

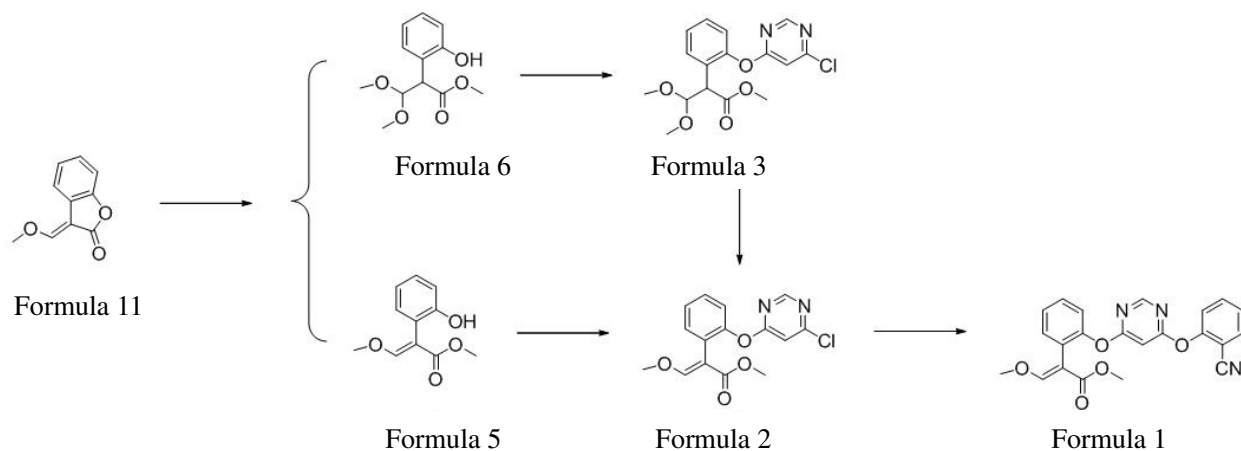
CATALYST SYSTEM AND METHOD FOR PREPARING AZOXYSTROBIN OR INTERMEDIATES THEREOF BY USING CATALYST SYSTEM

FIELD

5 [0001] The present disclosure belongs to the field of chemical industry, relates to the preparation of a bactericide, and especially relates to a catalyst system for preparing azoxystrobin and an intermediate thereof.

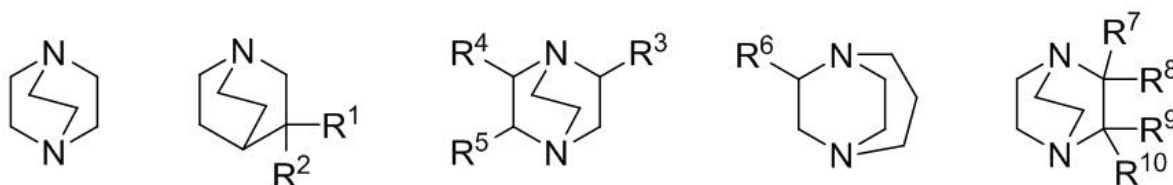
BACKGROUND

10 [0002] Azoxystrobin is a new type of high-efficiency, broad-spectrum, systemic methoxyacrylates fungicide, having a chemical name of methyl (E)-2-[2-6-(2-cyanophenoxy)pyrimidine-4-yloxy]phenyl]-3-methoxyacrylate, with a structural formula as shown in Formula 1. This fungicide may be used for stem and leaf spray, seed treatment, and soil treatment, and has good activity against almost all fungal diseases. It has no
15 cross resistance with existing fungicides and has been widely used in cereals, rice, grapes, potatoes, fruit trees and other crops. Azoxystrobin is widely consumed bactericide in the world. A large number of patent documents have disclosed its synthesis methods. Currently the main synthesis routes of azoxystrobin are as follows.



[0003] Wherein, the application of a catalyst in the preparation steps of the intermediate represented by Formula 3 and azoxystrobin can greatly increase the conversion rate and yield. The earliest patent WO 92/08703A1 for preparing azoxystrobin discloses a method for preparing azoxystrobin and its intermediates of Formula 2 and 3. In the synthetic route, the compound 3-(α -methoxy)methylenebezofuran-2-(3H)-one represented by Formula 11 is ring-opened by sodium methoxide and then couples with 4,6-dichloropyrimidine to obtain a mixture of compounds represented by Formula 2 and Formula 3. The mixture is processed to obtain a single compound of formula 2, and the compound of formula 2 then reacts with a salt of salicylonitrile to obtain azoxystrobin. WO 01/72719A1 discloses a method for preparing azoxystrobin by use of 1,4-diazabicyclo[2.2.2]octane as a catalyst, in which 6-chloro-4-aryloxy pyrimidine reacts with salicylonitrile to obtain azoxystrobin, under the catalysis of 2 mol%-40 mol% of 1,4-diazabicyclo[2.2.2]octane. CN 101163682A discloses a method for preparing azoxystrobin and its intermediates, in which the amount of 1,4-diazabicyclo[2.2.2]octane is greatly reduced, but the total yield of azoxystrobin is not significantly reduced under the catalysis of 0.1 mol% and 2 mol% of 1,4-diazabicyclo[2.2.2]octane. CN 104672146 discloses a method for preparing azoxystrobin and its intermediates using another type of azabicyclic compounds as a catalyst, in which the yield is improved. CN 103265496A and CN 103467387A point out that preparing azoxystrobin and its intermediates using 1,4-diazabicyclo[2.2.2]octane as a catalyst has disadvantages such as the reaction conditions are not easy to control and the yield is not high. In addition, they each have reported methods for preparing azoxystrobin and its intermediates under the catalysis of the azabicyclic tertiary amine compounds with different structures, and the production yield and product content of azoxystrobin have been improved under such catalytic system.

[0004] At present, in the preparation of azoxystrobin or its key intermediates, most of the publicly reported catalysts are two-membered bridged ring compounds containing an ethylene bridge, such as



SUMMARY OF THE INVENTION

Technical problems

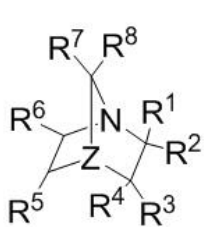
[0005] In order to find more efficient catalysts, the inventors designed and synthesized various azacyclic compounds, and thoroughly studied their catalytic activity. The present invention provides a new high-efficiency catalytic system for preparing azoxystrobin and its intermediates, which has characteristics of easy process control, short reaction time, high conversion rate, low energy consumption and the like, and is suitable for large-scale industrial production.

SOLUTIONS TO THE PROBLEM

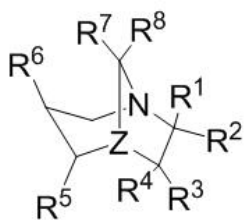
Technical solutions

[0006] Provided is a catalyst system, comprising one or more selected from an azabicyclic compound containing a methylene bridge, a salt of the azabicyclic compound containing a methylene bridge, an aza-cage compound, and a salt of the aza-cage compound.

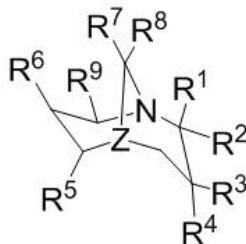
[0007] Furthermore, the azabicyclic [x.y.l] compound containing a methylene bridge includes one or more compounds represented by the following structural formula:



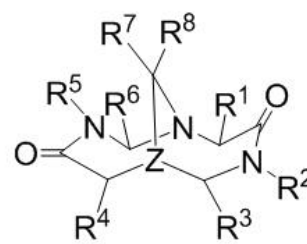
10A



10B



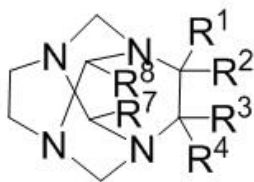
10C



10D

wherein N represents a nitrogen atom, and Z represents a carbon atom or a nitrogen atom.

[0008] The aza-cage compound has a following structural formula:



10E

[0009] In general structural Formulae 10A-10E, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are each independently hydrogen, halogen, hydroxyl, sulfhydryl, amino, a C1-C16 ester group, C1-C16 hydrocarbyl, C1-C16 alkoxy, C1-C16 alkylthio, C1-C16 alkylamino or dialkylamino.

5 **[0010]** Or, R^1 and R^2 , R^3 and R^4 , and R^7 and R^8 each independently combine into carbonyl, thiocarbonyl, a cycloalkyl thioether group, cycloalkoxy or a ketal structure.

[0011] Or, R^1 and R^3 , and R^5 and R^6 each combine into a cycloparaffin structure or a heterocyclic structure containing a nitrogen or oxygen heteroatom.

10 **[0012]** Or, R^7 and R^8 combine into cycloparaffin, cyclic aromatic hydrocarbon or an oxa- or aza-aromatic ring.

[0013] Furthermore, in Formula 10A, Formula 10B, Formula 10C, Formula 10D or Formula 10E, the substituent groups at adjacent atoms are present on the same side or different side of the cyclic structure.

15 **[0014]** Furthermore, the salt includes sulfates, hydrochlorides, methanesulfonates, besylates, *para*-toluenesulfonates, trifluoromethanesulfonates, tartrates, oxalates, borates, phenyl borates, citrates, formates, acetates, C1-C16 alkyl carboxylates, and substituted or unsubstituted aryl formates.

20 **[0015]** Provided is a method for preparing azoxystrobin or an intermediate thereof, in which in a solvent, in the presence of an acid-binding agent, the catalyst system described above is used to synthesize azoxystrobin (Formula 1), a precursor of azoxystrobin (Formula 7), and an intermediate of azoxystrobin (Formula 2, Formula 3 or Formula 4).

[0016] Specifically, it may comprise but not limited to the following reactions:

[0017] (1) reacting salicylonitrile (Formula 9) or a salt thereof with the compound of Formula 2 and Formula 3 respectively, to produce the azoxystrobin (Formula 1) or the precursor of azoxystrobin (Formula 7);

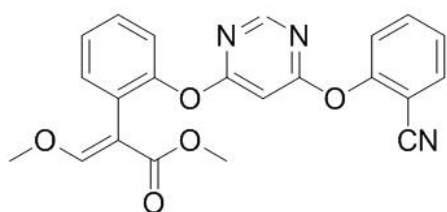
[0018] (2) reacting the compound of Formula 4 with the compound of Formula 5 and Formula 6 or a salt thereof respectively, to produce the azoxystrobin (Formula 1) or the precursor thereof (Formula 7);

[0019] (3) reacting the compound of Formula 5 and Formula 6 or a salt thereof respectively with 4,6-dichloropyrimidine (Formula 8), to produce the compound of Formula 2 or Formula 3; and

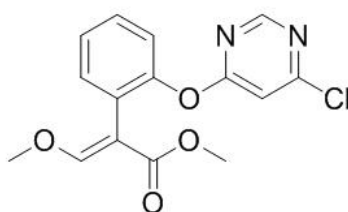
[0020] (4) reacting salicylonitrile (Formula 9) or a salt thereof with 4,6-dichloropyrimidine (Formula 8), to produce the compound of Formula 4.

[0021] Wherein, the salts of salicylonitrile, the compound of Formula 2, or the compound of Formula 3 refer to their alkali metal salts, including lithium salts, sodium salts, and potassium salts.

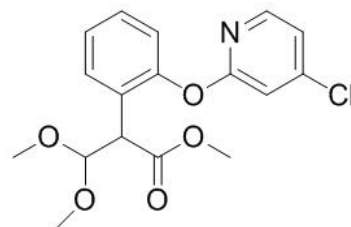
[0022] General structural Formula 1-9 are as follows:



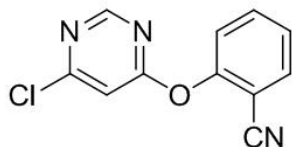
Formula 1



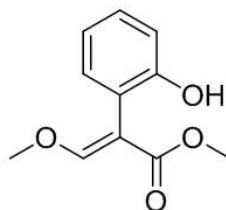
Formula 2



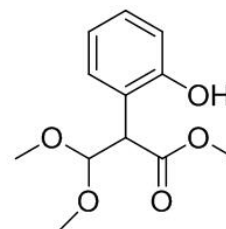
Formula 3



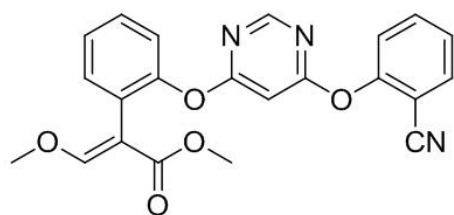
Formula 4



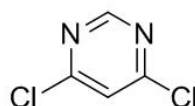
Formula 5



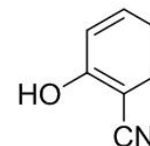
Formula 6



Formula 7



Formula 8



Formula 9

[0023] In the method, for 1 mol of salicylonitrile (Formula 9) or the salt thereof, the compound of Formula 5 or the salt thereof, the compound of Formula 6 or the salt thereof, 4,6-dichloropyrimidine (Formula 8), or the compound of Formula 2, Formula 3 or Formula 4 as the raw materials of the reaction, at least one of the compounds of Formula 10A-Formula 10E or the salts thereof as the catalysts are used in a total amount of 0.001 mol-0.1 mol, and preferably 0.005 mol-0.05 mol.

[0024] In the method, the solvent includes one or more selected from methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol, toluene, tetrahydrofuran, acetonitrile, dichloromethane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, sulfolane, sec-butyl acetate, n-butyl acetate, isopropyl acetate, n-propyl acetate, and ethyl acetate.

[0025] In the method, for 1 Kg of the salicylonitrile (Formula 9) or the salt thereof, the compound of Formula 5 or the salt thereof, the compound of Formula 6 or the salt thereof, 4,6-dichloropyrimidine (Formula 8), or the compound of Formula 2, Formula 3 or Formula 4 as the raw materials of the reaction, the solvent is used in a total amount of 1 L-20 L; if multiple solvents above are selected to form a mixed solvent, the amount of any single solvent in the mixed solvent is used in an amount of 0.05 L-10 L.

[0026] In the method, the acid-binding agent is an alkoxy compound, hydroxide, carbonate or bicarbonate of an alkali metal or an alkaline earth metal, including sodium methylate, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, potassium carbonate, sodium carbonate, cesium carbonate; or a tertiary amine containing a C2-C20 group, including one or more selected from triethylamine, triethanolamine, tributylamine, diisopropylethylamine, pyridine, N-methylpiperidine, and N-methylmorpholine.

[0027] In the method, for 1 mol of salicylonitrile (Formula 9) or the salt thereof, the compound of Formula 5 or the salt thereof, the compound of Formula 6 or the salt thereof, 4,6-dichloropyrimidine (Formula 8), or the compound of Formula 2, Formula 3 or Formula 4 as the raw materials of the reaction, the acid-binding agent is used in a total amount of 0.4 mol-2 mol, and preferably 0.8 mol-1.2 mol.

[0028] In the method, a phase-transfer catalyst may further be added in the process of the reaction to improve the catalytic activity of the catalyst system; the phase-transfer catalyst includes one or more selected from tetrabutylammonium fluoride, tetrabutyl ammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, cetyltrimethylammonium chloride, cetyltrimethylammonium bromide, dodecylbenzyltrimethylammonium chloride, cetyltrimethylbenzylammonium chloride, cetyltriphenylphosphonium chloride, (triphenylmethyl)triphenylphosphonium chloride, and tetraethylphosphonium chloride.

[0029] In the method, for 1 mol of salicylonitrile (Formula 9) or the salt thereof, 4,6-dichloropyrimidine (Formula 8), the compound of Formula 2, Formula 3, Formula 4, Formula 5, or Formula 6 or the salt thereof as the raw materials of the reaction, the phase-transfer catalyst is used in a total amount of 0.01mol-0.1 mol, and preferably 0.03 mol-0.06 mol.

[0030] In the method, for the preparation of the azoxystrobin or the precursor compound thereof, the reaction temperature is 40°C to 150°C, and preferably 70°C to 120°C; for the preparation of the intermediate of azoxystrobin, the reaction temperature is -20°C to 40°C, and preferably -5°C to 25°C.

BENEFICIAL EFFECTS OF THE INVENTION

Beneficial effects

[0031] The catalyst structure disclosed in the present invention has never been publicly reported in the literature related to the preparation of azoxystrobin and its intermediates. When this series of compounds or their compositions are used as a catalyst, azoxystrobin and its intermediates can be obtained in a higher yield in the presence of a suitable solvent and acid-binding agent. They are new high-efficiency catalytic systems for preparing azoxystrobin and its intermediates, have characteristics of short reaction time, high conversion rate and low energy consumption, and are suitable for large-scale industrial production.

EXAMPLES OF THE INVENTION

Embodiments of the invention

[0032] The technical solutions of the present invention will be clearly and completely described below.

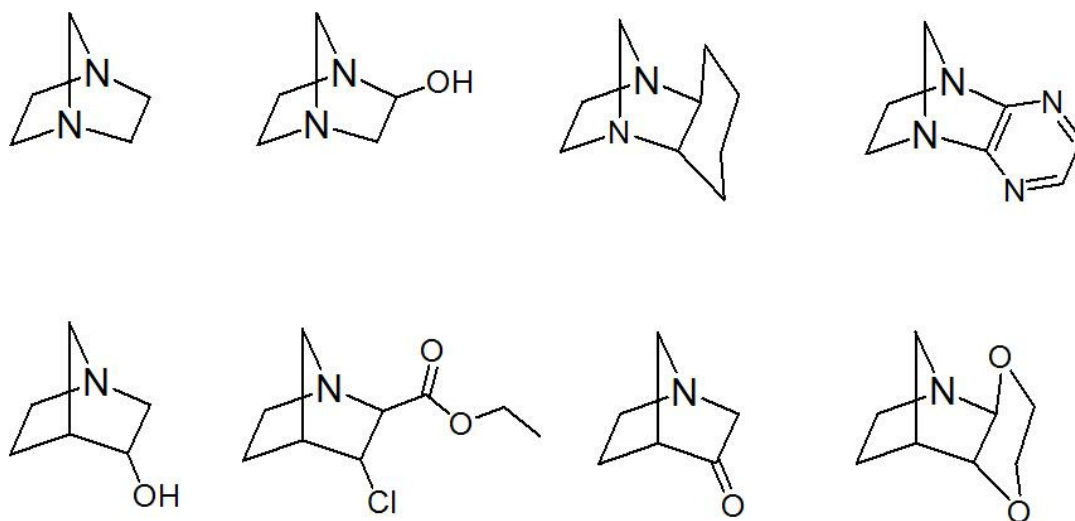
[0033] Catalyst system

[0034] As for the compounds represented by Formulae 10A-10E, when R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^8 , and R^9 are each independently hydrogen, halogen, hydroxyl, sulfydryl, amino, a C1-C16 ester group, C1-C16 hydrocarbyl, C1-C16 alkoxyl, C1-C16 alkylthio, C1-C16 alkylamino or dialkylamino; or, R^1 and R^2 , R^3 and R^4 , and R^7 and R^8 each independently combine into carbonyl, thiocarbonyl, a cycloalkyl thioether group, cycloalkoxyl or a ketal structure; or, R^1 and R^3 , and R^5 and R^6 each combine into a 5- to 8-membered cycloparaffin structure or a 5- to 8-membered heterocyclic structure containing a nitrogen or oxygen heteroatom; or, R^7 and R^8 combine into cycloparaffin, cyclic aromatic hydrocarbon or an oxa- or aza-aromatic ring, including the possibility that they have multiple identical substituents or multiple different substituents simultaneously.

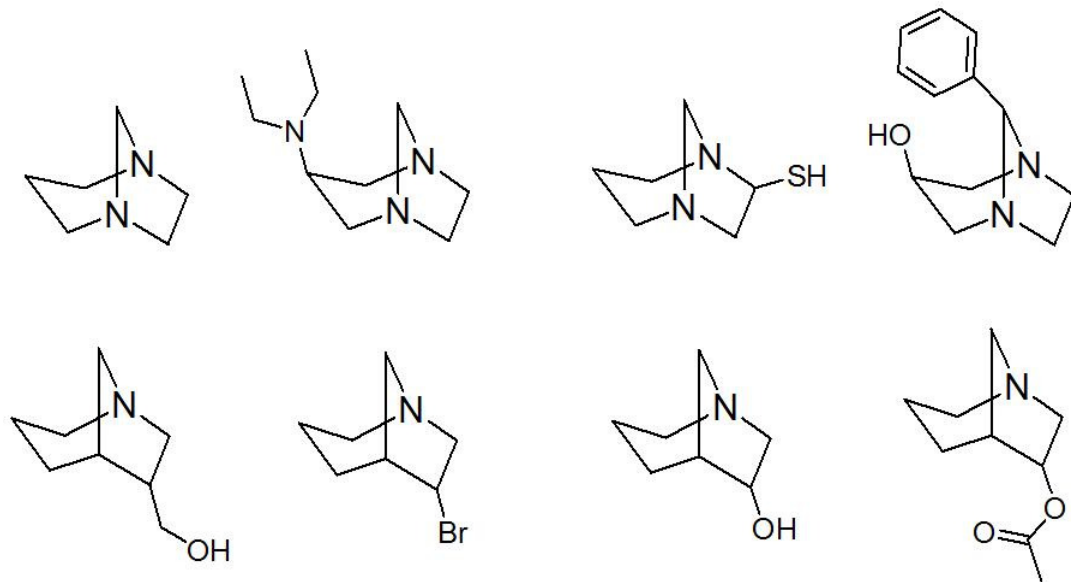
[0035] Wherein, the halogen includes fluorine, chlorine, bromine, and iodine. The C1-C16 ester group includes two structures of $-RCOOR'$ and $-R'OOCR$, where R and R' are alkyl respectively, having a total number of carbon atoms not exceeding 16. C1-C16 alkoxyl includes any combined structure of 1-16 carbon atoms and 1-2 oxygen atoms, such as methoxy, ethoxy, tert-butoxy, methoxymethyl, ethoxyethyl, dodecyloxy, and other structures. C1-C16 alkylmercapto includes any combined structure of 1-16 carbon atoms and 1-2 sulfur atoms, such

as methylmercapto, ethylmercapto, tert-butylmercapto, methylmercaptomethyl, ethylmercaptoethyl, dodecylmercapto, and other structures. C1-C16 alkylamino or dialkylamino includes amino, methylamino, dimethylamino, ethylamino, diethylamino, propylamino, dipropylamino, diisopropylamino, butylamino, dibutylamino, diisobutylamino, dodecylamino, 5 hexadecylamino, and other structures.

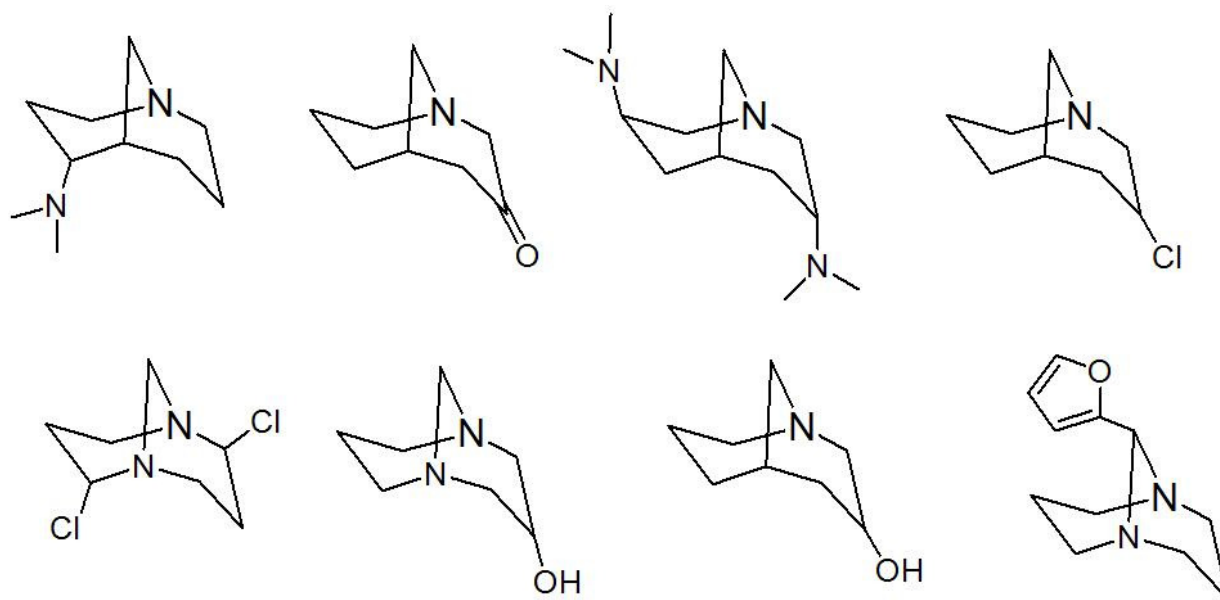
[0036] As for the compound of Formula 10A, its possible structures include but are not limited to the following compounds:



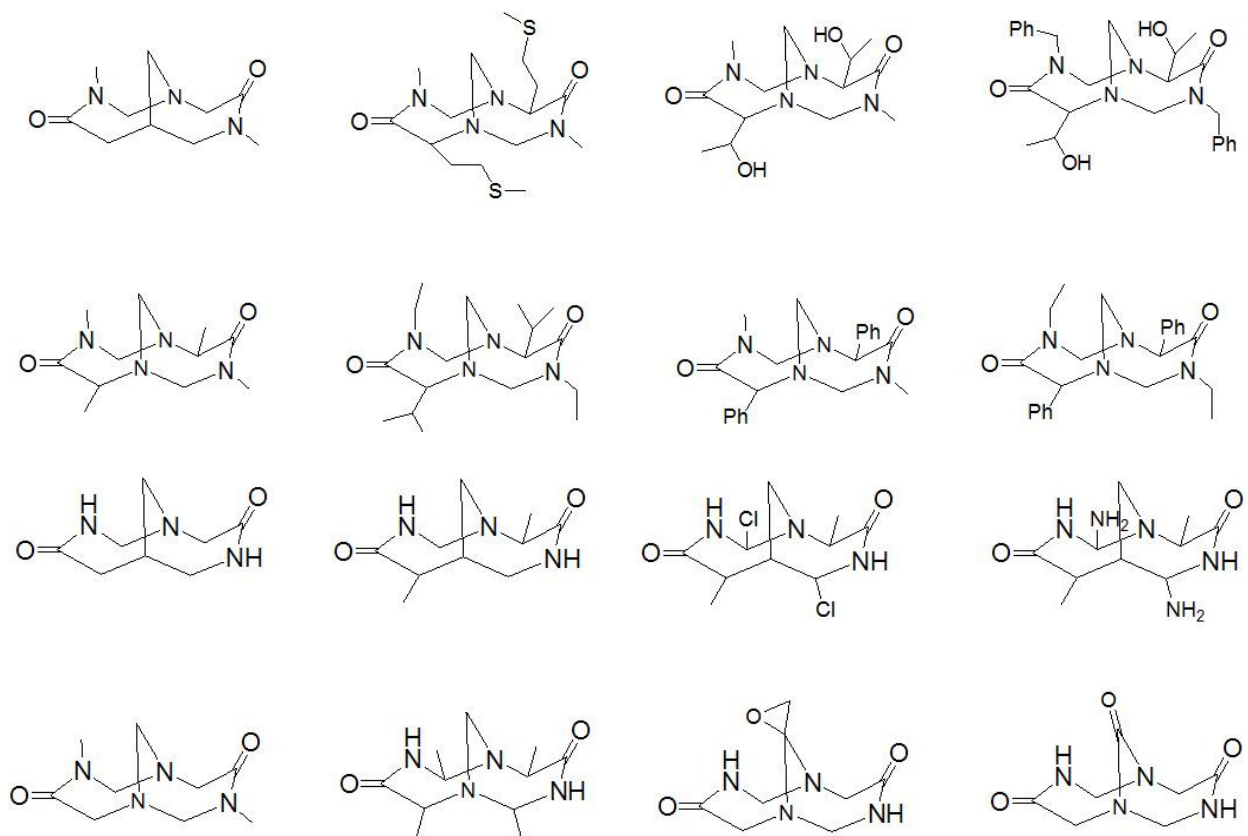
[0037] Similarly, as for the compound of Formula 10B, its possible structures include but are 10 not limited to the following compounds:



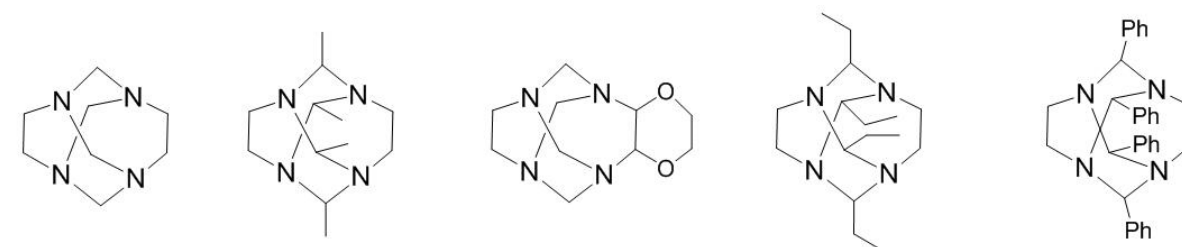
[0038] Similarly, as for the compound of Formula 10C, its possible structures include but are not limited to the following compounds:



5 **[0039]** Similarly, as for the compound of Formula 10D, its possible structures include but are not limited to the following compounds:



[0040] Similarly, as for the compound of Formula 10E, its possible structures include but are not limited to the following compounds:



5

[0041] As for the compounds represented by Formulae 10A-10E as the catalyst, since they all have a structure of tertiary amines, they may be present in the form of salts with inorganic or organic acids, including sulfates, hydrochlorides, methanesulfonates, besylates, *para*-toluenesulfonates, trifluoromethanesulfonates, tartrates, oxalates, formates, acetates, C1-C16 alkyl carboxylates, and substituted or unsubstituted aryl formates. Given that there are multiple nitrogen atoms in its structure, when this series of compounds are present in the form of salts, one molecule may bind with one or more acid molecules.

10

[0042] Preparation method

[0043] The method for preparing azoxystrobin or an intermediate thereof by use of the catalyst system described in the present disclosure includes at least:

5 **[0044]** (1) a method for preparing azoxystrobin represented by Formula 1 or a precursor of azoxystrobin represented by Formula 7, comprising in the presence of at least one compound represented by Formulae 10A-10E or a salt thereof, contacting the compound represented by Formula 2 or Formula 3 with salicylonitrile or a salt thereof, to obtain the azoxystrobin represented by Formula 1 or a precursor of azoxystrobin represented by Formula 7;

10 **[0045]** (2) a method for preparing azoxystrobin represented by Formula 1 or a precursor of azoxystrobin represented by Formula 7, comprising in the presence of at least one compound represented by Formula 10 or a salt thereof, contacting the compound represented by Formula 4 with the compound represented by Formula 5 or Formula 6 or a salt thereof, to obtain azoxystrobin represented by Formula 1 or a precursor of azoxystrobin represented by Formula 7;

15 **[0046]** (3) a method for preparing an intermediate of azoxystrobin represented by Formula 2 or Formula 3, comprising in the presence of at least one compound represented by Formulae 10A-10E or a salt thereof, contacting a compound represented by Formula 5 or Formula 6 or a salt thereof respectively with 4,6-dichloropyrimidine to obtain an intermediate of azoxystrobin represented by Formula 2 or Formula 3, wherein the compound of Formula 5 or Formula 6 may be a single compound after separation or mixed compounds, or comprising performing a
20 ring-opening reaction of 3-(α -methoxy)methylenebezofuran-2-(3H)-one (the compound represented by Formula 11) using sodium methoxide to obtain the compounds of Formula 5 and Formula 6, mixing the compounds of Formula 5 and Formula 6 in a reaction solution and directly contacting and reacting the resulting reaction solution with 4,6-dichloropyrimidine; and

25 **[0047]** (4) a method for preparing an intermediate of azoxystrobin represented by Formula 4, comprising in the presence of at least one compound represented by Formulae 10A-10E or a salt thereof, contacting 4,6-dichloropyrimidine with salicylonitrile or a salt thereof, to obtain an intermediate of azoxystrobin represented by Formula 4.

[0048] Wherein, for 1 mol of salicylonitrile, 4,6-dichloropyrimidine, the compound of Formula 2, Formula 3, Formula 4, Formula 5, Formula 6 or their salts as the raw materials of the reaction,

when the amount of catalyst was gradually reduced from 0.1 mol to 0.001 mol, the conversion rate and yield of the reaction did not decrease significantly, and the reaction time did not increase significantly. In a further research, the inventor found that when the amount of catalyst was gradually reduced to 0.005 mol, the same conversion rate and yield of the reaction were achieved by appropriately extending the reaction time. When the catalyst was gradually further reduced to 0.001 mol, the conversion rate and yield of the reaction decreased slightly, but still remained at a desired level.

[0049] Wherein, the salts of salicylonitrile, the compound of Formula 2, and the compound of Formula 3 refer to their alkali metal salts, including lithium salts, sodium salts, and potassium salts.

[0050] When any one of methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol, toluene, tetrahydrofuran, acetonitrile, dichloromethane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, sulfolane, sec-butyl acetate, n-butyl acetate, isopropyl acetate, and ethyl acetate is used as the reaction solvent, for 1 Kg of 4,6-dichloropyrimidine (Formula 8), salicylonitrile (Formula 9), the compound of Formula 2, Formula 3, Formula 4, Formula 5, or Formula 6 or their salts as the raw materials of the reaction, the solvent may be used in an amount ranging from 1 L to 20 L, while both of the conversion rate and yield of the reaction remain a high level.

[0051] When two or more of the above solvents are selected as the mixed solvent, the yield of the reaction can also be greatly improved. In this case, for 1 kg of 4,6-dichloropyrimidine (Formula 8), salicylonitrile (Formula 9), the compound of Formula 2, Formula 3, Formula 4, Formula 5, or Formula 6 or their salts as the raw materials of the reaction, any one of the solvents is used at a minimum amount of 0.05 L and at a maximum amount of 10 L.

[0052] Example 1 This example is used to illustrate the preparation of azoxystrobin represented by formula 1.

[0053] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.01 mol, 1.14 g) were successively added.

The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again.

5 The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.6% and a yield of 97.9%.

[0054] Example 2

[0055] This example is used to illustrate the effect of the amount of catalyst on the reaction in the preparation process of azoxystrobin represented by Formula 1.

10 **[0056]** To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (0.1 mol, 32.07 g) represented by Formula 2, potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.114 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of

15 salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.6% and a yield of 97.6%.

20 **[0057]** Example 3

[0058] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (0.1 mol, 32.07 g) represented by Formula 2, potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.0005 mol, 0.057 g) were successively added. The

25 mixture was stirred, heated to 85°C, and kept at the temperature for 8 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented

by Formula 1 with a content of 98.3% and a yield of 97.3%.

[0059] Example 4 This example is used to illustrate the effect of the amount of catalyst on the reaction in the preparation process of azoxystrobin represented by Formula 1.

[0060] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g),
5 the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.000 L mol, 0.0114 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 12 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to
10 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.7% and a yield of 93.9%.

[0061] Example 5 This example is used to illustrate the preparation of azoxystrobin
15 represented by Formula 1.

[0062] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g),
the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst N,N-diethyl-1,5-diazabicyclo[3.2.1]octane-3-amine (0.001 mol, 0.1833 g) were
20 successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%,. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain
25 azoxystrobin represented by Formula 1 with a content of 98.1% and a yield of 97.2%.

[0063] Example 6 This example is used to illustrate the preparation of azoxystrobin represented by Formula 1.

[0064] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g),
the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (0.1 mol,

32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 1-azabicyclo[3.2.1]octane-6-ol (0.001 mol, 0.1272 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 1%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.3% and a yield of 96.4%.

[0065] Example 7 This example is used to illustrate the preparation of azoxystrobin represented by Formula 1.

[0066] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 3,8-dimethylamino-1,3,8-triazabicyclo[4.4.1]undecane-4,9-dione (0.001 mol, 0.2413 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 1%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 97.8% and a yield of 96.7%.

[0067] Example 8 This example is used to illustrate the preparation of azoxystrobin represented by Formula 1.

[0068] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 1,3,6,8-tetraazatetracyclo[4.4.1.1^{3,8}]dodecane (0.001 mol, 0.1682 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was

removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 97.0% and a yield of 96.8%.

[0069] Example 9 This example is used to illustrate the preparation of azoxystrobin represented by Formula 1.

[0070] To a 250 mL reaction flask, dried toluene (100 mL), the compound 4-chloro-6-(2-cyanophenoxy)pyrimidine represented by Formula 4 (0.1 mol, 23.16 g), the compound methyl (E)-2-(2-hydroxyphenyl)-3-methoxyacrylate (0.102 mol, 21.24 g) represented by Formula 5, potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.3% and a yield of 96.2%.

[0071] Example 10 This example is used to illustrate the effect of the phase-transfer catalyst on the yield of the reaction in the preparation process of azoxystrobin represented by Formula 1.

[0072] To a 250 mL reaction flask, dried toluene (100 mL), the compound 4-chloro-6-(2-cyanophenoxy)pyrimidine represented by Formula 4 (0.1 mol, 23.16 g), the compound methyl (E)-2-(2-hydroxyphenyl)-3-methoxyacrylate represented by Formula 5 (0.102 mol, 21.24 g), potassium carbonate (0.08 mol, 11.06 g), tetrabutylammonium chloride (0.005 mol, 1.39 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.5% and a yield of 97.2%.

[0073] Example 11 This example is used to illustrate the preparation of azoxystrobin represented by Formula 1.

[0074] To a 250 mL reaction flask, dried toluene (100 mL), the compound 4-chloro-6-(2-cyanophenoxy)pyrimidine represented by Formula 4 (0.1 mol, 23.16 g), the compound methyl (E)-2-(2-hydroxyphenyl)-3-methoxyacrylate represented by Formula 5 (0.102 mol, 21.24 g), triethanolamine (0.08 mol, 11.95 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.1% and a yield of 96.9%.

[0075] Example 12 This example is used to illustrate the preparation method of the intermediate of azoxystrobin represented by Formula 4.

[0076] To a 250 mL reaction flask, dried toluene (50 mL), salicylonitrile (0.105 mol, 12.50 g), 4,6-dichloropyrimidine (0.1 mol, 14.90 g), potassium carbonate (0.08 mol, 11.06 g) and (0.001 mol, 0.1121 g) 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of 4,6-dichloropyrimidine detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry, to obtain a solid, an intermediate of azoxystrobin represented by Formula 4 with a content of 95.6% and a yield of 96.7%.

[0077] Example 13 This example is used to illustrate the preparation method of the intermediates of azoxystrobin represented by Formula 2 and Formula 3.

[0078] To a reaction flask, dried toluene (100 mL), the compound 3-(α -methoxy)methylenebezofuran-2-(3H)-one represented by Formula 11 (0.1 mol, 13.413 g),

4,6-dichloropyrimidine (0.105 mol, 14.90 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, cooled to 5°C. A methanol solution of 31% by weight of sodium methoxide was slowly added, and the mixture was kept at 5°C-15°C with stirring for 2 h after the completion of the addition. The remaining amount of the 3-(α -methoxy)methylenebezofuran-2-(3H)-one (the compound represented by Formula 11) detected by HPLC was less than 1% and the total remaining amount of the compounds of Formula 5 and Formula 6 as intermediates was less than 1%. 25 mL of water was slowly added dropwise, and the mixture was stirred and then allowed to stand for liquid separation. The toluene phase was evaporated until dry, to obtain a crude product containing the compounds represented by Formula 2 and Formula 3 with a total content of 95.4% and a yield of 94.9%.

[0079] Example 14 This example is used to illustrate the preparation of the precursor of azoxystrobin represented by Formula 7.

[0080] To a 250 mL reaction flask, dried toluene (100 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl 2-(2-((6-chloropyrimidin-4-yl)oxy)phenyl)-3,3-dimethoxyacrylate represented by Formula 3 (0.1 mol, 35.277 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain a precursor of azoxystrobin represented by Formula 7 with a content of 98.3% and a yield of 95.4%.

[0081] Example 15 This example is used to illustrate the preparation of the precursor of azoxystrobin represented by Formula 7.

[0082] To a 250 mL reaction flask, dried toluene (100 mL), the compound represented by Formula 4 (0.1 mol, 23.16 g), the compound methyl 2-(2-hydroxy)phenyl-3,3-dimethoxypropionate of Formula 6 (0.102 mol, 24.51 g), potassium

carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.1121 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 50°C, added with 20 mL of water, stirred, and stood for layering.

- 5 The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized to obtain a precursor of azoxystrobin represented by Formula 7 with a content of 98.0% and a yield of 96.1%.

[0083] Example 16

- 10 **[0084]** This example is used to illustrate the effect of the solvent amount on the reaction in the preparation process of azoxystrobin represented by Formula 1.

- [0085]** To a 250 mL reaction flask, dried toluene (32.07 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.01 mol, 1.14 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again.
- 15 The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.4% and a yield of 97.5%.
- 20

[0086] Example 17

[0087] This example is used to illustrate the effect of the amount of solvent on the reaction in the preparation process of azoxystrobin represented by Formula 1.

- 25 **[0088]** To a 250 mL reaction flask, dried toluene (320 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.114 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of

salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 80 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.9% and a yield of 97.1%.

[0089] Example 18

[0090] This example is used to illustrate the effect of the solvent amount on the reaction in the preparation process of azoxystrobin represented by Formula 1.

[0091] To a 250 mL reaction flask, dried toluene (641.4 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate (0.1 mol, 32.07 g) represented by Formula 2, potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.114 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 80 mL of water, stirred, and stood for layering. The aqueous phase was removed. The toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 98.9% and a yield of 97.8%.

[0092] Example 19

[0093] This example is used to illustrate the effect of using a mixed solvent on the reaction in the preparation process of azoxystrobin represented by Formula 1.

[0094] To a 250 mL reaction flask, dried toluene (100 mL), dried dimethyl sulfoxide (1.61 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.114 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The

toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 97.5% and a yield of 98.6%.

[0095] Example 19

- 5 This example is used to illustrate the effect of using a mixed solvent on the reaction in the preparation process of azoxystrobin represented by Formula 1.

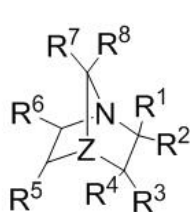
[0096] To a 250 mL reaction flask, dried toluene (320 mL), dried isopropyl acetate (320 mL), salicylonitrile (0.105 mol, 12.50 g), the compound methyl E-2-{2-[6-chloropyrimidin-4-yloxy]phenyl}-3-methoxyacrylate represented by Formula 2 (0.1
10 mol, 32.07 g), potassium carbonate (0.08 mol, 11.06 g) and a catalyst 2-carbonyl-1,4-diazabicyclo[2.2.1]heptane (0.001 mol, 0.114 g) were successively added. The mixture was stirred, heated to 85°C, and kept at the temperature for 4 h. The content of salicylonitrile detected by HPLC was less than 0.5%. The reaction system was cooled to 40-50°C, added with 20 mL of water, stirred, and stood for layering. The aqueous phase was removed. The
15 toluene phase was washed once with 10 mL of water and the aqueous phase was removed again. The toluene phase was evaporated until dry and recrystallized, to obtain azoxystrobin represented by Formula 1 with a content of 97.3% and a yield of 98.2%.

[0097] The examples mentioned above only describe the preferred embodiments of the present disclosure, but are not limited thereto. Those skilled in the art can easily understand the spirit of
20 the present disclosure based on the examples mentioned above and make different extensions and changes. Without departing from the spirit of the present disclosure, they are all within the protection scope of the present disclosure.

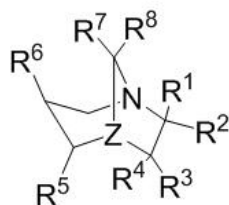
CLAIMS

1. A high-efficiency catalyst system for preparing azoxystrobin and an intermediate thereof, comprising one or more selected from an azabicyclic compound containing a methylene bridge or a salt thereof, and an aza-cage compound or a salt thereof;

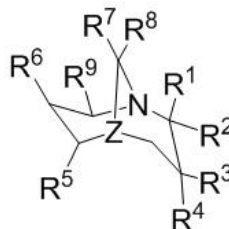
5 the azabicyclic compound containing a methylene bridge is one of the compounds represented by the following general structural formulae:



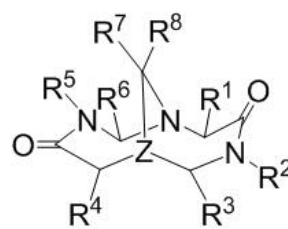
10A



10B



10C

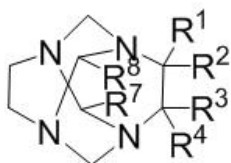


10D

;

wherein, N represents a nitrogen atom, and Z represents a carbon atom or a nitrogen atom;

the aza-cage compound is represented by the following general structural formula:



10E

;

in the general structural formula, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, and R⁹ are each independently hydrogen, halogen, hydroxyl, sulfhydryl, amino, a C1-C16 ester group, C1-C16 hydrocarbyl, C1-C16 alkoxy, C1-C16 alkylthio, C1-C16 alkylamino or dialkylamino;

or, R¹ and R², R³ and R⁴, and R⁷ and R⁸ each independently combine into carbonyl, thiocarbonyl, a cycloalkyl thioether group, cycloalkoxyl or a ketal structure;

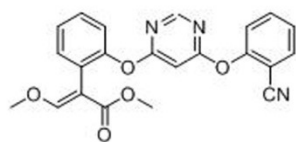
or, R¹ and R³, and R⁵ and R⁶ each combine into a cycloparaffin structure or a heterocyclic structure containing a nitrogen or oxygen heteroatom;

or, R⁷ and R⁸ combine into cycloparaffin, cyclic aromatic hydrocarbon or an oxa- or

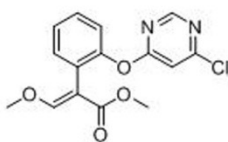
aza-aromatic ring.

2. The catalyst system according to claim 1, wherein the salt includes sulfates, hydrochlorides, methanesulfonates, besylates, *para*-toluenesulfonates, trifluoromethanesulfonates, tartrates, oxalates, borates, phenyl borates, citrates, formates, acetates, C1-C16 alkyl carboxylates, and substituted or unsubstituted aryl formates.

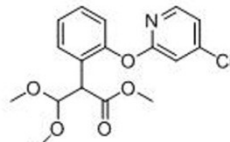
3. A method for preparing azoxystrobin or an intermediate thereof, wherein in a solvent, in the presence of an acid-binding agent, the catalyst system according to claim 1 or 2 is used to synthesize the azoxystrobin represented by Formula 1, a precursor of azoxystrobin represented by Formula 7, and an intermediate of azoxystrobin represented by Formula 2, Formula 3 or Formula 4;



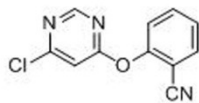
Formula 1



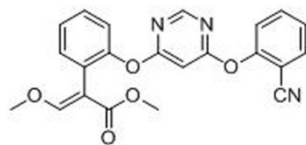
Formula 2



Formula 3



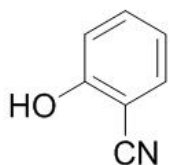
Formula 4



Formula 7

4. The method according to claim 3, comprising one of the following reactions:

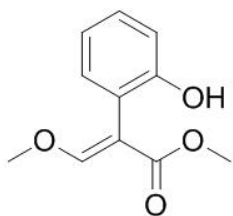
(1) reacting salicylonitrile represented by Formula 9 or a salt thereof with the intermediate represented by Formula 2 and Formula 3 respectively, to produce the azoxystrobin represented by Formula 1 or the precursor of azoxystrobin represented by Formula 7,



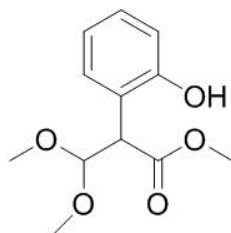
Formula 9

;

(2) reacting the intermediate represented by Formula 4 with the compound of Formula 5 and Formula 6 or a salt thereof respectively, to produce the azoxystrobin represented by Formula 1 or the precursor of azoxystrobin represented by Formula 7,



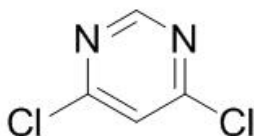
Formula 5



Formula 6

;

(3) reacting the compound of Formula 5 and Formula 6 or a salt thereof respectively with 4,6-dichloropyrimidine represented by Formula 8 to produce the intermediate represented by Formula 2 or Formula 3, and



Formula 8

;

(4) reacting salicylonitrile represented by Formula 9 or a salt thereof with 4,6-dichloropyrimidine represented by Formula 8, to produce the intermediate represented by Formula 4.

5. The method according to claim 4, wherein for 1 mol of raw materials of the reaction, the

catalysts of Formula 10A-Formula 10E are used in a total amount of 0.001 mol-0.1 mol, and preferably 0.005 mol-0.05 mol.

6. The method according to claim 4, wherein the solvent includes one or more selected from methanol, ethanol, propanol, isopropanol, n-butanol, isobutanol, toluene, tetrahydrofuran, acetonitrile, dichloromethane, N,N-dimethylformamide, N,N-dimethylacetamide, dimethyl sulfoxide, sulfolane, sec-butyl acetate, n-butyl acetate, isopropyl acetate, n-propyl acetate, and ethyl acetate.

7. The method according to claim 4 or claim 5, wherein for 1 Kg of the salicylonitrile represented by Formula 9 or the salt thereof, the compound of Formula 5 or the salt thereof, the compound of Formula 6 or the salt thereof, the 4,6-dichloropyrimidine represented by Formula 8, or the intermediates represented by Formula 2, Formula 3 and Formula 4 as the raw materials of the reaction, the solvent is used in a total amount of 1 L-20 L; if one or more solvents are used, any one of the solvents is used in an amount of 0.05 L-10 L.

8. The method according to claim 4, wherein the acid-binding agent is an alkoxy compound, hydroxide, carbonate or bicarbonate of an alkali metal or an alkaline earth metal, including sodium methyrate, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide, lithium hydroxide, sodium hydroxide, potassium hydroxide, lithium carbonate, potassium carbonate, sodium carbonate, and cesium carbonate; or a tertiary amine containing a C₂-C₂₀ group, including one or more selected from triethylamine, triethanolamine, tributylamine, diisopropylethylamine, pyridine, N-methylpiperidine, and N-methylmorpholine; and

for 1 mol of the raw materials of the reaction, the acid-binding agent is used in an amount of 0.4 mol-2 mol, and preferably 0.8 mol-1.2 mol.

9. The method according to claim 4, wherein a phase-transfer catalyst is added in the process of the reaction to improve the catalytic activity of the catalyst system; wherein

the phase-transfer catalyst includes one or more selected from tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, tetrabutylammonium iodide, cetyltrimethylammonium chloride, cetyltrimethylammonium bromide, dodecylbenzyltrimethylammonium chloride, cetyltrimethylbenzylammonium chloride, cetyltriphenylphosphonium chloride, (triphenylmethyl)triphenylphosphonium chloride, and

tetraethylphosphonium chloride.

10. The method according to claim 4, wherein for the preparation of azoxystrobin or the precursor compound thereof, the reaction temperature is 40°C to 150°C, and preferably 70°C to 120°C; for the preparation of the intermediate of azoxystrobin, the reaction temperature is -20°C to 40°C, and preferably -5°C to 25°C.
- 5