesulfonyl fluoride compounds can be represented by the general

formula R_1SO_2F , where R_1 is selected from the group consisting of fluorinated alkyl groups having from 1 to about 10 carbon atoms and fluorinated cycloalkyl groups having from about 4 to about 8 carbon atoms. Preferably, R_1 is a perfluorinated alkyl group.

5 Representative samples of fluoroalkanesulfonyl fluoride compounds suitable for the use in the process of this invention include CF_3SO_2F , $C_2F_5SO_2F$, $C_4F_9SO_2F$, $C_6F_{13}SO_2F$, $C_8F_{17}SO_2F$, $C_{10}F_{21}SO_2F$, cyclo- $(C_6F_{11})SO_2F$, C_2F_5 -cyclo- $(C_6F_{10})SO_2F$, $H(CF_2)_4SO_2F$, $H(CF_2)_8SO_2F$, and mixtures thereof. Preferably, perfluorobutanesulfonyl fluoride, perfluorohexanesulfonyl fluoride, perfluorooctane
10 sulfonyl fluoride, and mixtures thereof are utilized. Most preferably, perfluorobutanesulfonyl fluoride is utilized in the process of the present invention.

 The fluoroalkanesulfonyl fluoride compounds of the present invention are industrially produced and available commercially as fine chemicals. Representative methods of preparing the fluoroalkanesulfonyl fluoride compounds of formula (II) are
15 described in U.S. Patent Nos. 2,732,398; 5,318,674 and 5,486,281. Other representative methods of preparing the fluoroalkanesulfonyl fluoride compounds used in the present invention are described in M. Novikova et al., J. Fluorine Chem. 58, 326 (1992) and N.D. Volkov et al., Syntheses, 972 (1979). The preparative teachings of these references are incorporated herein by reference.

20 The fluoroalkanesulfonyl fluoride compound may be used in molar ratios (moles sulfonyl fluoride compound to moles amino alcohol) ranging from about 100 to 0.1:1, more preferably from about 10 to 0.1:1, most preferably about 1.5 : 1.

 This claimed method for converting acylamino alcohols to oxazoline compounds by fluoroalkanesulfonyl fluoride compounds may be performed with
25 untreated organic basic reagents commonly containing 0.1 - 4 percent of water,

more preferably about 0.05 - 0.5 percent of water. Organic basic reagents suitable for use in the process of the invention include a non-aqueous base such as lithium diisopropyl amide, lithium hexamethylsilazide, sodium hexamethylsilazide and potassium hexamethylsilazide; or potassium t-butoxide and sodium methoxide. The

5 base can be an alkali metal carbonate such as sodium, potassium, lithium or cesium carbonate or an alkaline earth metal carbonate such as calcium or barium carbonate; hydroxides such as sodium and potassium hydroxides; and hydrides such as sodium or potassium hydrides. The base can also be ammonia (NH₃) or an organic base including urea; a secondary amine such as dimethylamine, diphenylamine, N-methyl
10 N-propylamine, diethylamine, diisopropylamine, N-methylaniline, piperazine, piperidine, pyrrolidine; or a tertiary amine such as diisopropylethylamine (DIPEA), trimethylamine, dimethylaniline, N,N-dimethylpropylamine, N,N-dimethylpiperidine, N,N-dimethylbutylamine, triethylamine (TEA). The base can also be an heterocyclic nitrogen containing compound such as isoquinoline, morpholine, purine, pyridine,
15 pyrazine, pyrimidine, quinoline or polyvinyl pyridine, preferably DMAP or DBU.

Where appropriate, mixtures of any of the above bases can be employed.

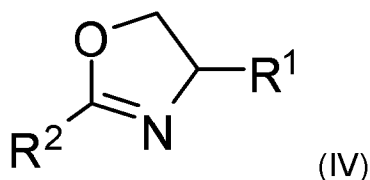
The organic basic reagent may be used in molar ratios (moles base to moles amino alcohol) ranging from about 1,000 to 0.001:1, more preferably from about 10 to 0.01:1, most preferably about 3:1.

20 If desired, the claimed method of the present invention may be performed by additionally including an inert organic solvent such as toluene, hexane, pentane, benzene, acetonitrile, acetone, tetrahydrofuran (THF), ethyl acetate, dichloromethane (CH₂Cl₂ or DCM), triethylamine, CDCl₃ or a mixture of solvents thereof. Preferably, the method of the present invention includes dichloromethane or
25 CDCl₃.

In the process of preparing the oxazoline compound of formula (I), the N-acylamino alcohol of formula (III) is contacted with a fluoroalkanesulfonyl fluoride compound of formula (II) and an organic basic reagent in amounts and under conditions effective to yield the desired oxazoline compound. The contacting may optionally be performed in an inert organic solvent. The fluoroalkanesulfonyl fluoride compound (II) and organic basic reagent are contacted with the N-acylamino alcohol at temperatures ranging from 19-25°C, preferably from about 21-23°C, most preferably at 22°C. The contact is performed at ambient pressures although pressures greater or less than ambient can be employed. The contacting of the reactants can be carried out for about 3 minutes to about 48 hours until the reaction is substantially completed, preferably from about 5 minutes about 24 hours. The mixture is preferably stirred while the reactants are being contacted.

Upon completion of the reaction, oxazoline can be removed from remaining water by extraction from methylene chloride or other methods well known to one skilled in the art. The oxazoline is preferably formed in yield of at least about 55 percent based upon the initial amount of the N-acylamino alcohol, more preferably in yields of at least 85 percent, and most preferably in yields of at least about 87 percent.

The effectiveness of the method of the present invention is illustrated in Table 1 for the synthesis of 2,4-substituted oxazoline compounds having the formula (IV):



wherein

R₁ is sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; and

R₂ is sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl.

Table 1 illustrates that the method of the present invention may be used with a wide range of acylamino alcohol substrates to form their corresponding oxazoline compound. All the substituted derivatives 1a - 1q (entries 1-17), including those amides containing heterocyclic substituents 1l and 1m, were readily converted to their corresponding oxazolines in nearly quantitative yields.

The present invention is an effective method for the preparation of an oxazoline compound with high chemoselectivity. Cyclization of N-acylamino alcohols bearing an unprotected second hydroxyl group can be achieved with careful addition of perfluorobutanesulfonyl fluoride with DBU as a base. As illustrated in Table 1, N-acylamino alcohol 1q bearing an unprotected secondary hydroxyl group was cyclized to form oxazoline compound 2q (93% isolated yield) with careful addition of 1.1-1.2 equiv of PFBSF with DBU as base in 5 mL of dichloromethane as solvent.

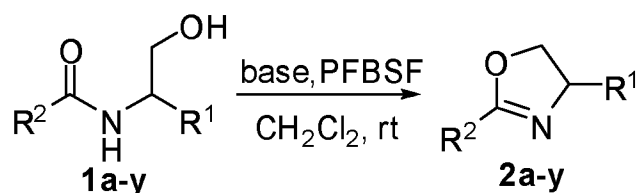
In one particular embodiment, the present invention provides a method for the preparation of serine-derived oxazolines, which are interesting moieties of some natural products. N-acylamino alcohols may be reacted with a fluorinated, sulfonyl fluoride and organic basic reagent to form oxazolines derived from serine. As illustrated in Table 1, this embodiment of the present invention preferably uses perfluorobutanesulfonyl fluoride as the fluoroalkanesulfonyl fluoride compound. This embodiment of the present invention also uses DIPEA or DMAP as an organic basic

reagent. Oxazoline compounds 2r – 2w were synthesized using perfluorobutanesulfonyl fluoride and DMAP at approximately 90 percent yield.

Further, oxazoline compounds 2x and 2y were synthesized using perfluorobutanesulfonyl fluoride and DIPEA at 85-87 percent yield .

5

Table 1. Synthesis of 2,4-substituted oxazolines^a



entry	substrates (R ¹ , R ²)	base	time	products	yield ^b
1	1a (R)-Ph-, Ph-	DBU	5min	2a	99
2	1b (S)-t-Bu-, Ph-	DBU	5min	2b	99
3	1c (S)-Et-, Ph-	DBU	5min	2c	97
4	1d dimethyl-, Ph-	DBU	5min	2d	96
5	1e (R)-Ph-, 2-tolyl	DBU	5min	2e	98
6	1f (R)-Ph-, 3-tolyl	DBU	5min	2f	95
7	1g (R)-Ph-, 4-tolyl	DBU	5min	2g	95
8	1h (R)-Ph-, t-Bu-	DBU	5min	2h	96
9	1i (R)-Ph-, 4-MeOPh-	DBU	5min	2i	99
10	1j (R)-Ph-, 4-NO ₂ Ph-	DBU	5min	2j	91
11	1k (R)-Ph-, 2,6-(MeO) ₂ Ph-	DBU	5min	2k	99
12	1l (R)-Ph-, 2-furyl-	DBU	5min	2l	98
13	1m (R)-Ph-, 2-pyridinyl-	DBU	5min	2m	98
14	1n (R)-Ph-, Me ₂ N-	DBU	5min	2n	94
15	1o (R)-Ph-, CF ₃ -	DBU	5min	2o	92
16	1p (R)-Ph-, Me-	DBU	5min	2p	92
17	1q (S,S)-PhCH(OH)-, Ph-	DBU	5min	2q	93 ^c
18	1r (S)-CO ₂ Me, Ph-	DMAP	3h	2r	92
19	1s (S)-CO ₂ Me, o-tolyl	DMAP	3h	2s	87
20	1t (S)-CO ₂ Me, m-tolyl	DMAP	3h	2t	88
21	1u (S)-CO ₂ Me, p-tolyl-	DMAP	3h	2u	93
22	1v (S)-CO ₂ Me, p-MeOPh-	DMAP	3h	2v	92
23	1w (S)-CO ₂ Me, t-Bu-	DMAP	3h	2w	92
24	1x (S)-CO ₂ Me, 2-furyl-	DIPEA	24h	2x	85
25	1y (S)-CO ₂ Me, 4-NO ₂ Ph-	DIPEA	24h	2y	87

a. 0.5 mmol of amides, 3 equiv of base and 1.5 equiv of PFSBF in 5 mL of CH₂Cl₂ at rt. b. Isolated yield(%). c. 1.1-1.2 equiv of PFSBF was used with ¹H NMR trace.

In an alternative embodiment, the method of the present invention may be used to prepare 2,4,5-trisubstituted oxazoline compounds of formula (I), wherein R₁ and R₂ are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or R₁ and R₂ combined together with the carbon atoms to which they are attached form an optionally substituted fused 6-member aromatic ring provided that R₁ and R₂ are attached to carbon atoms adjacent to each other; and R₃ is sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl. In the process of preparing the 2,4,5-trisubstituted oxazoline compound, an N-acyl-1,2-disubstituted amino alcohol is contacted with a fluoroalkanesulfonyl fluoride compound of formula (II) and an organic basic reagent in amounts and under conditions effective to yield the desired oxazoline compound. The fluoroalkanesulfonyl fluoride compound (II) and organic basic reagent are contacted with the N-acylamino alcohol at temperatures ranging from 19-25°C, preferably from about 21-23°C, most preferably at 22°C. The contact is performed at ambient pressures although pressures greater or less than ambient can be employed. The contacting of the reactants can be carried out for about 3 minutes to about 48 hours until the reaction is substantially completed, preferably from about 5 minutes about 24 hours. The mixture is preferably stirred while the reactants are being contacted.

Table 2 illustrates that the method of the present invention may be used to prepare 2,4,5-trisubstituted oxazoline compound with regiochemical specificity. It is known that the analogous reaction using conventional activating reagents (e.g. TsCl) often requires more forceful conditions because of increased steric hindrance for the cyclization with secondary alcohols. Moreover, it is further known that 1,2-

disubstituted amino alcohols are rather prone to epimerization via the S_N1 pathway.

In one embodiment, the method of the present invention may be used to convert 1, 2-disubstituted amino alcohols to an oxazoline compound with an inverted

configuration. As set forth in Table 2, the acylamino alcohol 3a may be contacted

5 with perfluorobutanesulfonyl fluoride and DBU to synthesize the oxazoline compound 4a at 98% yield.

The method of the present invention may be used to produce numerous 2, 4, 5- trisubstituted oxazoline compounds at high yield. By reacting a 1,2-disubstituted amino alcohol with a suitable amount of fluoroalkanesulfonyl fluoride compound and

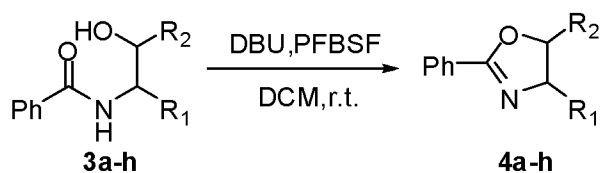
10 organic basic reagent, the method of the present invention may be efficiently employed with a variety of substrates, including for example, substrates derived from *erythro*-amino alcohols, *N*-acylamino indanol, and other common 1,2-disubstituted amino alcohols that are known to one skilled in the art.

In another embodiment, the method of the present invention may be used to
15 synthesize higher yields of 4, 5-oxazoline from *threo*-amides than available with conventional techniques using, for example, reagents such as BF₃·Et₂O or TsCl.

Formation of 4,5-oxazoline from *threo*-amide is known to be problematic due to unfavored non-bonding interaction resulting in the formation of the thermally stable 4,5-*trans*-isomer rather than *cis*-oxazoline. For example, as illustrated in Table 2,

20 the method of the present invention may be used to effect cyclization of *threo*-amide compound 3h with a suitable amount of perfluorobutanesulfonyl fluoride and DBU as base to form *cis*-4h in 55% isolated yield along with < 10% *trans*-isomer (entry 8).

Table 2. Synthesis of 2,(4,)5-substituted oxazolines^a



entry	substrates	products	time	yield ^b
1	3a	4a	5 min	98
2	3b	4b	30 min	99.7 ^d
3	3c	4c	5 min	95
4	3d	4d	5 min	98
5	3e	4e	5 min	99
6	3f	4f	2h ^e	98
7	3g	4g	6h ^e	96
8	3h	4h	5 min	55

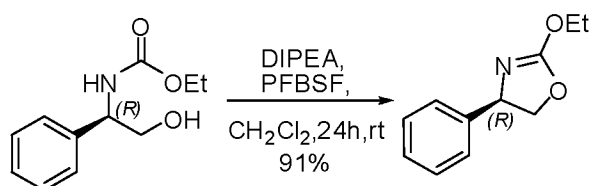
a. All reactions were performed on 0.5 mmol of amide with 3equiv of DBU and 1.5 equiv of PFBSF. b. Isolated yield. d. Reaction with 5mmol substrates. e. DMAP as

base.

Oxazolines synthesized by the present process are useful monomers for making known functional polymers that are used as effective auxiliaries and ligands for selected asymmetric syntheses, monomers in ring opening polymerizations, and valuable intermediates in organic synthesis. The present invention providing a process to efficiently prepare a high yield of highly chemoselective oxazoline compounds from acylamino alcohol compounds under mild conditions and relatively short reaction time. The simple protocol for the present invention provides an excellent opportunity for large-scale applications.

The following Examples are intended to further illustrate the invention and are not to be construed as being limitations otherwise. The structure of products and starting materials is confirmed by standard analytical methods, e.g., microanalysis, melting point, high pressure liquid chromatography (HPLC) and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations are those conventional in the art.

Example 1 – Synthesis of 2-ethoxy-4-phenyl-4,5-dihydrooxazole



N-ethoxycarbonyl amino alcohol (0.5 mmol), perfluorobutanesulfonyl fluoride (0.75 mmol), and DIPEA (1.5 mmol) are charged into a 25 mL flask with a magnetic stirring bar. 5 mL of CH₂Cl₂ is added to the 25 mL flask. The mixture is stirred for 24 hours at 22°C. The residue is purified by flash column chromatography on silica gel

(1:10 ethyl acetate: hexane) giving (R)- 2-ethoxy-4-phenyl-4,5-dihydrooxazole in 91 percent yield.

$[\alpha]_D^{20} = -17.5$ ($c = 2.0$, CHCl_3), $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.42 – 7.18 (m, 5H), 5.13 (dd, $J = 7.9, 9.3$, 1H), 4.71 (dd, $J = 8.3, 9.4$, 1H), 4.45 – 4.28 (m, 2H), 4.17 (t, $J = 7.9$, 1H), 1.39 (t, $J = 7.1$, 3H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 163.6, 142.7, 128.6, 127.5, 126.3, 75.5, 67.0, 66.7, 14.3. [NMR: Fraile, J. M.; Garcia, J. I.; Herrerias, C. I.; Mayoral, J. A.; Reiser, O.; Socuellamos, A.; Werner, H. *Chem.--Eur. J.* **2004**, *10*, 2997-3005.]

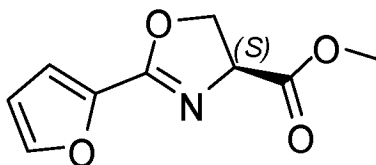
10 Example 2 – Synthesis of 2,4-diphenyl-4,5-dihydrooxazole



N-acylamino alcohol (0.5 mmol), DBU (3.0 mmol) and 5 mL of CH_2Cl_2 at 0°C are charged into a 25 mL flask with a magnetic stirring bar.

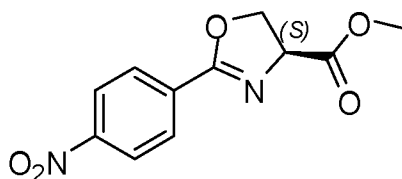
Perfluorobutanesulfonyl fluoride (1.5 mmol) is added to the 25 mL flask. The mixture is stirred for 5 minutes at room temperature and then concentrated under reduced pressure. The residue is purified by flash column chromatography on silica gel (1:10 ethyl acetate: hexane) giving 2,4-diphenyl-4,5-dihydrooxazole in 99 percent yield.

$[\alpha]_D^{20} = +48.3$ ($c = 1.0$, CHCl_3), $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.10 - 8.04 (m, 2H), 7.56 - 7.26 (m, 8H), 5.40 (dd, $J = 8.2, 10.1$, 1H), 4.81 (dd, $J = 8.4, 10.1$, 1H), 4.29 (t, $J = 8.3$, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 164.7, 142.3, 131.5, 128.7, 128.5, 128.4, 127.6, 127.5, 126.7, 74.9, 70.0. [NMR: Gorunova, O. N.; Keuseman, K. J.; Goebel, B. M.; Kataeva, N. A.; Churakov, A. V.; Kuz'mina, L. G.; Dunina, V. V.; Smoliakova, I. P. *J. Organomet. Chem.* **2004**, *689*, 2382-2394.]

Example 4 – Synthesis of (S)-methyl 2-(furan-2-yl)-4,5-dihydrooxazole-4-carboxylate

N-acylamino alcohol (compound 1q)(0.5 mmol), perfluorobutanesulfonyl fluoride (0.75 mmol), and DIPEA (1.5 mmol) are charged into a 25 mL flask with a magnetic stirring bar. 5 mL of CH₂Cl₂ is added to the 25 mL flask. The mixture is stirred for 24 hours at room temperature. The residue is purified by flash column chromatography on silica gel (1:10 ethyl acetate: hexane) giving (S)-methyl 2-(furan-2-yl)-4,5-dihydrooxazole-4-carboxylate as a white waxy solid in 85 percent yield:

$[\alpha]_D^{20} = +85.3$ (c = 2.0, CHCl₃), ¹H NMR (500 MHz, CDCl₃) δ 7.52 (dd, J = 0.6, 1.6, 1H), 7.00 (d, J = 3.5, 1H), 6.46 (dd, J = 1.8, 3.5, 1H), 4.91 (dd, J = 7.9, 10.4, 1H), 4.64 (dd, J = 8.1, 8.5, 1H), 4.54 (dd, J = 8.7, 10.4, 1H), 3.77 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.2, 158.3, 145.6, 142.1, 115.5, 111.6, 69.6, 68.3, 52.7. [NMR: Pirrung, M. C.; Tumey, L. N. J. Comb. Chem., 2, 675-680 (2000).]

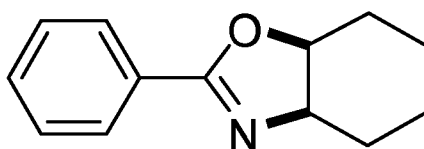
Example 5 – Synthesis of (S)-methyl 2-(4-nitrophenyl)-4,5-dihydrooxazole-4-carboxylate

N-acylamino alcohol (compound 1r)(0.5 mmol), perfluorobutanesulfonyl fluoride (0.75 mmol), and DIPEA (1.5 mmol) are charged into a 25 mL flask with a magnetic stirring bar. 5 mL of CH₂Cl₂ is added to the 25mL flask. The mixture is

stirred for 24 hours at room temperature. The residue is purified by flash column chromatography on silica gel (1:10 ethyl acetate: hexane) giving (S)-methyl 2-(4-nitrophenyl)-4,5-dihydrooxazole-4-carboxylate as a white waxy solid in 87 percent yield: mp = 86-87°C [α]_D²⁰ = + 33.9 (c = 1.0, CHCl₃), ¹H NMR (500 MHz, CDCl₃) δ

5 8.28 - 8.20 (m, 2H), 8.17 - 8.09 (m, 2H), 4.99 (dd, *J* = 8.2, 10.6, 1H), 4.74 (t, *J* = 8.5, 1H), 4.65 (dd, *J* = 8.8, 10.6, 1H), 3.81 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 171.0, 164.3, 149.7, 132.6, 129.6, 123.5, 70.0, 68.7, 52.8. [NMR: Pirrung, M. C.; Tumey, L. N. J. Comb. Chem., 2, 675-680 (2000).]

10 Example 6 – Synthesis of 2-phenyl-3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole



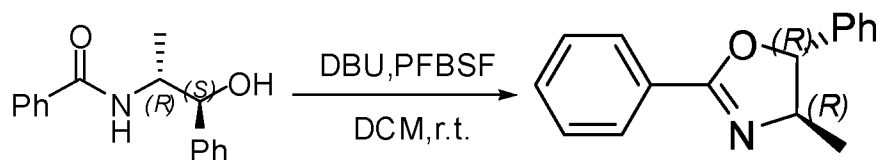
N-acylamino alcohol (compound 1x)(0.5 mmol), perfluorobutanesulfonyl fluoride (0.75 mmol), and DIPEA (1.5 mmol) are charged into a 25 mL flask with a magnetic stirring bar. 5 mL of CH₂Cl₂ is added to the 25mL flask. The mixture is

15 stirred for 24 hours at room temperature. The residue is purified by flash column chromatography on silica gel (1:10 ethyl acetate: hexane) giving 2-phenyl-

3a,4,5,6,7,7a-hexahydrobenzo[d]oxazole as a white waxy solid in 98 percent yield: ¹H NMR (500 MHz, CDCl₃) δ 8.00 - 7.91 (m, 2H), 7.54 - 7.33 (m, 3H), 4.68 (dt, *J* = 5.3, 8.1, 1H), 4.13 (dt, *J* = 6.3, 8.0, 1H), 1.99 - 1.27 (m, 8H).; ¹³C NMR (126 MHz,

20 CDCl₃) δ 164.2, 131.1, 128.3, 128.2, 128.1, 78.8, 63.5, 27.7, 26.2, 19.8, 19.1. [NMR: Crosignani, S.; Swinnen, D. J. Comb. Chem., 7, 688-96 (2005).]

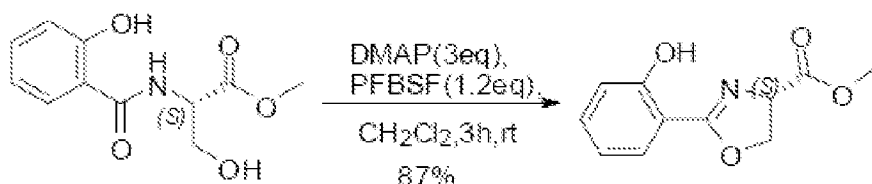
Example 7 – Synthesis of 4-methyl-2,5-diphenyl-4,5-dihydrooxazole



Amide 3b (5.0 mmol), perfluorobutanesulfonyl fluoride (7.50 mmol), and DBU (15.0 mmol) are charged into a 50 mL flask with a magnetic stirring bar. 10 mL of CH₂Cl₂ is added to the 50mL flask. The mixture is stirred for 30 minutes at room temperature. The residue is purified by flash column chromatography on silica gel (1:10 ethyl acetate: hexane) giving 4-methyl-2,5-diphenyl-4,5-dihydrooxazole in 99 percent yield.

$[\alpha]_D^{20} = -46.7$, ($c = 2.0$, CHCl₃), ¹H NMR (500 MHz, CDCl₃) δ 8.03 (d, $J = 7.3$, 2H), 7.59 - 7.28 (m, 8H), 5.11 (d, $J = 7.8$, 1H), 4.25 - 4.17 (m, 1H), 1.50 (d, $J = 6.7$, 3H); ¹³C NMR (126 MHz, CDCl₃) δ 162.7, 140.5, 131.4, 128.8, 128.4, 128.3, 128.3, 127.7, 125.6, 88.2, 71.0, 21.4. [**NMR**, Lafargue, P.; Guenot, P.; Lellouche, J. P. *Heterocycles* **1995**, 41, 947-958.]

Example 8 – Synthesis of optically pure antibiotic

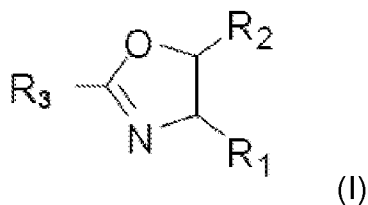


Bis-hydroxyl amide (0.5 mmol), perfluorobutanesulfonyl fluoride (0.6 mmol), and DMAP (1.5 mmol) are charged into a 25 mL flask with a magnetic stirring bar. 5 mL of CH₂Cl₂ is added to the 25mL flask. The mixture is stirred for 3 hours at 22°C. Purification by chromatography column provided analytical pure title compound in 87 percent yield.

$[\alpha]_D^{20} = +87.1$ (c = 2.0, CHCl₃), +81.5 (c = 2.0, MeOH), ¹H NMR (500 MHz, CDCl₃) δ 11.67 (s, 1H), 7.64 (dd, J = 1.4, 7.9, 1H), 7.42 – 7.34 (m, 1H), 7.00 (d, J = 8.4, 1H), 6.86 (t, J = 7.6, 1H), 4.96 (dd, J = 7.5, 10.4, 1H), 4.66 (t, J = 8.1, 1H), 4.55 (dd, J = 8.9, 10.4, 1H), 3.79 (s, 4H); ¹³C NMR (126 MHz, CDCl₃) δ 170.9, 167.4, 159.8, 133.9, 128.3, 118.7, 116.8, 109.9, 68.8, 67.1, 52.7. **[NMR:** Sasaki, T.; Otani, T.; Yoshida, K.; Unemi, N.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1997**, 50, 881-883.]

What is claimed is:

1. A process preparing an oxazoline compound of the formula



wherein

- 5 R_1 and R_2 are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or

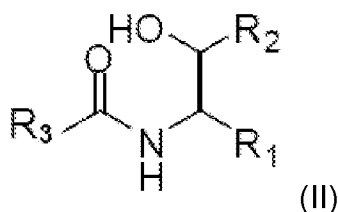
R_1 and R_2 combined together with the carbon atoms to which they are attached to form an optionally substituted fused 6-member aromatic ring provided

- 10 that R_1 and R_2 are attached to carbon atoms adjacent to each other; and

R_3 is hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl;

or an enantiomer thereof; or an enantiomeric mixture thereof;

- 15 comprising contacting a fluoroalkanesulfonyl fluoride compound and an organic basic reagent with an N-acylamino alcohol compound of the formula



wherein, R_1 , R_2 and R_3 are as defined above, or a salt thereof.

2. A process according to claim 1, wherein

R_1 and R_2 combined together with the carbon atoms to which they are attached to form an optionally substituted fused 6-member aromatic ring provided that R_1 and R_2 are attached to carbon atoms adjacent to each other.

3. A process according to claim 1, wherein the fluoroalkanesulfonyl fluoride compound is a perfluoroalkanesulfonyl fluoride.

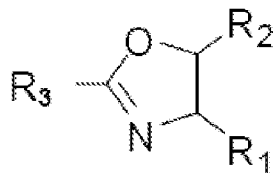
4. A process according to claim 4, wherein the perfluoroalkanesulfonyl fluoride is perfluorobutanesulfonyl fluoride.

5. A process according to claim 1, wherein the organic basic reagent is DBU.

6. A process according to claim 1, wherein the organic basic reagent is DMAP.

7. A process according to claim 1, wherein the organic basic reagent is DIPEA.

8. A process according to claim 1, wherein a compound of formula (I) has the formula



wherein

R_1 is an optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl;

R_2 is a hydrogen; and

R_3 is an optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or an enantiomer thereof; or an enantiomeric mixture thereof.

9. A process according to claim 8, wherein the fluoroalkanesulfonyl fluoride compound is a perfluoroalkanesulfonyl fluoride.

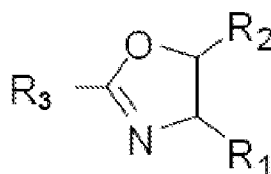
10. A process according to claim 9, wherein the perfluoroalkanesulfonyl fluoride is perfluorobutanesulfonyl fluoride.

11. A process according to claim 8, wherein the organic basic reagent is DBU.

12. A process according to claim 8, wherein the organic basic reagent is DMAP.

5 13. A process according to claim 1, wherein the organic basic reagent is DIPEA.

14. A process according to claim 1, wherein a compound of formula (I) has the formula



wherein

10 R_1 and R_2 are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or

R_1 and R_2 combined together with the carbon atoms to which they are attached to form an optionally substituted fused 6-member aromatic ring provided

15 that R_1 and R_2 are attached to carbon atoms adjacent to each other; and

R_3 is an optionally substituted aryl;

or an enantiomer thereof; or an enantiomeric mixture thereof.

15. A process according to claim 6, wherein R_3 is an optionally substituted phenyl.

16. A process according to claim 14, wherein the fluoroalkanesulfonyl fluoride

20 compound is a perfluoroalkanesulfonyl fluoride.

17. A process according to claim 16, wherein the perfluoroalkanesulfonyl fluoride is perfluorobutanesulfonyl fluoride.

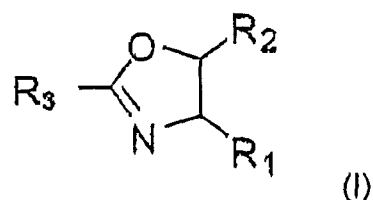
18. A process according to claim 14, wherein the organic basic reagent is DBU.

19. A process according to claim 14, wherein the organic basic reagent is DMAP.
20. A process according to claim 14, wherein the organic basic reagent is DIPEA.

received by the International Bureau on 28 December 2009(28.12.2009)

What is claimed is:

1. A process preparing an oxazoline compound of the formula



wherein

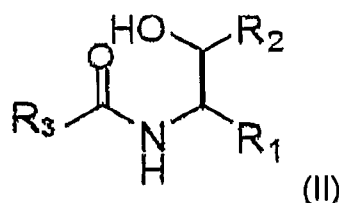
- 5 R₁ and R₂ are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or

- R₁ and R₂ combined together with the carbon atoms to which they are attached to form an optionally substituted fused 6-member aromatic ring provided
10 that R₁ and R₂ are attached to carbon atoms adjacent to each other; and

- R₃ is hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl;

or an enantiomer thereof; or an enantiomeric mixture thereof;

- 15 comprising contacting a fluoroalkanesulfonyl fluoride compound and an organic basic reagent with an N-acylamino alcohol compound of the formula

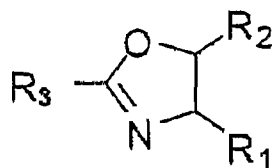


wherein, R₁, R₂ and R₃ are as defined above, or a salt thereof.

2. A process according to claim 1, wherein

R₁ and R₂ combined together with the carbon atoms to which they are attached to form an optionally substituted fused 6-member aromatic ring provided that R₁ and R₂ are attached to carbon atoms adjacent to each other.

- 5 3. A process according to claim 1, wherein the fluoroalkanesulfonyl fluoride compound is a perfluoroalkanesulfonyl fluoride.
4. A process according to claim 3, wherein the perfluoroalkanesulfonyl fluoride is perfluorobutanesulfonyl fluoride.
5. A process according to claim 1, wherein the organic basic reagent is DBU.
- 10 6. A process according to claim 1, wherein the organic basic reagent is DMAP.
7. A process according to claim 1, wherein the organic basic reagent is DIPEA.
8. A process according to claim 1, wherein a compound of formula (I) has the formula



15 wherein

R₁ is an optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl;

R₂ is a hydrogen; and

R₃ is an optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl;

20 or an enantiomer thereof; or an enantiomeric mixture thereof.

9. A process according to claim 8, wherein the fluoroalkanesulfonyl fluoride compound is a perfluoroalkanesulfonyl fluoride.

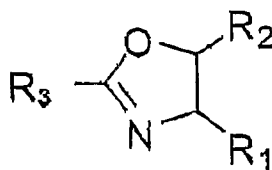
10. A process according to claim 9, wherein the perfluoroalkanesulfonyl fluoride is perfluorobutanesulfonyl fluoride.

11. A process according to claim 8, wherein the organic basic reagent is DBU.

12. A process according to claim 8, wherein the organic basic reagent is DMAP.

5 13. A process according to claim 1, wherein the organic basic reagent is DIPEA.

14. A process according to claim 1, wherein a compound of formula (I) has the formula



wherein

10 R₁ and R₂ are independently hydrogen, sulfide, sulfoxide, sulfonyl, optionally substituted lower alkyl, optionally substituted aralkyl, optionally substituted aryl or optionally substituted polycyclic aryl; or

R₁ and R₂ combined together with the carbon atoms to which they are attached to form an optionally substituted fused 6-member aromatic ring provided

15 that R₁ and R₂ are attached to carbon atoms adjacent to each other; and

R₃ is an optionally substituted aryl;

or an enantiomer thereof; or an enantiomeric mixture thereof.

15. A process according to claim 6, wherein R₃ is an optionally substituted phenyl.

20 16. A process according to claim 14, wherein the fluoroalkanesulfonyl fluoride compound is a perfluoroalkanesulfonyl fluoride.

17. A process according to claim 16, wherein the perfluoroalkanesulfonyl fluoride is perfluorobutanesulfonyl fluoride.

18. A process according to claim 14, wherein the organic basic reagent is DBU.

19. A process according to claim 14, wherein the organic basic reagent is DMAP.
20. A process according to claim 14, wherein the organic basic reagent is DIPEA.

Statement under Article 19(1)

In view of the fact that original claim 4 further defines the term “perfluoroalkanesulfonyl fluoride” which is recited in claim 3, original claim 4 has been amended to depend on claim 3, so as to remove the obvious clerical error that claim 4 cites itself. The foregoing amendment does not add any new material. In addition, the amended claim 4 depends on claim 3 which further depends on claim 1, and thus the amendment is also consistent with the International Searching Authority’s analysis since they commented that “the opinion for claim 4 is made on the basis that could reasonably be expected to be claimed, i.e. considering claim 4 citing claim 1.”

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/073136

A. CLASSIFICATION OF SUBJECT MATTER

See extra sheet

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D

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

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

WPI, EPODOC, PAJ, CNPAT, CNKI, CA,STN: +oxazol+; +fluor+; +sulfonyl+; fluoride; perfluoroalkanesulfonyl fluorides; perfluoromethanesulfonyl fluoride; perfluorobutanesulfonyl fluoride;375-72-4;335-05-7;354-87-0

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US2005075506A1(HANDA, Vijay Kumar et al.),07 April 2005(07.04.2005), see the whole document, cited in the application	1-20
A	US5318674A(MINNESOTA MINING & MFG CO),07 June 1994 (07.06.1994), see the whole document	1-20

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:	“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
“A” document defining the general state of the art which is not considered to be of particular relevance	“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
“E” earlier application or patent but published on or after the international filing date	“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
“L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)	“&”document member of the same patent family
“O” document referring to an oral disclosure, use, exhibition or other means	
“P” document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search 10 Oct. 2009 (10.10.2009)	Date of mailing of the international search report 29 Oct. 2009 (29.10.2009)
Name and mailing address of the ISA/CN The State Intellectual Property Office, the P.R.China 6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088 Facsimile No. 86-10-62019451	Authorized officer HE Xiaoping Telephone No. (86-10)62084365

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2009/073136

Patent Documents referred in the Report	Publication Date	Patent Family	Publication Date
US2005075506A1	07.04.2005	INCHE200300806A	26.05.2006
		US7126005B2	24.10.2006
US5318674A	07.06.1994	WO9501467A1	12.01.1995
		ZA9404080A	28.02.1996
		EP0706584A1	17.04.1996
		JP8512095T	17.12.1996
		EP0706584B1	16.07.1997
		DE69404312E	21.08.1997
		CN1126502A	10.07.1996
		CN1050867C	29.03.2000

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CN2009/073136

CLASSIFICATION OF SUBJECT MATTER

C07D263/00 (2006.01) i

C07D407/04 (2006.01) i