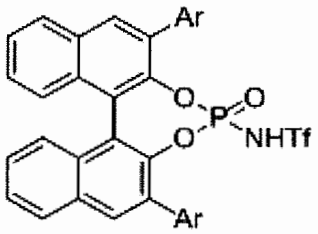
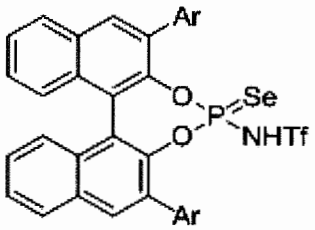
[20] If the chiral acid is used for the catalysis, the compound of formula VI with optical activity will be produced, and if the achiral acid is used as catalyst, a racemic compound of formula VI will be produced.

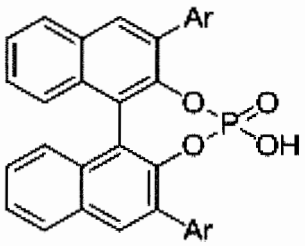
[21] The chiral ~~phosphoric~~ acid is selected the compound of formula VII, the compound of formula VIII, the compound of formula IX, the compound of formula X, and the compound of formula XI.



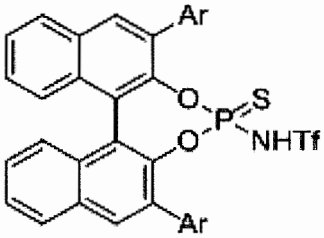
Formula VII



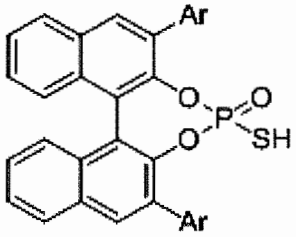
Formula VIII



Formula IX



Formula X



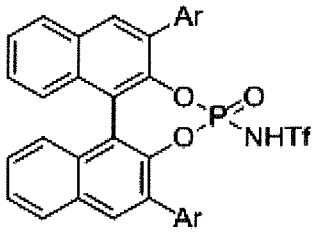
Formula XI

[22] Wherein, Ar is selected from the group consisting of H, Ph,

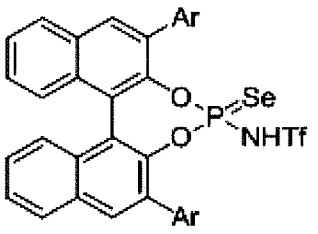
consisting of acetonitrile or propionitrile.

[64] If the chiral acid is used for the catalysis, the compound of formula VI with optical activity will be produced, and if the achiral acid is used as catalyst, a racemic compound of formula VI will be produced.

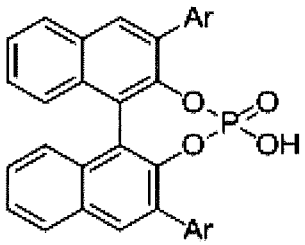
[65] The chiral ~~phosphoric~~ acid is selected from the group consisting of the compound of formula VII, the compound of formula VIII, the compound of formula IX, the compound of formula X, and the compound of formula XI.



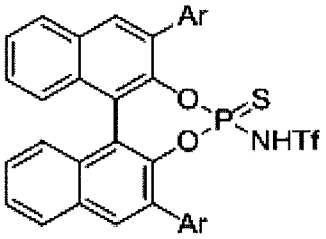
Formula VII



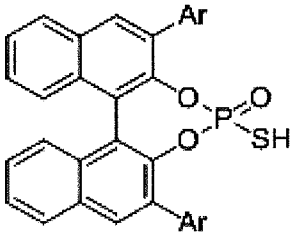
Formula VIII



Formula IX



Formula X



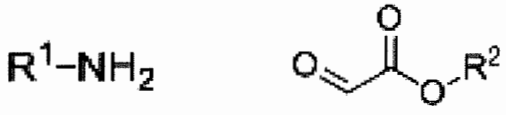
Formula XI

CLAIMS

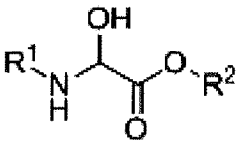
1. A method of synthesizing levorotatory p-hydroxyphenylglycine compounds, characterized in that, the method comprises the following steps:

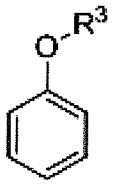
step 1: the compound of formula II and the compound of formula III undergo nucleophilic addition reaction in a first solvent, to produce the compound of formula IV; wherein the first solvent is selected from the group consisting of ether solvent, ester solvent, haloalkane solvent, C_5~C_{10} hydrocarbon solvent, nitrile solvent, and ketone solvent;

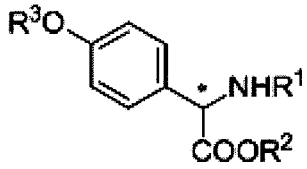
step 2: the compound of formula IV and the compound of formula V undergo a Friedel-Crafts-like reaction in a second solvent, using acid as catalyst, to produce the levorotatory p-hydroxyphenylglycine compound having the structure of formula VI; wherein the second solvent is selected from the group consisting of nitrile solvent, haloalkane solvent, C_5-C_{10} hydrocarbon solvent; the acid is a chiral acid ~~or an achiral acid, wherein the chiral acid is selected from the group consisting of D-tartaric acid, L-tartaric acid, D-camphorsulfonic acid, L-camphorsulfonic acid, L-proline, D-proline, and chiral phosphoric acid, and the achiral acid is selected from the group consisting of methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, sulfuric acid, and hydrochloric acid~~;



Formula II Formula III



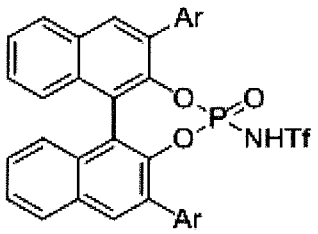


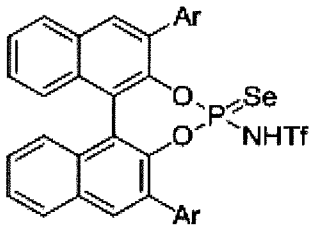


Formula IV Formula V Formula VI

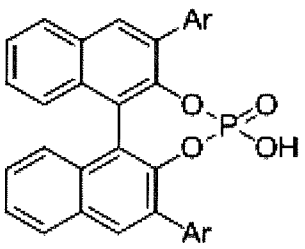
wherein, R^1 is selected from the group consisting of acetyl, benzoyl, tert-butoxycarbonyl, benzyloxycarbonyl, formamido, and pivalyl; R^2 is selected from the group consisting of methyl, ethyl, isopropyl, tert-butyl, and benzyl; and R^3 is selected from the group consisting of hydrogen, methyl, trimethylsilyl, tert-butyldimethylsily, and triisopropylsilyl,

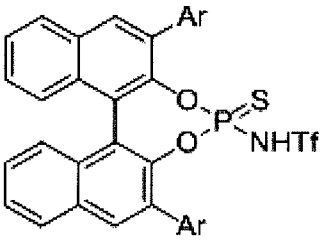
the chiral acid is selected from the group consisting of the compound of formula VII, the compound of formula VIII, the compound of formula IX, the compound of formula X, and the compound of formula XI,





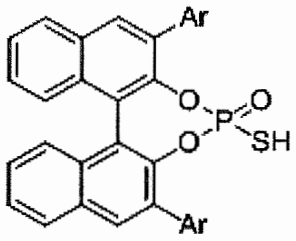
Formula VII Formula VIII





Formula IX

Formula X



Formula XI

wherein, Ar is selected from the group consisting of hydrogen, phenyl, 2,4,6-triisopropylphenyl, 3,5-bis(trifluoromethyl)phenyl, β-naphthyl, triphenylsilyl, 9-anthryl, 4-biphenylyl, 4-nitrophenyl, 9-phenanthryl, 4-methoxyphenyl, and 4-nitrophenyl.

2. The method according to claim 1, characterized in that, in step 1, the molar ratio of the compound of formula II to the compound of formula III is 1:0.5~1:2.1.

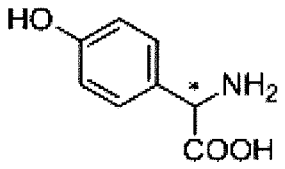
3. The method according to claim 1, characterized in that, in step 1, the nucleophilic addition reaction is carried out at a temperature of 25~110.6 ℃ for a period of 0.5~144 h.

4. The method according to claim 1, characterized in that, in step 2, the molar ratio of the compound of formula IV to the compound of formula V is 1:0.2~1:5.

5. The method according to claim 1, characterized in that, in step 2, the molar ratio of the compound of formula IV or the compound of formula V to the catalyst is 1~200:1.

6. The method according to claim 1, characterized in that, in step 2, the Friedel-Crafts-like reaction is carried out at a temperature of 40~82 °C for a period of 13.5-96 h.

7. A method of synthesizing a levorotatory p-hydroxyphenylglycine having the structure of formula I,



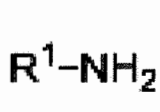
Formula I

characterized in that, the method comprises the following steps:

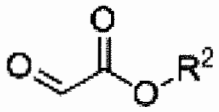
step 1: the compound of formula II and the compound of formula III undergo nucleophilic addition reaction in a first solvent, to produce the compound of formula IV; wherein the first solvent is selected from the group consisting of ether solvent, ester solvent, haloalkane solvent, C_5~C_{10} hydrocarbon solvent, nitrile solvent, and ketone solvent;

step 2: the compound of formula IV and the compound of formula V

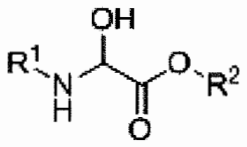
undergo a Friedel-Crafts-like reaction in a second solvent, using acid as catalyst, to produce the levorotatory p-hydroxyphenylglycine compound having the structure of formula VI; wherein the second solvent is selected from the group consisting of nitrile solvent, haloalkane solvent, C_5-C_{10} hydrocarbon solvent; the acid is a chiral acid ~~or an achiral acid, wherein the chiral acid is selected from the group consisting of D-tartaric acid, L-tartaric acid, D-camphorsulfonic acid, L-camphorsulfonic acid, L-proline, D-proline, and chiral phosphoric acid, and the achiral acid is selected from the group consisting of methanesulfonic acid, p-toluenesulfonic acid, trifluoromethanesulfonic acid, sulfuric acid, and hydrochloric acid~~;



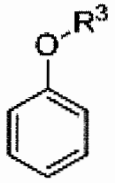
Formula II



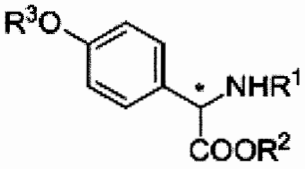
Formula III



Formula IV



Formula V



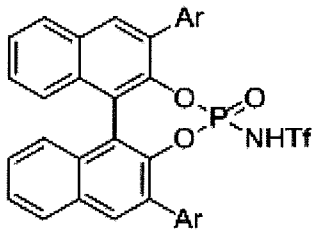
Formula VI

wherein, R^1 is selected from the group consisting of acetyl, benzoyl, tert-butoxycarbonyl, benzyloxycarbonyl, formamido, and pivalyl; R^2 is selected from the group consisting of methyl, ethyl, isopropyl, tert-butyl, and benzyl; and R^3 is hydrogen;

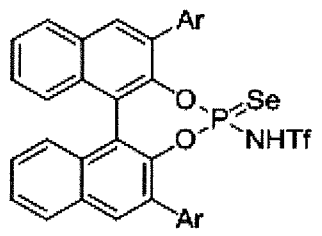
step 3: in a mixed solution of alcohol and water, or in water, the

compound of formula VI undergoes hydrolysis reaction by adjusting the pH value to be <2, then the solution is neutralized with a base to a pH value of 5.2~5.6, to obtain the compound of formula I,

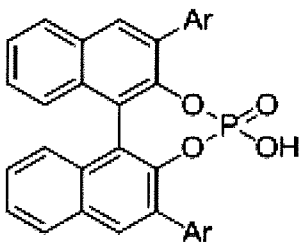
the chiral acid is selected from the group consisting of the compound of formula VII, the compound of formula VIII, the compound of formula IX, the compound of formula X, and the compound of formula XI,



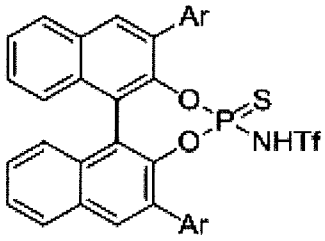
Formula VII



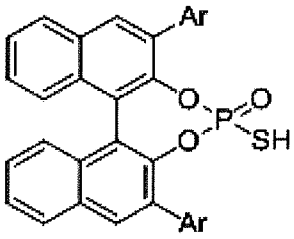
Formula VIII



Formula IX



Formula X



Formula XI

wherein, Ar is selected from the group consisting of hydrogen, phenyl,

2,4,6-triisopropylphenyl, 3,5-bis(trifluoromethyl)phenyl, β-naphthyl, triphenylsilyl, 9-anthryl, 4-biphenylyl, 4-nitrophenyl, 9-phenanthryl, 4-methoxyphenyl, and 4-nitrophenyl.

8. The method according to claim 7, characterized in that, in step 3, the hydrolysis reaction is carried out at a temperature of 60~100 °C.

9. The method according to claim 7, characterized in that, in step 3, the acid is selected from the group consisting of hydrochloric acid, sulfuric acid, methanesulfonic acid, and trifluoromethanesulfonic acid.

10. The method according to claim 7, characterized in that, in step 3, the base is selected from the group consisting of sodium hydroxide, sodium bicarbonate, sodium carbonate, potassium hydroxide, and aqueous ammonia.

ABSTRACT

The present invention relates to the field of chemical synthesis, particularly to a method of synthesizing levorotatory p-hydroxyphenylglycine compounds, which eliminates the subsequent processes of resolution, racemization processings, etc., simplifies operational steps; and acids with small organic molecule are chosen as catalyst in the second step, which not only is conducive to the realization of a industrialized production, but also makes the ee value of the end products be 88.1~98.0% by determining the catalyst, the reaction solvent, the reactive substance, the reaction temperature, and the reaction duration; non-aqueous solvent is used in the second step, to avoid the discharging of phenol-containing waste water, thus environmental pollution is reduced.