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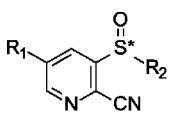
(54) Title: SYNTHESIS OF ENANTIOENRICHED 2-CYANO PYRIDYL SULFOXIDES

(57) Abstract: A process for the preparation of enantioenriched pyridine compounds of formula (I) is provided, where R_1 and R_2 are as defined in the description.



(I)

Synthesis of Enantioenriched 2-Cyano Pyridyl Sulfoxides

The present invention relates to the synthesis of enantioenriched sulfoxide compounds as intermediates for enantioselective preparation of sulfoximines.

In recent years sulfoximines have attracted great interest from the agrochemical and pharmaceutical industries as isosteres of sulfones and sulfonamides due to the ability to tune their four substituents and optimize physicochemical properties (J. Med. Chem. 2020, 63, 14243, Eur. J. Med. Chem. 2021, 209, 112885). N-unsubstituted sulfoximines are of particular interest as they differ by only a single atom from a sulfone but can have significantly different properties due to the presence of a hydrogen bond donating group. Consequently, there has been a great interest in methods to introduce NH-sulfoximines and several different approaches have recently been developed as reviewed in Chem. Eur. J. 2021, 27, 17293. A particularly favorable method for a larger scale synthesis is an enantiospecific iron catalyzed imination of enantioenriched sulfoxides with amino 4-nitrobenzoate salts (Angew. Chem. Int. Ed. 2018, 57, 324).

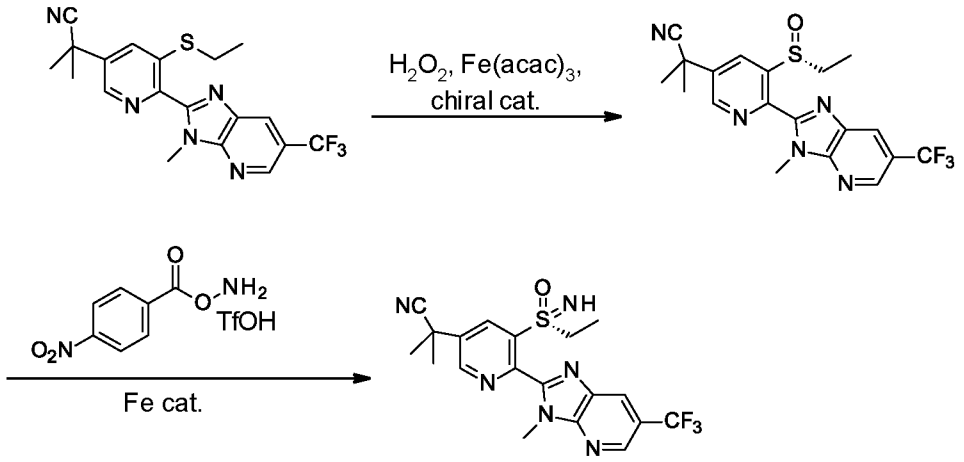
Enantioenriched sulfoxides could be prepared from corresponding sulfides by a variety of oxidation methods (reviewed in Chem. Rev. 2020, 120, 4578; Chem. Rev. 2010, 110, 4303; Pitchen Philippe et al, Tetrahedron Letters, 1 January 1984, pages 1049-1052). Notable methods include Kagan's titanium mediated oxidation using a tartrate ligand (J. Am. Chem. Soc. 1984, 106, 8188). A catalytic version of this protocol has been developed that avoids the use of stoichiometric titanium (Synlett. 1996, 404). Bolm has developed highly enantioselective methods using a chiral Schiff base in complex with either vanadium (Angew. Chem. Int. Ed. 1996, 34, 2640) or iron (Chem. Eur. J, 2005, 11, 1086, Angew. Chem. Int. Ed. 2004, 43, 4225) and there are related methods from Maguire using copper catalysis (J. Org. Chem. 2012, 77, 3288) or Jacobsen using manganese catalysis (Tet. Lett. 1992, 33, 7111) but these often suffer from lower selectivity. More recently List has disclosed practical organocatalytic methods that avoid metal catalysts but replace them with highly complex chiral acids (J. Am. Chem. Soc. 2012, 134, 10765, J. Am. Chem. Soc. 2021, 143, 14835). Biocatalysis using engineered enzymes offers an efficient and sustainable option for enantioselective sulfide oxidation (Catalysts, 2018, 8, 624) however the efficiency of such enzymes is highly substrate dependent and often requires extensive optimization for a single substrate.

Despite the availability of several methods for chiral sulfoxide synthesis, the enantioselectivity and yield of many methods for enantioselective sulfoxide synthesis are very substrate dependent, particularly in the case of complex heterocyclic substrates that can often interfere with metal catalyzed reactions, and optimization of the oxidation system is often required. This need for individual optimization is exemplified by the enantioselective synthesis of esomeprazole using titanium mediated oxidation as described in Tet. Assym. 2000, 11, 3819, or iron catalysis as described in ACS Catalysis, 2018, 8, 9738. In both cases non-obvious alterations to the originally published procedures were crucial to obtain high yield and

enantioselectivity on this complex substrate. Thus, while many methods for the synthesis of chiral sulfoxides exist, it is not trivial to find a suitable method for a complex substrate that will be appropriate for a large-scale use.

The synthesis of various enantioenriched sulfoximine compounds showing activity as insecticides has been described in WO2022/253841. The latter stages of the synthetic strategy consist of enantioselective oxidation of sulfide followed by and enantiospecific iron catalyzed imination as shown in Scheme 1 for one specific example (see patent application listed above for details).

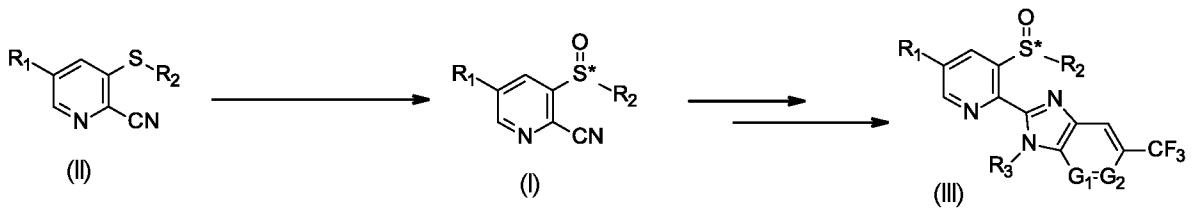
Scheme 1



This is a viable strategy for the synthesis of enantioenriched sulfoximines however the presence of a large substituent ortho to sulfide makes the oxidation less efficient and it must be optimized separately for every scaffold. It would be advantageous if the stereocenter on the sulfur could be installed at an earlier stage on a simpler substrate.

The present invention describes such a strategy starting from thio derivatives of formula (II) which after stereoselective oxidation yield sulfoxides of formula (I) which could later be elaborated to enantioenriched sulfoxides of formula (III). These can then be converted to enantioenriched sulfoximines as described above.

Scheme 2



R_1 is hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cyanocycloalkyl or optionally substituted aryl;

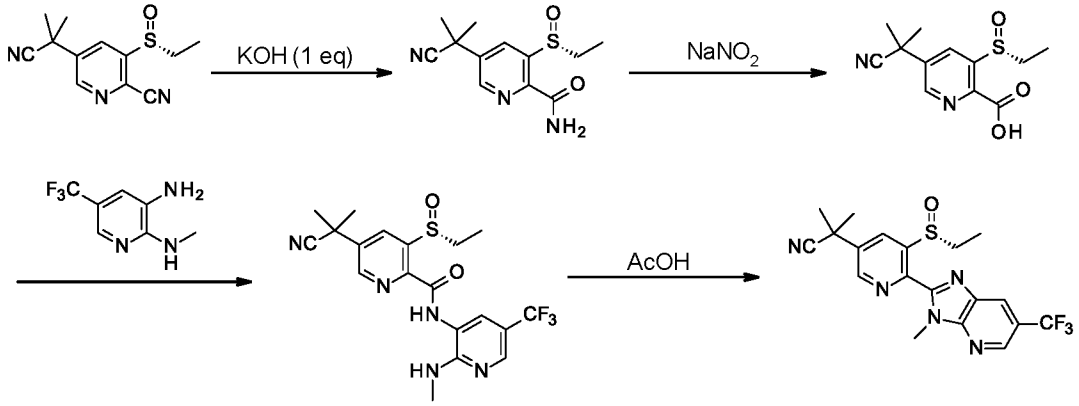
R_2 is C_1-C_4 alkyl

R_3 is C_1-C_4 alkyl

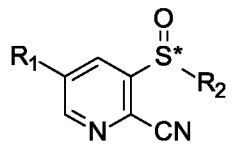
G_1 and G_2 are independently CH or N

Several methods for elaboration of compounds of formula (I) to compounds of formula (III) could be envisaged. A particularly favorable approach, as shown in Scheme 3 for a specific example, consist of selective hydrolysis of nitrile in the 2-position of pyridine via first basic hydrolysis followed by nitrosation of the primary amide. The acid thus produced is then coupled with a functionalized amino pyridine derivative and the resulting product cyclized under acidic conditions to yield the desired sulfoxide. This sequence of reactions is described in more detail in the experimental part of this invention.

Scheme 3



The present invention provides a process for the preparation of enantiomerically enriched sulfoxides of formula (I)



(I)

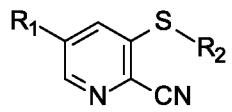
wherein

S* is a stereogenic sulfur atom which is in R- or S-configuration;

R_1 is hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cyanocycloalkyl or optionally substituted aryl;

R_2 is C_1-C_4 alkyl

by stereoselective oxidation of a sulfanyl compound of formula (II)

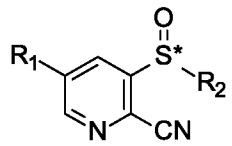


(II)

wherein R_1 and R_2 are as defined for compounds of formula (I);

in the presence of an oxidant, in the presence of a chiral reagent or catalyst, optionally in the presence of a suitable acid additive, in an appropriate solvent (or diluent);

to produce a sulfinyl compound of formula (I)



(I)

Wherein R_1, R_2 and S* are as defined previously.

In one embodiment the invention comprises:

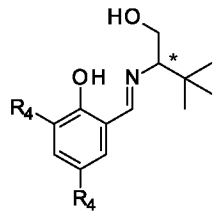
Oxidizing a sulfanyl compound of formula (II), in the presence of an oxidant, in the presence of a metal derivative, in the presence of a chiral ligand (such as a reagent or catalyst), in an appropriate solvent (or diluent) and optionally in the presence of a suitable acid additive.

Examples of suitable and preferred oxidants are inorganic peroxides, such as hydrogen peroxide or organic peroxides, such as tert-butyl hydroperoxide. Preferably the oxidant is hydrogen peroxide. The ratio of the oxidant used, compared to the sulfanyl compound of formula (II), is in the range from 8:1 to 0.8:1, preferably between 5:1 and 1:1, more preferably between 3:1 and 1:1.

Example of suitable and preferred metal derivatives are salts of vanadium and iron. Preferably iron salts are used. Suitable examples include but are not limited to $VOCl_2$, $VO(acac)_2$, $Fe(acac)_3$, $Fe(acac)_2$. The amount of metal catalyst used, compared to the sulfanyl compounds of formula (II) is in the range from 0.1 mol% to 50 mol%; preferably in the range between 0.5 mol % and 10 mol%.

Examples of suitable and preferred chiral ligands are selected from Schiff bases formed from salicylaldehyde derivatives and chiral amines.

In a preferred embodiment of the invention the metal derivative is iron and the chiral ligand is a Schiff base formed from salicylaldehyde derivatives and chiral amino-alcohols represented by a compound of formula (IV),



(IV)

Wherein R_4 is halogen and * represents (where appropriate) an enantioenriched chiral center in either R or S configuration. Preferably R_4 is chloro, iodo or bromo

The chiral ligand is used as an enantioenriched compound. The enantiomeric ratio of the ligand is from 80:20 to 100:0 [R]:[S] or [S]:[R], preferably the enantiomeric ratio of the ligand is from 90:10 to 100:0 [R]:[S] or [S]:[R].

The amount of the ligand used, compared to the sulfanyl compound of formula (II), is in the range from 0.1 to 30 mol %, preferably from 1 to 15 mol%, most preferably from 2 to 10 mol%.

Optionally the ligand can be formed *in situ* in the reaction by adding the appropriate salicylaldehyde derivative and an appropriate amino alcohol. Alternatively, the ligand can be prepared in a separate step.

Example of suitable and preferred additives are carboxylic acids. Preferably the additive is a benzoic acid, optionally mono-, di- or tri-substituted by methyl, ethyl, isopropyl, methoxy or dimethylamino, optionally in form of a lithium, sodium or potassium salt. More preferably the additive is a methoxybenzoic acid or a dimethylaminobenzoic acid (optionally in form of a lithium, sodium or potassium salt), even more preferably 4-methoxybenzoic acid. The amount of the additive used, compared to the sulfanyl compound of formula (II), is in the range from 0.1 to 10 mol %, most preferably from 0.5 to 5 mol %.

In the most preferred embodiment the oxidizing agent is hydrogen peroxide the metal salt is $Fe(acac)_3$, the ligand is selected from:

(2R)-2-[(E)-(3,5-diiodophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol,

(2S)-2-[(E)-(3,5-diiodophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol,

(2R)-2-[(E)-(3,5-dibromophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol,

(2S)-2-[(E)-(3,5-dibromophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol,

(2R)-2-[(E)-(3,5-dichlorophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol,

(2S)-2-[(E)-(3,5-dichlorophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol,
and the additive is 4-methoxybenzoic acid.

Examples of suitable and preferred solvents (or diluents) are esters, nitriles, alcohols, ethers, and aliphatic, aromatic or halogenated hydrocarbons. Examples include but are not limited to: ethyl acetate, isopropyl acetate, acetonitrile, butyronitrile, ethanol, methanol, isopropanol, n-propanol, tetrahydrofuran, 2-methyl tetrahydrofuran, cyclopentylmethyl ether, t-butylmethyl ether, diethyl ether, 1,4-dioxane pentane, hexane, cyclohexane, heptane, dichloromethane, 1,2-dichloroethane, chloroform, benzene, toluene, xylene, chlorobenzene, fluorobenzene, dichlorobenzene, methoxybenzene, trifluoromethylbenzene, p-cymene, mesitylene, ethylbenzene, isopropylbenzene, or mixtures thereof.

Preferably the solvent is an aromatic or halogenated hydrocarbon, for example: dichloromethane, 1,2-dichloroethane, chloroform, benzene, toluene, xylene, chlorobenzene, fluorobenzene, dichlorobenzene, methoxybenzene, trifluoromethylbenzene, p-cymene, mesitylene, ethylbenzene, isopropylbenzene, or mixtures thereof.

More preferably the solvent is selected from: dichloromethane, toluene, xylene, chlorobenzene, methoxybenzene or mixtures thereof.

The ratio of enantiomers produced is from 50.5:49.5 to 100:0 [R]:[S] or [S]:[R]. Preferably the enantiomeric ratio of the product is from 70:30 to 100:0 [R]:[S] or [S]:[R], even more preferably 90:10 to 100:0 [R]:[S] or [S]:[R] The enantiomeric ratio of the product can be either lower or higher than the enantiomeric ratio of the chiral ligand used in the reaction.

The ratio of enantiomers produced can be increased by crystallization if required. Such methods are known to those skilled in the art and include crystallization from an organic solvent, a mixture of organic solvents or a mixture of organic solvents with water.

It has been proven by X-ray crystallography (see Example 8) that the chiral ligand of formula (IV) enriched in R enantiomer provides an enantioenriched sulfoxide of formula (I) enriched in R enantiomer. Correspondingly, the chiral ligand of formula (IV) enriched in S enantiomer yields enantioenriched sulfoxide of formula (I) enriched in S enantiomer.

Definitions:

The term "alkyl" as used herein, in isolation or as part of a chemical group, represents straight-chain orbranched hydrocarbons, preferably with 1 to 6 carbon atoms, for example methyl, ethyl, n-propyl,isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, pentyl, 1- methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-

dimethylpropyl, 1,1 -dimethylpropyl, 2,2- dimethylpropyl, 1 -ethylpropyl, hexyl, 1 -methylpentyl, 2-methylpentyl, 3-methylpentyl, 4- methylpentyl, 1,2-dimethylpropyl, 1,3-dimethylbutyl, 1,4-dimethylbutyl,2,3-dimethylbutyl, 1,1- dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1- ethylbutyl and 2-ethylbutyl. Alkyl groups with 1 to 4 carbon atoms are preferred, forexample methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl or t-butyl.

The term "aryl" represents a mono-, bi- or polycyclical aromatic system with preferably 6 to 14, more preferably 6 to 10 ring-carbon atoms, for example phenyl, naphthyl, anthryl, phenanthrenyl, preferably phenyl. "Aryl" also represents polycyclic systems, for example tetrahydronaphtyl, indenyl, indanyl, fluorenyl, biphenyl. Arylalkyls are examples of substituted aryls, which may be further substituted with the same or different substituents both at the aryl or alkyl part. Benzyl and 1 —phenylethyl are examples of such arylalkyls.

The term "halogen" or "halo" represents fluoro, chloro, bromo or iodo, particularly fluoro, chloro or bromo. The chemical groups which are substituted with halogen, for example haloalkyl, halocycloalkyl, haloalkyloxy, haloalkylsulfanyl, haloalkylsulfinyl or haloalkylsulfonyl are substituted one or up to the maximum number of substituents with halogen. If "alkyl", "alkenyl" or "alkynyl" are substituted with halogen, the halogen atoms can be the same or different and can be bound at the same carbon atom or different carbon atoms.

Where not otherwise defined the term “optionally substituted” means that the group in question can be substituted with zero up to the maximum number of substituents with groups independently selected from: halogen, methyl, ethyl, propyl, isopropyl, t-butyl, cyclopropyl, cyclobutyl, cyclopropyl, cyclohexyl, trifluoromethyl, difluoromethyl, chlorodifluoromethyl, trichloromethyl, methoxy, ethoxy, trifluoromethoxy, difluoromethoxy, nitro, cyano, hydroxy, sulfhydryl, acetyl, acetoxy, COOH, COOMe, COOEt, $CONH_2$, CONHMe, $CONMe_2$, amino, methylamino, dimethylamino, phenyl.

The term "enantiomerically enriched" means that one of the enantiomers of the compound is present in excess in comparison to the other enantiomer. This excess will hereafter be referred to as enantiomeric excess or ee. The ee may be determined by chiral GC, HPLC or SFC analysis. The ee is equal to the difference between amounts of enantiomers divided by the sum of the amounts of the enantiomers, which quotient can be expressed as a percentage after multiplication by 100.

Compounds of formula (II) when not commercially available were synthesized according to synthetic methods described below. Other combinations of substituents not specifically exemplified could be made by similar methods well understood by a person skilled in the art.

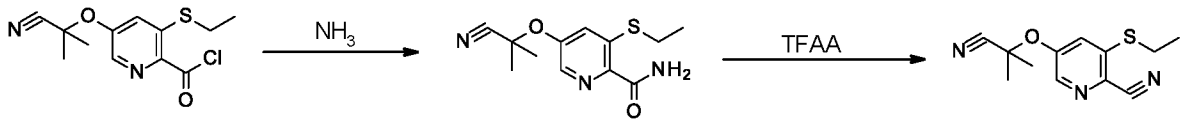
R_1 is Br, R_2 is ethyl: as described in WO2018095795

R_1 is CF_3, R_2 is ethyl: as described in WO2014104407

R_1 is cyanocyclopropyl, R_2 is ethyl: as described in WO2022074214

R_1 is cyanoisopropoxy, R_2 is ethyl: as shown in Scheme 4

Scheme 4



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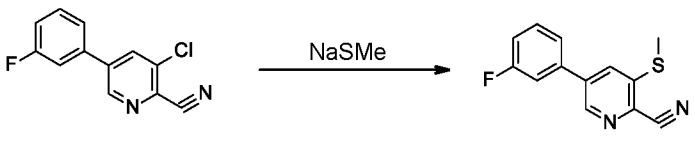
Acid chloride prepared previously was reacted with aqueous ammonia to yield primary amide which was dehydrated using trifluoracetic anhydride (TFAA) to yield the compound of formula (II) with this substitution pattern.

R_1 is 3-fluorophenyl, R_2 is methyl: as shown in Scheme 5

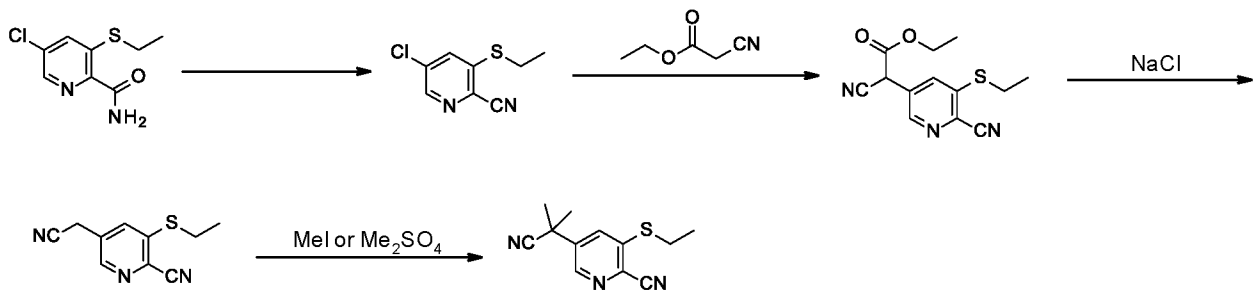
Scheme 5



Chloro derivative prepared as described in WO2016118858 was reacted with sodium methylthiolate to yield compound of formula (II) with this substitution pattern

R_1 is cyanoisopropyl, R_2 is ethyl: as shown in Scheme 6

Scheme 6



Primary amide, prepared as described in WO2021175959, was dehydrated to 2-cyano pyridine derivative. In the second step coupling with ethyl cyanoacetate in the presence of a base yielded coupling product which was decarboxylated using sodium chloride in acetic acid. Finally double methylation with either methyl iodide or dimethyl sulfate provided a compound of formula (II) with this substitution pattern.

Certain preferred embodiments according to the invention are provided as set out below.

Embodiment 1 provides a process for the preparation of enantiomerically enriched sulfoxides of formula (I) as defined above.

Embodiment 2 provides a process for the preparation of a compound of formula (I) which process comprises: stereoselective oxidation of a sulfanyl compound of formula (II) in the presence of an oxidant, in the presence of a chiral reagent or catalyst, optionally in the presence of a suitable additive, in an appropriate solvent (or diluent), to produce a compound of formula (I) as defined above.

Embodiment 3 provides preferred alternatives of the oxidant, metal derivative, chiral ligand, solvent (or diluent) and acid additive that are used in the process of embodiments 1 – 2 and which are, in any combination thereof, as set out above.

With respect to embodiments 1 - 3, preferred values of R_1 and R_2 are, in any combination thereof, as set out below:

Preferably, R_1 is hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cyanocycloalkyl or optionally substituted aryl.

More preferably, R_1 is hydrogen, halogen, C_1-C_4-haloalkyl, C_1-C_4-cyanoalkyl, C_1-C_4-cyanoalkoxy, C_3-C_4-cyanocycloalkyl or optionally substituted aryl.

Most preferably, R_1 is hydrogen, halogen, trifluoromethyl, cyanoisopropoxy, cyanoisopropyl, cyanocyclopropyl or optionally substituted phenyl. Preferably, optionally substituted phenyl is phenyl or halo-phenyl.

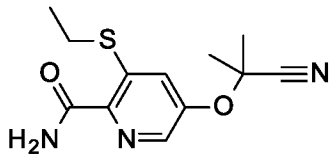
Preferably, R_2 is C_1-C_4 alkyl; more preferably, R_2 is methyl or ethyl; most preferably, R_2 is ethyl.

The following examples serve to illustrate the present invention:

Experimental procedures and data:

Synthesis of sulfide starting materials:

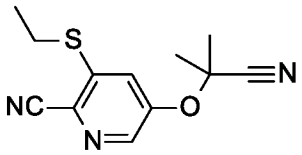
Example 1: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carboxamide



To a suspension of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carboxylic acid (1.00 g, 98% purity, 3.68 mmol) in ethyl acetate (9.0 mL) was added few drops of DMF. Oxalyl chloride (0.360 mL, 4.05 mmol) was then added drop wise at room temperature over 2 hours. Thus prepared acid chloride solution was slowly dosed to a biphasic mixture of sodium bicarbonate (0.372 g, 4.42 mmol), water (2.7 mL), ethyl acetate (2.5 mL) and ammonium hydroxide in water (4.31 g, 36.9 mmol) and cooled to 0 °C. After addition the reaction mixture was stirred for further 1 h at ambient temperature. Phases were separated and the aqueous layer extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound (1.00 g, 83% purity, 85% yield) as a brown solid.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.18 (d, *J*=2.3 Hz, 1H), 7.99 (s, 1H), 7.54 (m, 2H), 2.89 (q, *J*=7.3 Hz, 2H), 1.77 (s, 6H), 1.27 (t, *J*=7.3 Hz, 3H).

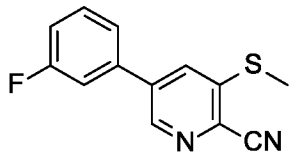
Example 2: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carbonitrile



To a solution of of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carboxamide (10.0 g, 87.5% purity, 33.0 mmol) and Et_3N (18 mL, 132 mmol) in THF (100 mL) was added trifluoro acetic anhydride (14.1 mL, 80.42 mmol) dropwise over the period of 15 minutes at 0°C. After complete addition the reaction mixture was allowed to warm to room temperature. After 1 h of stirring water and saturated sodium bicarbonate was slowly added. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (8.98 g, 82% purity, 90% yield) as a white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (d, *J*=2.4 Hz, 1 H), 7.74 (d, *J*=2.4 Hz, 1H), 3.20 (q, *J*=7.3 Hz, 2 H), 1.81 (s, 6H), 1.29 (t, *J*=7.3 Hz, 3H).

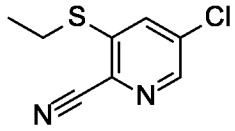
Example 3: Preparation of 5-(3-fluorophenyl)-3-methylsulfanyl-pyridine-2-carbonitrile



To a solution of 3-chloro-5-(3-fluorophenyl)pyridine-2-carbonitrile (3.47 g, 94.5% purity, 14.1 mmol) in tetrahydrofuran (17 mL) was added sodium methanethiolate (2.6 g, 35.2 mmol). The reaction mixture was stirred at 60 °C for 2 hours followed cooling to ambient temperature and quenching with ice cold water. The resulting mixture was extracted with ethyl acetate. The combined organic layers was wash with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using ethyl acetate and cyclohexane as an eluent to yield the title compound (2.60 g, 94% purity, 71% yield) as a brown solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.83 (d, *J*=2.0 Hz, 1H), 8.13 (d, *J*=1.83 Hz, 1H), 7.78-7.83 (m, 1H), 7.73 (d, *J*=7.5 Hz, 1H), 7.56 - 7.63 (m, 1H), 7.35 (d, *J*=2.6 Hz, 1H), 2.74 (s, 3H)

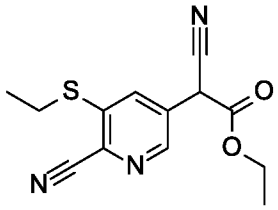
Example 4: Preparation of 5-chloro-3-ethylsulfanyl-pyridine-2-carbonitrile



To a solution of 5-chloro-3-ethylsulfanyl-pyridine-2-carboxamide (15.0 g, 97% purity, 67.0 mmol) and Et_3N (23.5 mL, 167.5 mmol) in dry THF (255 mL) was added trifluoro acetic anhydride (11.3 mL, 80.4 mmol) over 15 min while keeping the internal temperature under 5 °C. The reaction mixture was allowed to warm to room temperature and stirred for further 2 h. Most of THF was evaporated under reduced pressure and water (45 mL) was slowly added. The obtained brown precipitate was filtered and washed on filter with cold water. The precipitate was dissolved in acetone (60 mL) and the solution was slowly added to water (150 mL) under vigorous stirring. The obtained light brown colored precipitate was filtered and dried under reduced pressured to afford the title compound (13.25 g, 97% purity, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, *J*=2.1 Hz, 1H), 7.66 (d, *J*=2.1 Hz, 1H), 3.07 (q, *J*=7.3 Hz, 2 H), 1.41 (t, *J*=7.4 Hz, 3 H).

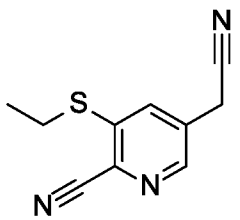
Example 5: Preparation of 2-cyano-2-(6-cyano-5-ethylsulfanyl-3-pyridyl) acetate



To a solution of 5-chloro-3-ethylsulfanyl-pyridine-2-carbonitrile (20.0 g, 97% purity, 97.6 mmol) in dry DMF (100 mL) was added powdered potassium carbonate (34.4 g, 244 mmol). The resulting suspension was then heated at 100 °C and ethyl cyanoacetate (15.9 mL, 146 mmol) was dosed over a period of 1 h. After full consumption of starting material the reaction mixture was cooled to room temperature, diluted with EtOAc and the precipitate (inorganic salts) was filtered off. The filtrate was neutralized using aq 2N HCl and the resulting mixture was extracted with EtOAc. The combined organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography using ethyl acetate and cyclohexane as an eluent to afford the title compound (19.12 g, 95.5% purity, 87% yield) as a gray solid.

^{1}H NMR (400 MHz, CD_3CN) δ 8.50 (d, *J*=2.0 Hz, 1H), 7.90 (d, *J*=2.0 Hz, 1 H), 5.21 (s, 1 H), 4.23 (q, *J*=7.1 Hz, 2 H), 3.14 (q, *J*=7.4 Hz, 2 H), 1.34 (t, *J*=7.3 Hz, 3 H), 1.24 (t, *J*=7.1 Hz, 3 H).

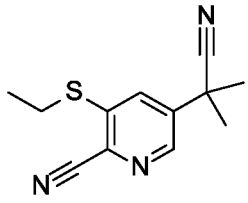
Example 6: Preparation of 5-(cyanomethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile



To a solution of ethyl 2-cyano-2-(6-cyano-5-ethylsulfanyl-3-pyridyl) acetate (10.00 g, 95% purity, 34.51 mmol) in a mixture of acetic acid (44 mL) and water (22.5 ml) was added sodium chloride (5.07 g, 86.3 mmol). The reaction mixture was then stirred at 100 °C until the full consumption of starting material. The reaction mixture was the cooled to ambient temperature and cold water (100 mL) was added. The resulting mixture was then neutralized by the portion wise addition of solid sodium bicarbonate under vigorous stirring and the neutralized solution was extracted with EtOAc. The combined organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude material was dissolved in acetone (20 mL) and slowly added into water (100 ml) at 0°C under vigorous stirring. The obtained off-white colored precipitate was filtered off, washed on filter with water (50 mL) and dried under reduced pressure to afford the title compound (7.17 g, 93% purity, 95% yield) as an off-white powder.

^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.50 (d, *J*=1.8 Hz, 1H), 8.04 (d, *J*=1.7 Hz, 1 H), 4.21 (s, 2 H), 3.18 (q, *J*=7.3 Hz, 2 H), 1.30 (t, *J*=7.3 Hz, 3 H).

Example 7: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile



To a solution of 5-(cyanomethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (10.00 g, 96% purity, 47.23 mmol) in acetonitrile (150 ml) was added Cs_2CO_3 (47.1 g., 141.7 mmol) followed by iodomethane (6.0 mL, 94.5 mmol) and the reaction mixture was stirred at 80°C for 1 hour. After full consumption of starting material, the reaction mixture was cooled to ambient temperature and quenched by addition of water. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (11.45 g, 85% purity, 89% yield) as a white powder.

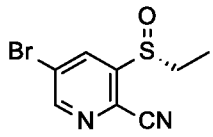
^{1}H NMR (400 MHz, DMSO-d6) δ 8.69 (d, J=2.1 Hz, 1 H), 8.03 (d, J=2.2 Hz, 1 H), 3.25 (q, J=7.3 Hz, 2 H), 1.78 (s, 6 H) , 1.29 (t, J=7.3 Hz, 3 H)

Preparation of racemic sulfoxides for development of chiral analytical methods:

Racemic samples of sulfoxides were prepared according to the following general procedure:
Sulfide (1 eq) was dissolved in acetic acid (5 mL/mmol) and hydrogen peroxide (1.05 equiv, 30 mass%) was added at room temperature. The reaction mixture was stirred at 40°C for 20 h or until complete consumption of the starting material was observed by LCMS. Aqueous $NaHCO_3$ was added dropwise to the reaction mixture followed by ethyl acetate. The phases were separated, and the aqueous phase was extracted with another portion of ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to afford the desired sulfoxide. The material was used directly for the development of a chiral HPLC method.

Preparation of enantioenriched sulfoxides:

Example 8: Preparation of 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-bromo-3-ethylsulfanyl-pyridine-2-carbonitrile (2.157 g, 93% purity, 8.25 mmol) in anisole (8.3 ml) was added (2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol) (0.235 g, 97% purity, 0.602 mmol), 4-methoxybenzoic acid (43 mg, 0.28 mmol) and $Fe(acac)_3$ (0.277 g, 0.0784 mmol). The resulting dark red solution was cooled to 10 °C and 30% aq H_2O_2 (1.35 ml, 13.2 mmol) was added. The resulting biphasic mixture was stirred at 10 °C for 22 h. At this stage (full conversion of starting material) the reaction was quenched by addition of crushed ice (4 g) and 40% aq $NaHSO_3$ (2.6 ml). After warming to ambient temperature, the mixture was diluted with EtOAc (8 ml) and treated with 1M aqueous H_2SO_4 (0.83 ml). After stirring for 30 min phases were separated, organic phase washed with aq $NaHCO_3$ (8 ml) and brine (8 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to yield a crude product. Quantitative NMR analysis using 1,3,5-trimethoxy benzene as an internal standard indicates a chemical yield of 91% for the desired 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile. The crude product was purified by a reverse phase HPLC (MeCN/water/0.1% formic acid mobile phase) to yield the title compound (1.63 g, >99% purity, >99.5% ee, 76% isolated yield) as a white powder.

^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.45 Hz, 3 H), 2.99 (dq, J=14.0, 7.2 Hz, 1 H), 3.15 - 3.36 (m, 1 H), 8.50 (d, J=2.2 Hz, 1 H), 8.85 (d, J=2.2 Hz, 1 H)

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IC, 3µm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: IPA gradient: 20-60% B in 2 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 240 nm

Sample concentration: 1 mg/mL in ACN

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 1.14	Retention time (min) ~ 1.35
Enantiomeric excess: >99.5% (R enantiomer, S enantiomer below HPLC detection limits)	

A single crystal grown from di-isopropyl ether was selected for X-ray data analysis. The crystal sample mounted had dimensions of 0.4 mm x 0.3 mm x 0.3 mm and was a colorless prism. Data collection was performed on a Rigaku Oxford Diffraction Supernova diffractometer at 293 K. The unit cell was determined to be orthorhombic (space group P212121), and the structure contained one molecule in the crystal asymmetric unit (Figure 1, a thin stick representation labelled by chirality. Figure 1 generated in Flare software package). The stereochemistry was unambiguously determined to be the R isomer, with a Flack parameter of 0.02 +/- 0.03. Crystallographic data is summarized in Table 1 and selected geometric parameters are listed in Table 2.

Table 1. Crystal data and structure refinement for 5-bromo-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile

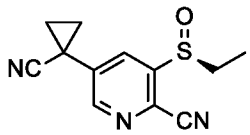
Crystal data	
Chemical formula	$C_8H_7BrN_2OS$
M_r	259.13
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Temperature (K)	293
a, b, c (Å)	6.7404 (2), 9.2441 (3), 15.8051 (5)
V (Å^3)	984.80 (6)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	7.37
Crystal size (mm)	0.40 × 0.30 × 0.30
Data collection	
Diffractometer	Oxford Diffraction SuperNova
Absorption correction	Multi-scan *CrysAlis PRO*, (Agilent, 2011)
T_{min}, T_{max}	0.11, 0.11
No. of measured, independent and observed [$I > 2.0\sigma(I)$] reflections	4140, 2032, 1962
R_{int}	0.037
(sin θ/λ)$_{max}$ (Å^{-1})	0.632
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.041, 0.117, 0.91
No. of reflections	2024
No. of parameters	120
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.40, −0.72
Absolute structure	Flack (1983), 814 Friedel-pairs
Absolute structure parameter	0.02 (3)

Computer programs: SuperNova, (Oxford Diffraction, 2010), CrysAlis PRO, (Agilent, 2011), SIR92 (Altomare et al., 1994), CRYSTALS (Betteridge et al., 2003), CAMERON (Watkin et al., 1996)

Table 2. Selected geometric parameters (Å, °)

Br1—C2	1.874 (4)	S5—C7	1.806 (4)
C2—C3	1.380 (5)	C7—C8	1.510 (6)
C2—C11	1.394 (6)	C9—N10	1.341 (4)
C3—C4	1.392 (5)	C9—C12	1.436 (5)
C4—S5	1.808 (3)	N10—C11	1.328 (5)
C4—C9	1.388 (5)	C12—N13	1.153 (6)
S5—O6	1.491 (3)		
Br1—C2—C3	121.0 (3)	O6—S5—C7	107.64 (19)
Br1—C2—C11	118.8 (2)	S5—C7—C8	114.3 (3)
C3—C2—C11	120.3 (3)	C4—C9—N10	123.7 (3)
C2—C3—C4	117.2 (3)	C4—C9—C12	121.2 (3)
C3—C4—S5	118.3 (3)	N10—C9—C12	115.1 (3)
C3—C4—C9	118.9 (3)	C9—N10—C11	117.3 (3)
S5—C4—C9	122.6 (3)	C2—C11—N10	122.6 (3)
C4—S5—O6	105.15 (17)	C9—C12—N13	179.2 (4)
C4—S5—C7	98.29 (15)		

Example 9a: Preparation of 5-(1-cyanocyclopropyl)-3-[(S)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (241.5 mg, 95% purity, 1.00 mmol), $Fe(acac)_3$ (17.5 mg, 0.0500 mmol), 4-methoxybenzoic acid (3.8 mg, 0.0250 mmol) and 2-[(E)-[(1S)-1-(hydroxymethyl)-2,2- dimethyl-propyl]iminomethyl]-4,6-diiodo-phenol (48.8 mg, 97% purity, 0.100 mmol) in PhMe (4.0 ml) was added 30% aq H_2O_2 (0.20 ml, 2.00 mmol) at ambient temperature. After stirring vigorously for 2.5 h the reaction mixture was poured into EtOAc (23 ml) and quenched by addition of 1.0M $Na_2S_2O_3$ (2.4 ml). Phases were separated and the organic phase was washed with 1.0M HCl (2.3 ml) and aq $NaHCO_3$. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN/0.1% formic acid mobile phase) to yield the title compound (234 mg, 97%ee, 95% yield) as a white powder.

^1H NMR (400 MHz, DMSO-d6) δ 8.77 (d, *J* = 2.3 Hz, 1H), 8.18 (d, *J* = 2.3 Hz, 1H), 3.26 (dq, *J* = 13.6, 7.3 Hz, 1H), 3.04 (dq, *J* = 13.6, 7.3 Hz, 1H), 2.09 –1.79 (m, 4H), 1.12 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, d6-DMSO) δ = 165.7, 146.0, 144.4, 142.8, 136.0, 131.1, 121.2, 48.9, 19.2, 12.0, 6.3

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IA, 3□m, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: IPA gradient: 20-60% B in 1.8 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: DAD 210-500 nm

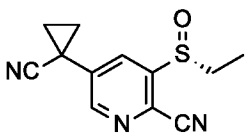
Sample preparation: dissolved in MeOH

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.59	Retention time (min) ~ 1.04
Enantiomeric excess: 97% (S enantiomer)	

Example 9b: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (237.0 mg, 97% purity, 1.00 mmol), $Fe(acac)_3$ (3.6 mg, 0.0101 mmol), 4-methoxybenzoic acid (3.8 mg, 0.0251 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2- dimethyl-propyl]iminomethyl]-4,6-dichloro-phenol (32.8 mg, 98% purity, 0.110 mmol) in PhOMe (1.0 ml) was added 30% aq H_2O_2 (0.23 ml, 2.11 mmol) at 0 °C over 1 h using a syringe pump. The resulting reaction mixture was stirred for further 20 h at the same temperature. The reaction mixture was poured into EtOAc (23 ml) and quenched by addition of 1.0M $NaHSO_3$ (2.4 ml). Phases were separated and the organic phase was washed with 1.0M HCl (2.3 ml) and aq $NaHCO_3$. The organic phase

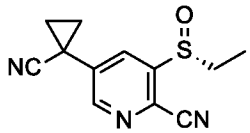
was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN/0.1% formic acid mobile phase) to yield the title compound (230 mg, >99.5%ee, 93% yield) as a white powder.

Chiral SFC method: Identical to Example 2a

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.59	Retention time (min) ~ 1.04
Enantiomeric excess: >99.5% (R enantiomer)	

Example 9c: Preparation of 5-(1-cyanocyclopropyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyanocyclopropyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (10.61 g, 98% purity, 45.5 mmol), $Fe(acac)_3$ (0.153 g, 0.432 mmol), 4-methoxybenzoic acid (0.234 g, 1.54 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol (1.281 g, 97% purity, 3.30 mmol) in anisole (46 ml) was added 30% aq H_2O_2 (7.8 ml, 76.3 mmol) at 10 ºC over 2 h using a syringe pump. The resulting reaction mixture was stirred vigorously for further 22 h at the same temperature. The reaction was quenched by addition of 40% aq NaHSO3 (10.6 ml) and diluted with anisole (53 ml). Phase were separated and the organic phase was washed with 1M H_2SO_4 (21 ml), aq saturated $NaHCO_3$ (21 ml) and brine (21 ml). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by a reverse phase HPLC (water/MeCN as a mobile phase) to yield the title compound (10.44 g, >99.5% ee, 93% yield) as a white powder.

Chiral SFC method:

SFC: Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IA, 3µm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: IPA gradient: 5-20% B in 9.8 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 238 nm

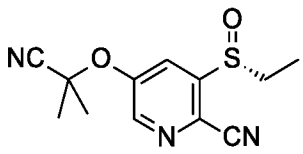
Sample preparation: 1mg/mL in ACN

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 3.07	Retention time (min) ~ 5.73
Enantiomeric excess: >99.5% (R enantiomer)	

Example 10: Preparation of 5-(1-cyano-1-methyl-ethoxy)-3-[(*R*)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyano-1-methyl-ethoxy)-3-ethylsulfanyl-pyridine-2-carbonitrile (2.00 g, 82% purity, 6.64 mmol), iron(III) acetylacetonate (46.9 mg, 0.133 mmol), 2,4-dichloro-6-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]phenol (0.602 g, 1.99 mmol), p-anisic acid (51 mg, 0.332 mmol) in toluene (13 mL) was added 30% aq H_2O_2 (1.36 ml, 50.1 mmol) at ambient temperature over 1h. The reaction mixture was stirred for further 5 h and then quenched by adding aq saturated sodium thiosulphate at 0 °C. The organic layer was separated, and aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure to get the crude compound. The crude material was purified by silica gel chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (1.55 g, 89% purity, >99.5% ee, 79% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 8.71 (d, *J*=2.6 Hz, 1H) 8.02 (d, *J*=2.75 Hz, 1H) 3.28 - 3.33 (m, 1H) 2.96-3.02 (m, 1H), 1.84 (s, 6H), 1.09 (t, *J*=7.3 Hz, 3H)

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IA (4.6mm x 250mm) 5µm

Mobile phase: A: TBME B: IPA isocratic: 20% B in 13 min

Flow rate: 1.0 ml/min

Detection: 240 nm

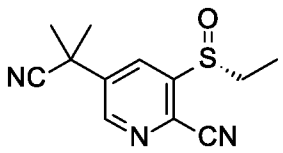
Sample preparation: 1mg/mL in EtOH

Injection: 2 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 5.32	Retention time (min) ~ 6.8
Enantiomeric excess (%) >99.5% (R enantiomer, opposite enantiomer below HPLC detection limits)	

Example 11: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(1-cyano-1-methyl-ethyl)-3-ethylsulfanyl-pyridine-2-carbonitrile (6.00 g, 96.5% purity, 25.0 mmol), iron(III) acetylacetonate (0.177 g, 0.5 mmol), 2,4-dibromo-6-[(E)-[(1R)-1-(hydroxymethyl) -2,2-dimethyl-propyl]iminomethyl]phenol (1.47 g, 3.75 mmol) in toluene (90 mL) was added 30% aq hydrogen peroxide (2.0 equiv., 50.1 mmol) drop wise over 1h at 0 °C. The reaction mixture was stirred for 2 h at 24°C and then quenched by adding saturated $Na_2S_2O_3$ at 0 °C. The organic layer was separated, and aqueous layer extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude product. The crude material was purified by column chromatography using cyclohexane and ethyl acetate as an eluent to yield the title compound (5.48 g, 91% purity, 97% ee, 81% yield).

^{1}H NMR (400 MHz, DMSO-d6) δ 9.10 (d, *J*=2.3 Hz, 1H), 8.35 (d, *J*=2.3 Hz, 1H), 3.28 (m , 1H), 3.04 (m, 1H), 1.82 (d, *J*=1.9 Hz, 6H), 1.12 (t, *J*=7.3 Hz, 3H)

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IC (4.6mm x 250mm) 5µm

Mobile phase: A: n-hexane B: EtOH isocratic: 30% B in 30 min

Flow rate: 1.0 ml/min

Detection: 225 nm

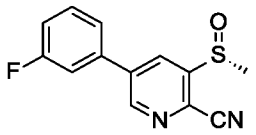
Sample preparation: 1mg/mL in EtOH

Injection: 2 µL

Results:

R enantiomer	S enantiomer
Retention time (min) ~ 18.2	Retention time (min) ~ 21.8
Enantiomeric excess: 97% (R enantiomer)	

Example 12: Preparation of 5-(3-fluorophenyl)-3-[(R)-methylsulfinyl]pyridine-2-carbonitrile



To a solution of 5-(3-fluorophenyl)-3-methylsulfanyl-pyridine-2-carbonitrile (0.800 g, 90% purity, 2.95 mmol), iron(III) acetylacetonate (10.4 mg, 0.0295 mmol), 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-diiodo-phenol (0.213 g, 0.442 mmol), p-anisic acid (11.3 mg, 0.0737 mmol) in toluene (6.0 ml) was added 30% aq H_2O_2 (0.6 mL, 5.9 mmol) drop wise over 15 minutes and the reaction mixture was continued to stir for further 1 hour. The reaction mixture was quenched by saturated sodium thiosulphate and the resulting mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to get crude material. Purification by silica gel chromatography using cyclohexane and ethyl acetate as an eluent yielded the title compound (0.73 g, 94% purity, 97% ee, 89% yield)

^{1}H NMR (400 MHz, DMSO-d6) δ 9.29 (d, *J*=2.1 Hz, 1H), 8.64 (d, *J*=2.1 Hz, 1H), 7.89 (m, 1 H), 7.80 (d, *J*=7.8 Hz, 1H), 7.64 (m, 1H), 7.41 (m, 1H), 3.04 (s, 3 H)

Method of chiral analysis:

Chiral HPLC: WATERS ACQUITY UPLC

Column: Chiralpack-IA (4.6mm x 250mm) 5µm

Mobile phase: A: TBME B: IPA isocratic: 30% B in 30 min

Flow rate: 1.0 ml/min

Detection: 225 nm

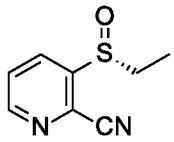
Sample preparation: 1mg/mL in EtOH

Injection: 2 µL

Results:

S enatiomer	R enantiomer
Retention time (min) ~ 11.0	Retention time (min) ~ 14.9
Enantiomeric excess: 97% (R enantiomer)	

Example 13: Preparation of 3-[(R)-ethylsulfinyl]pyridine-2-carbonitrile



A solution of 3-ethylsulfanylpyridine-2-carbonitrile (182.0 mg, 90% purity, 1.00 mmol), $Fe(acac)_3$ (3.4 mg, 0.0095 mmol), 4-methoxybenzoic acid (5.3 mg, 0.034 mmol) and 2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol (28.5 mg, 0.073 mmol) in PhOMe (1 ml) was prepared. The resulting deep red solution was cooled to 10°C and 30% aq. H_2O_2 (163 µl, 1.60 mmol) was added slowly. The resulting biphasic mixture was stirred at 10°C for 22h. The reaction was quenched by cooling to 0°C and the addition of 40% aq. $NaHSO_3$ (0.315 ml, 1.60 mmol). After warming to ambient temperature, the mixture was diluted with EtOAc (10 ml) and conc. H_2SO_4 (50 µl) was added to acidify the mixture. After stirring for 30 min phases were separated and the aqueous layer was again extracted with EtOAc (15 ml). The combined organic layer was washed with sat. aq. $NaHCO_3$ (8 ml) and brine (8 ml). The organic layer was dried over anhydrous $MgSO_4$ concentrated under reduced pressure. The crude material was purified by silica gel chromatography (Cyclohexane / EtOAc 100:0 to 0:100) to yield the title compound (112 mg, 95 % purity, 94 % ee, 59% yield) as a colourless solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (t, *J*=7.3 Hz, 3 H) 2.88 - 3.07 (m, 1 H) 3.15 - 3.33 (m, 1 H) 7.80 (dd, *J*=8.0, 4.7 Hz, 1 H) 8.40 (dd, *J*=8.2, 1.6 Hz, 1 H) 8.83 (dd, *J*=4.7, 1.4 Hz, 1 H)

Chiral SFC method

SFC: Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IA, 3µm, 0.3cm x 10cm, 40 °C

Mobile phase: A: CO_2 B: MeOH isocratic 5% B in 5 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 260 nm

Sample concentration: 1 mg/mL in MeOH

Injection: 1 µL

Results:

S enantiomer	R enantiomer
Retention time (min) ~ 2.02	Retention time (min) ~ 2.96
Enantiomeric excess: 94 % (R enantiomer)	

Example 14: Preparation of 3-[(R)-ethylsulfinyl]-5-(trifluoromethyl)pyridine-2-carbonitrile

To a solution of 3-Ethylsulfanyl-3-(trifluoromethyl)pyridine-2-carbonitrile (0.237 g, 98% purity, 1.00 mmol) in anisole (1.0 ml) was added (2-[(E)-[(1R)-1-(hydroxymethyl)-2,2-dimethyl-propyl]iminomethyl]-4,6-dibromo-phenol) (28.5 mg, 97% purity, 0.073 mmol), 4-methoxybenzoic acid (5.3 mg, 0.034 mmol) and $Fe(acac)_3$ (3.4 mg, 0.010 mmol). The resulting dark red solution was cooled to 10 °C and 30% aq H_2O_2 (0.136 ml, 1.6 mmol) was added. The resulting biphasic mixture was stirred at 10 °C for 22 h. At this stage (full conversion of starting material) the reaction was quenched by addition of crushed ice (4 g) and 40% aq $NaHSO_3$ (0.30 ml). After warming to ambient temperature, the mixture was diluted with EtOAc (10 ml) and treated with conc. H_2SO_4 (50 µl). After stirring for 30 min phases were separated and the aqueous layer was again extracted with EtOAc (15 ml). The combined organic layer was washed with sat. aq. $NaHCO_3$ (8 ml) and brine (8 ml). The organic layer was dried over anhydrous $MgSO_4$ concentrated under reduced pressure. The crude material was purified by silica gel chromatography (Cyclohexane / EtOAc 100:0 to 60:40) to yield the title compound (127 mg, 98% purity, >99% ee, 50% yield) as a colourless solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.27 - 1.40 (m, 3 H), 2.95 - 3.09 (m, 1 H), 3.21 - 3.37 (m, 1 H) 8.65 (d, *J*=1.45 Hz, 1 H), 9.06 (d, *J*=1.09 Hz, 1 H)

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.80 (s, 3 F)

Chiral SFC method

SFC:Waters Acquity UPC^2/QDa

PDA Detector Waters Acquity UPC^2

Column: Daicel SFC CHIRALPAK® IC, 3µm, 0.3cm x 10cm, 40°C

Mobile phase: A: CO_2 B: MeOH isocratic 3% B in 2 min

ABPR: 1800 psi

Flow rate: 2.0 ml/min

Detection: 270 nm

Sample concentration: 1 mg/mL in MeOH

Injection: 1 µL

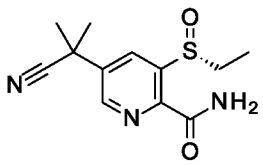
Results:

S enantiomer	R enantiomer
Retention time (min) ~ 0.95	Retention time (min) ~ 1.26
Enantiomeric excess: >99 % (R enantiomer; S enantiomer below HPLC detection limits)	

Further synthetic elaboration of enantioenriched sulfoxides

In this section further functionalization of one specific enantioenriched sulfoxide towards agrochemically important intermediates (Scheme 3) is shown.

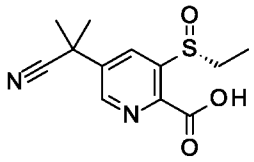
Example 15: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl] pyridine-2-carboxamide



A suspension of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl] pyridine-2-carbonitrile (3.2 g, 91% purity, 11.81 mmol) in *tert*-butanol (32 mL) was heated to 60 °C and potassium hydroxide (2.34 g, 35.4 mmol) was added to the resulting solution. The resulting reaction mixture was stirred at 60 °C for 1.5 h. The reaction mixture was cooled to room temperature and quenched with 2N aq. HCl to pH ~ 7. The reaction mixture was then extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography using EtOAc/cyclohexane as an eluent to yield the title compound (1.80 g, 93% purity, 53% yield) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d6) δ 8.91 (d, *J*=2.3 Hz, 1H), 8.50 (d, *J*=2.3 Hz, 1H), 8.43 (br s, 1H), 8.05 (br s, 1H), 3.21-3.28 (m, 1H), 2.77-2.80 (m, 1H), 1.81 (s, 6H), 1.08 (t, *J*=7.4 Hz, 3H).

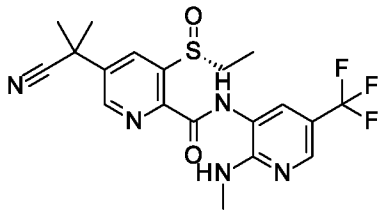
Example 16: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl] pyridine-2-carboxylic acid



To a solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl] pyridine-2-carboxamide (0.490 g, 93% purity, 1.72 mmol) in AcOH (5.15 mL) was added tert-butyl nitrite (0.69 mL, 5.15 mmol) at room temperature. The reaction mixture was then heated at 70 °C for 5 h. The reaction mixture was then cooled to ambient temperature and evaporated under reduced pressure. The crude residue was evaporated with toluene to remove residual acetic acid and dried under high vacuum to yield the title compound (0.470 g, 86% purity, 89% yield) as a semi solid which was used for the next step without further purification

^{1}H NMR (400 MHz, CD_3CN) δ 8.89 (d, *J*=2.2 Hz, 1 H), 8.59 (s, 1 H), 6.83 (br s, 1 H), 3.12 - 3.33 (m, 1 H), 2.79 - 2.89 (m, 1 H), 1.84 (s, 3 H), 1.83 (s, 3 H), 1.17 (t, *J*=7.4 Hz, 3 H).

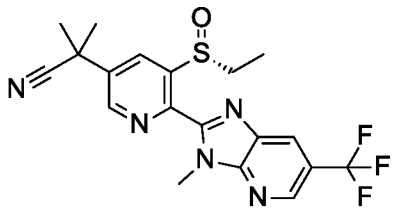
Example 17: Preparation of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-N-[2-(methylamino)-5-(trifluoromethyl)-3-pyridyl] pyridine-2-carboxamide



To a solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl] pyridine-2-carboxylic acid (440 mg, 86% purity, 1.43 mmol) in a mixture of pyridine (1.3 mL) and ethyl acetate (0.9 mL) was added solution of 1-propanephosphonic anhydride in ethyl acetate (2.2 mL, 3.57 mmol, 50% w/w) at room temperature and stirring was continued for 10 minutes. N2-methyl-5-(trifluoromethyl) pyridine-2,3-diamine (344 mg, 1.71 mmol) was then added, and the reaction mixture was stirred at 70 °C for 2 h. The reaction mixture was then cooled to ambient temperature and diluted with cold water. The resulting mixture was extracted with EtOAc, the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude residue was purified by silica gel chromatography using ethyl acetate/cyclohexane as an eluent to yield the title compound (220 mg, 91% purity, 32% yield) as a light brown solid.

^{1}H NMR (400 MHz, CD_3CN) δ 9.58 (s, 1H), 8.90 (d, *J*=2.2 Hz, 1H), 8.62 (d, *J*=2.2 Hz, 1H), 8.35 (s, 1H), 7.74 (d, *J*=2.2 Hz, 1H), 5.82 (br s, 1H), 3.21 - 3.31 (m, 1 H), 2.93 (d, *J*=4.0 Hz, 3H), 2.82 - 2.86 (m, 1 H), 1.84 (s, 3H), 1.83 (s, 3H), 1.17 (t, *J*=8.0 Hz, 3H).

Example 18: Preparation of 2-[5-[(R)-ethylsulfinyl]-6- [3-methyl-6-(trifluoro methyl) imidazo[4,5-b] pyridin-2-yl]-3-pyridyl]-2-methyl-propanenitrile

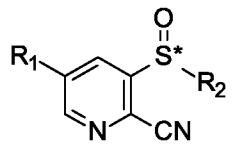


A solution of 5-(1-cyano-1-methyl-ethyl)-3-[(R)-ethylsulfinyl]-N-[2-(methylamino)-5-(trifluoromethyl)-3-pyridyl] pyridine-2-carboxamide (200 mg, 91% purity, 0.414 mmol) in acetic acid (1.4 mL) was heated at 110 °C for 2 h. After full consumption of starting material, the reaction mixture was evaporated under reduced pressure. The crude material was purified by silica gel chromatography using ethyl acetate/cyclohexane as an eluent to afford the title compound (130 mg, 97% purity, 72% yield) as a brown solid.

^{1}H NMR (400 MHz, CD_3CN) δ 9.01 (d, *J*=2.4 Hz, 1H), 8.82 (d, *J*=1.2 Hz, 1H), 8.64 (d, *J*=2.4 Hz, 1H), 8.47 (d, *J*=1.6 Hz, 1H) 4.27 (s, 3H), 3.56-3.62 (m, 1H), 2.98-3.03 (m, 1H), 1.88 (s, 3H), 1.87 (s, 3H), 1.37 (t, *J*=7.4 Hz, 3H).

Claims:

1. A process for the preparation of enantiomerically enriched sulfoxides of formula (I)



(I)

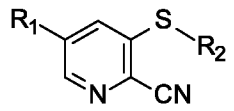
wherein

S* is a stereogenic sulfur atom which is in R- or S-configuration;

R_1 is hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cyanocycloalkyl or optionally substituted aryl; and

R_2 is C_1-C_4 alkyl

by stereoselective oxidation of a sulfanyl compound of formula (II)



(II)

wherein R_1 and R_2 are as defined for compounds of formula (I);

in the presence of an oxidant, in the presence of a metal derivative, in the presence of a chiral ligand, optionally in the presence of a suitable acid additive, in an appropriate solvent (or diluent);

to produce the sulfinyl compound of formula (I).

2. The process according to claim 1, wherein R_1 is hydrogen, halogen, C_1-C_4-haloalkyl, C_1-C_4-cyanoalkyl, C_1-C_4-cyanoalkoxy, C_3-C_4-cyanocycloalkyl or optionally substituted aryl.

3. The process according to claim 1, wherein R_1 is hydrogen, halogen, trifluoromethyl, cyanoisopropoxy, cyanoisopropyl, cyanocyclopropyl or optionally substituted phenyl.

4. The process according to claim 1, wherein R_2 is methyl or ethyl; preferably, R_2 is ethyl.

5. The process according to any one of the previous claims, wherein the oxidant is an inorganic peroxide.

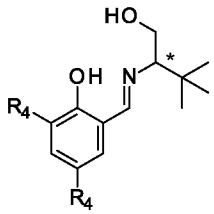
6. The process according to any one of the previous claims, wherein the oxidant is an organic peroxide.

7. The process according to any one of claim 5 or claim 6, wherein the ratio of oxidant used, compared to the sulfanyl compound of formula (II), is in the range from 8:1 to 0.8:1.

8. The process according to any one of the previous claims, wherein the metal derivative is selected from salts of vanadium and salts of iron.

9. The process according to any one of the previous claims, wherein the chiral ligand is selected from Schiff bases formed from salicylaldehyde derivatives and chiral amines.

10. The process according to any one of the previous claims, wherein the metal derivative is iron and the chiral ligand is a Schiff base formed from salicylaldehyde derivatives and chiral amino-alcohols represented by a compound of formula (IV)



(IV)

wherein R_4 is halogen and * represents an enantioenriched chiral center in either R or S configuration.

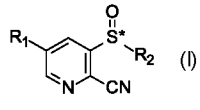
11. The process according to any one of the previous claims, wherein the additive is a benzoic acid, optionally mono-, di- or tri-substituted by methyl, ethyl, isopropyl, methoxy or dimethylamino, optionally in form of a lithium, sodium or potassium salt.

12. The process according to any one of the previous claims, wherein
the oxidizing agent is hydrogen peroxide;
the metal salt is $Fe(acac)_3$;
the ligand is selected from: (2R)-2-[(E)-(3,5-diiodophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2S)-2-[(E)-(3,5-diiodophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2R)-2-[(E)-(3,5-dibromophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2S)-2-[(E)-(3,5-dibromophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, (2R)-2-[(E)-(3,5-dichlorophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol, and (2S)-2-[(E)-(3,5-dichlorophenyl)methyleneamino]-3,3-dimethyl-butan-1-ol; and
the additive is 4-methoxybenzoic acid.

13. The process according to any one of the previous claims, wherein the solvent (or diluent) is selected from esters, nitriles, alcohols, ethers, and aliphatic, aromatic or halogenated hydrocarbons and mixtures thereof.

14. The process according to claim 13, wherein the solvent is an aromatic or halogenated hydrocarbon selected from dichloromethane, 1,2-dichloroethane, chloroform, benzene, toluene, xylene, chlorobenzene, fluorobenzene, dichlorobenzene, methoxybenzene, trifluoromethylbenzene, p-cymene, mesitylene, ethylbenzene, isopropylbenzene, and mixtures thereof.

15. A compound of formula I:


(I)

wherein

S* is a stereogenic sulfur atom which is in R- or S-configuration;

R_1 is hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cyanocycloalkyl or optionally substituted aryl; and

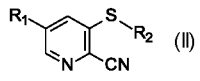
R_2 is C_1-C_4 alkyl.

16. A compound according to claim 15 wherein S* is a stereogenic sulfur atom which is in R-configuration.

17. A compound according to claim 15 wherein S* is a stereogenic sulfur atom which is in S-configuration.

18. A compound according to any one of claims 15 – 17 wherein R_1 is hydrogen, halogen, trifluoromethyl, cyanoisopropoxy, cyanoisopropyl, cyanocyclopropyl or optionally substituted phenyl; and R_2 is C_1-C_4 alkyl; more preferably, R_2 is methyl or ethyl; most preferably, R_2 is ethyl.

19. A compound of formula (II)


(II)

wherein

R_1 is hydrogen, halogen, C_1-C_6-haloalkyl, C_1-C_6-cyanoalkyl, C_1-C_6-cyanoalkoxy, C_3-C_6-cyanocycloalkyl or optionally substituted aryl; and

R_2 is C_1-C_4 alkyl.

20. A compound according to claims 19 wherein R_1 is hydrogen, halogen, trifluoromethyl, cyanoisopropoxy, cyanoisopropyl, cyanocyclopropyl or optionally substituted phenyl; and R_2 is methyl or ethyl.

DRAWINGS

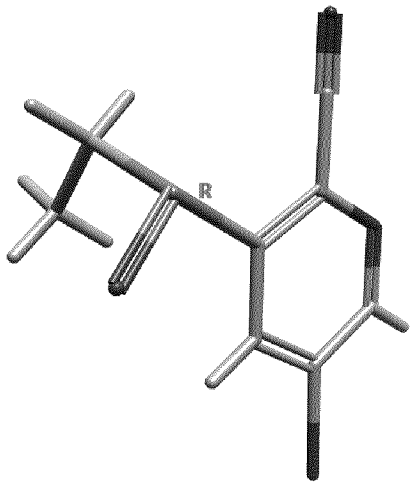


Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/065669

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D211/54 C07D401/12 C07D487/04 A01N43/90
ADD.

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)
C07D A01N

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)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Pitchen Philippe ET AL: "AN EFFICIENT ASYMMETRIC OXIDATION OF SULFIDES TO SULFOXIDES", Tetrahedron Letters, 1 January 1984 (1984-01-01), pages 1049-1052, XP093117024, Great Britain Retrieved from the Internet: URL:https://www.sciencedirect.com/science/article/pii/S0040403901800976 [retrieved on 2024-01-09] page 1049, lines 9-13;; table 1 -----	1-20
X	WO 2022/253841 A1 (SYNGENTA CROP PROTECTION AG [CH]) 8 December 2022 (2022-12-08) cited in the application claim 19 -----	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2024	18/09/2024

Name and mailing address of the ISA/	Authorized officer
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Information on patent family members

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