

# **SYNTHESIS METHOD OF CHIRAL PHOSPHORIC ACID CATALYST**

## **TECHNICAL FIELD**

**[0001]** The present application relates to the technical field of compound synthesis, and in particular, to a synthesis method of chiral phosphoric acid catalyst.

## **BACKGROUND ART**

**[0002]** Chiral phosphoric acid is a kind of Brønsted acid catalysts having the characteristics of a bifunctional catalysts, with a hydroxyl group attached to a phosphorus atom that can provide protons or form hydrogen bonding of Brønsted acid sites and basic sites of P=O that can provide lone electron pairs, making it a great alternative to a metal catalyst and chiral auxiliaries.

**[0003]** The conventional synthesis of chiral phosphoric acid is generally based on 2-naphthol, which is protected by a protecting group, and the synthesis process includes lithium-halide exchange reaction, Suzuki coupling reaction, Kumada coupling reaction and Sonogashira reaction to synthesize chiral phosphoric acid based on BINOL skeleton. However, the lithium-halide exchange reaction uses butyl lithium, which is dangerous and has cumbersome process steps. Another method includes subjecting raw materials to hydrocarbon activation and coupling reaction to produce the chiral phosphoric acid directly. This method is more simple and efficient. However, metal iridium used in catalytic hydrocarbon activation process is too expensive, and the price is much higher than commonly used precious metal like palladium, so that the synthesis of chiral phosphoric acid is much costly, not conducive to large-scale production in industry. If rhodium is used, the universality of the substrate is relatively poor, and the substrate with a larger steric hindrance will mainly lead to a product with unilateral substitution.

**[0004]** Therefore, it is important to find a synthesis method of chiral phosphoric acid catalyst with fewer process steps, no hydrocarbon activation, and suitability for large-scale production in industry.

## **SUMMARY**

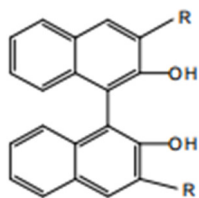
**[0005]** In order to simplify the process steps of the synthesis method of chiral phosphoric acid catalyst, eliminate the step of hydrocarbon activation, and meet the requirement for large-scale production in industries, the present application provides a synthesis method of chiral phosphoric acid catalyst.

**[0006]** The present application provides a synthesis method of chiral phosphoric acid catalyst, using the following technical solutions:

[0007] A synthesis method of chiral phosphoric acid catalyst, including the following steps:

[0008] step S1, halogenation reaction, performed by using a [1,1'-binaphthyl]-2,2'-diol and a halogenating agent as raw materials to obtain an intermediate I;

[0009] step S2, Suzuki coupling reaction, performed by using the intermediate I and a boronic acid compound as raw materials to obtain an intermediate II, wherein the intermediate II is represented as general formula (I);



[0010] General formula (I):

[0011] where, in the general formula (I), R is selected from phenylmethyl, phenanthryl, phenyl, tert-butyl phenyl, trifluoromethyl phenyl, nitrophenyl, and triisopropyl phenyl;

[0012] step S3, phosphorylation of the intermediate II, to obtain a crude chiral phosphate catalyst; and

[0013] step S4, chromatographing and eluting of the crude phosphate acid catalyst in silica gel column, to obtain a chiral phosphoric acid catalyst.

[0014] In the above technical solutions, by using commercially available naphthol and N-chlorosuccinimide as raw materials, and by means of the effect of parallel screening of catalysts, halogen atoms can be selectively introduced into naphthol to obtain the intermediate product halonaphthol. Then the above intermediate product is coupled with the boronic acid compound to obtain compounds represented as the general formula (I) under the effect of palladium catalyst. The above two steps can also be combined into a one-pot reaction, eliminating the need of post-processing, to realize the synthesis of chiral phosphoric acid catalyst rapidly and efficiently. Finally, the chiral phosphoric acid catalyst is obtained by phosphorylation reaction, with a product yield of more than 91% and a purity of 98-99%.

[0015] The synthesis method of the present application is not subjected to hydrocarbon activation reaction in the overall reaction process, and thus eliminate the need of using expensive precious metal catalyst, so that the synthesis cost is reduced greatly, and the reaction steps are decreased, achieving simple and efficient synthetic route and mild and safe reaction conditions, which provides a large-scale production in industries.

[0016] Preferably, in step S1, the specific steps of the halogenation reaction includes: stirring and mixing [1,1'-binaphthyl]-2,2'-diol and the halogenating agent as raw materials, a solvent and a catalyst to obtain the intermediate I,

[0017] wherein a feeding ratio of the [1,1'-binaphthyl]-2,2'-diol, the halogenating agent, and the

catalyst is 1 g:(0.45-0.7) g:(0.005-0.03) g.

**[0018]** In the above technical solutions, when the feeding ratio of the [1,1'-binaphthyl]-2,2'-diol, the N-chlorosuccinimide, and an ammonium salt is in the above range, the purity and yield of the chiral phosphoric acid catalyst can be improved, and the yield reaches more than 89% and the purity reaches more than 94%.

**[0019]** Preferably, the catalyst is an ammonium salt in step S1.

**[0020]** Preferably, the halogenating agent is a N-chlorosuccinimide in step S1.

**[0021]** Preferably, the [1,1'-binaphthyl]-2,2'-diol is one of R-type and S-type in step S1.

**[0022]** Preferably, in step S2, the specific steps of the Suzuki coupling reaction includes:

**[0023]** stirring and mixing the intermediate I and the boronic acid compound as raw materials, palladium catalyst, and a  $\text{Na}_2\text{CO}_3$  as an alkali in a solvent to obtain the Intermediate II represented as general formula (I);

**[0024]** wherein the feeding ratio of the Intermediate I, the boronic acid compound, the palladium catalyst, and the  $\text{Na}_2\text{CO}_3$  is 1 g:(0.4-0.65) g:(0.005-0.05) g:(0.01- 0.05) g.

**[0025]** In the above technical solutions, when the feeding ratios of the intermediate I, the boronic acid compound, the palladium catalyst, and the  $\text{Na}_2\text{CO}_3$  is in the above range, the ratio is appropriate, the reaction is more adequate, and the chiral phosphoric acid catalyst has a higher yield and purity.

**[0026]** Preferably, in step S2, the boronic acid compound is one of aryl boronic acid, 4-(9'-phenanthryl) benzene boronic acid, ([1,1'-biphenyl]-4-yl) boronic acid, (4'-(tert-butyl)-[1,1'-biphenyl]-4-yl) boronic acid, (4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl) boronic acid, (4'-nitro-[1,1'-biphenyl]-4-yl) boronic acid, (5'-phenyl-[1,1':3',1''-terphenyl]-4-yl) boronic acid, (2',4',6'-triisopropyl-[1,1'-biphenyl]-4-yl) boronic acid.

**[0027]** Preferably, in step S2, the solvent is a mixed solution of DMF and water at a weight ratio of 1:(0.4-0.65).

**[0028]** In the above technical solution, when the weight ratio of DMF and water is in the above range, the intermediate I and the boronic acid compound have a better solubility, leading to complete reaction, and in turn, the chiral phosphoric acid catalyst having a relatively high yield and purity.

**[0029]** In summary, the present application can achieve at least the following beneficial effects.

**[0030]** 1. In the present application, the naphthol and the halogenating agent are used as raw materials, and the halogen atoms are selectively introduced into naphthol under the parallel screening of catalysts, then subjected to the coupling reaction and the phosphorylation reaction to obtain the chiral phosphoric acid catalysts. In the overall synthetic route, the cost of the reaction is reduced due to the absence of hydrocarbon activation and, in turn, no use of any precious metal

catalysts, and the halogenation and coupling steps can be combined, so that the synthetic route becomes simple and efficient, and the chiral phosphoric acid catalysts produced with higher yield and purity, which can satisfy the needs of industrialization of large-scale production.

**[0031]** 2. In the present application, the yield and purity of the phosphorus acid catalyst have been improved, reaching a yield of more than 89% and a purity of more than 94%, by controlling the feeding ratio of the [1,1'-binaphthyl]-2,2'-diol, the N-chlorosuccinimide, and the catalyst.

**[0032]** 3. In the present application, high yield and purity of the chiral phosphoric acid catalyst is guaranteed by controlling the feeding ratio of the intermediate I, the boronic acid compound, the palladium catalyst, and the  $\text{Na}_2\text{CO}_3$ .

### BRIEF DESCRIPTION OF THE DRAWINGS

**[0033]** FIGs. 1-7 are nuclear magnetic resonance hydrogen spectra of chiral phosphate catalysts in Examples 2-8 of the present application; and

**[0034]** FIGs. 8-15 are HPLC detection diagrams of chiral phosphate catalysts in Examples 1-8 of the present application.

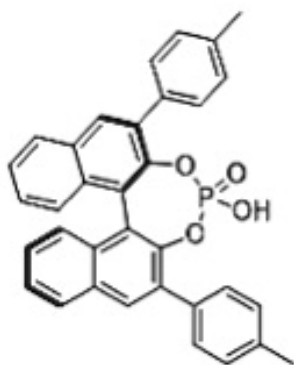
### DETAILED DESCRIPTION

**[0035]** The present application is further described in detail below in combination with the Drawings.

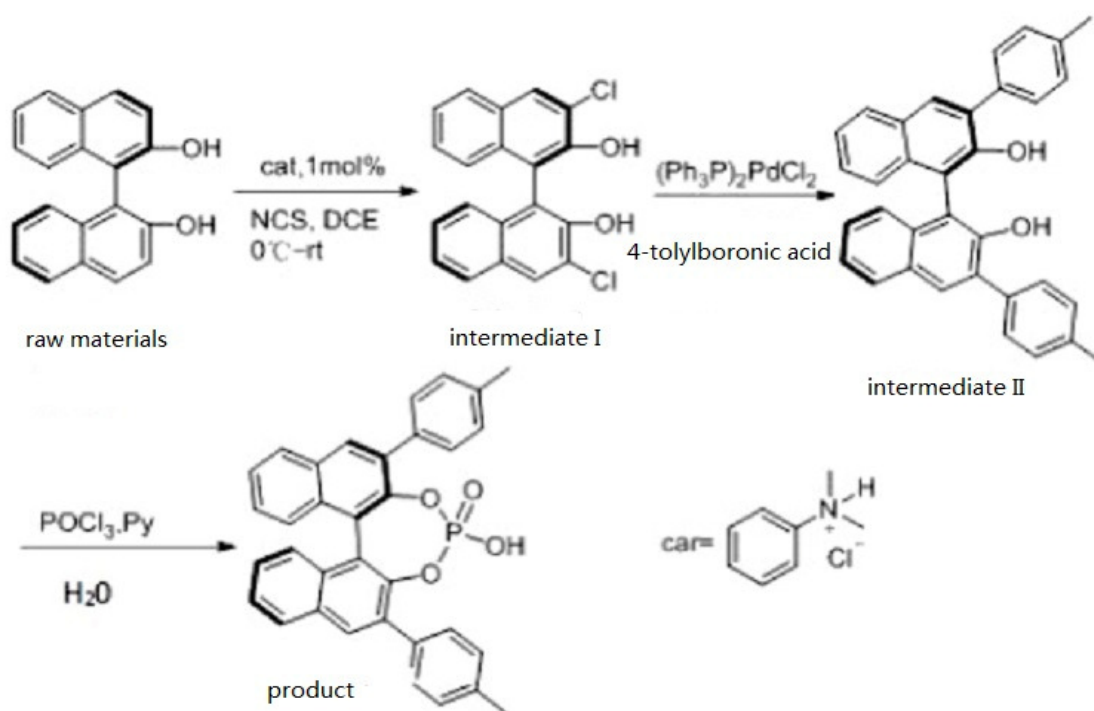
**[0036]** Example

**[0037]** Example 1

**[0038]** A chiral phosphoric acid catalyst with the following structure formula was provided:



**[0039]** The above chiral phosphoric acid catalyst was synthesized as follows:



**[0040]** Specific steps of the above reaction were:

**[0041]** step S1, (R)-[1,1'-binaphthyl]-2,2'-diol and N-chlorosuccinimide (NCS) were added to dichloroethane, added with a catalyst N,N-dimethylaniline hydrochloride, stirred and mixed, and reacted at 20°C for 1h to obtain 1.2 g of an intermediate I, [<sup>1</sup>H NMR (CdCl<sub>3</sub>, 270 MHz) δ 5.55 (s, 2H), 7.09 (d, 2H, J=8.4 Hz), 7.28 - 7.40 (m, 8H), 7.80 (d, 2H, J=8.6 Hz), 8.06 (s, 2H); mp 167 - 170 °C], [α] CHCl<sub>3</sub>=90.3°;

**[0042]** where a feeding ratio of (R)-[1,1'-binaphthyl]-2,2'-diol, NCS, N,N-dimethylaniline hydrochloride and the solvent was 1 g:0.56 g:0.02 g:5 ml;

**[0043]** step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps:the intermediate I and aryl boronic acid were used as raw materials, and the Suzuki coupling reaction was preformed under conditions of alkaline environment (with Na<sub>2</sub>CO<sub>3</sub> as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.5 as the solvent, and catalyst of palladium catalyst (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> at 90 °C for 6 h, to obtain 1.4 g of intermediate II, [<sup>1</sup>H NMR (400 MHz, CdCl<sub>3</sub>):δ8.00 (s, 2H), 7.91 (d, J=8 Hz, 2H), 7.63 (d, J=8 Hz, 4H), 7.40 - 7.36 (m, 2H), 7.33 - 7.29 (m, 6H), 7.23 - 7.21 (m, 2H) 5.36 (s, 2H), 2.43 (s, 6H)], [α] CHCl<sub>3</sub> = -118.23°;

**[0044]** where the aryl boronic acid was 4-tolylboronic acid; and

**[0045]** a feeding ratio of the intermediate I, 4-tolylboronic acid, (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, Na<sub>2</sub>CO<sub>3</sub> and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

**[0046]** step S3, after termination of the reaction was monitored by TLC, the intermediate II was

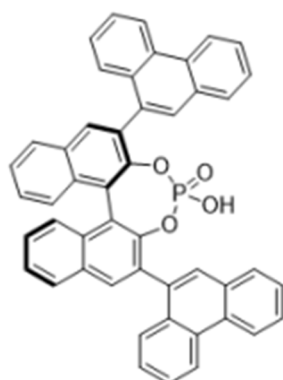
subjected to phosphorylation reaction by the following steps: 1 g of the intermediate II was added to 5 ml of pyridine solution, dripped with 0.82 g of phosphorus oxychloride, stirred and mixed, and reacted at 60 °C for 7 h. After termination of the reaction was monitored by TLC, the reaction solution was cooled to 25 °C, added with 2 ml of water, and heated to 60 °C to react for 6 h. After termination of the reaction was monitored by TLC, the reaction solution was concentrated under reduced pressure, dissolved in dichloromethane, washed twice with 5 ml of 4M hydrochloric acid, and then concentrated under reduced pressure to obtain 1.2 g of crude chiral phosphate catalyst.

**[0047]** step S4, the above crude chiral phosphoric acid catalyst was chromatographed on a 200-mesh silica gel column, and then eluted with a mixed solvent of petroleum ether/ethyl acetate at a volume ratio of 1:4, at a flow rate of 10 ml/min, to obtain 1.1 g of pure chiral phosphoric acid catalyst, [<sup>1</sup>H NMR(400 MHz, CdCl<sub>3</sub>) δ 8.01 (s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.52 (m, 3H), 7.31 (dt, J = 18.8, 5.5 Hz, 5H), 7.02 (d, J = 20.5 Hz, 1H), 2.34 (s, 3H)], the HPLC detection diagram was shown in FIG. 8, [α]<sub>D</sub> DMF = -271.04°, the yield was 97% and the purity was 99%;

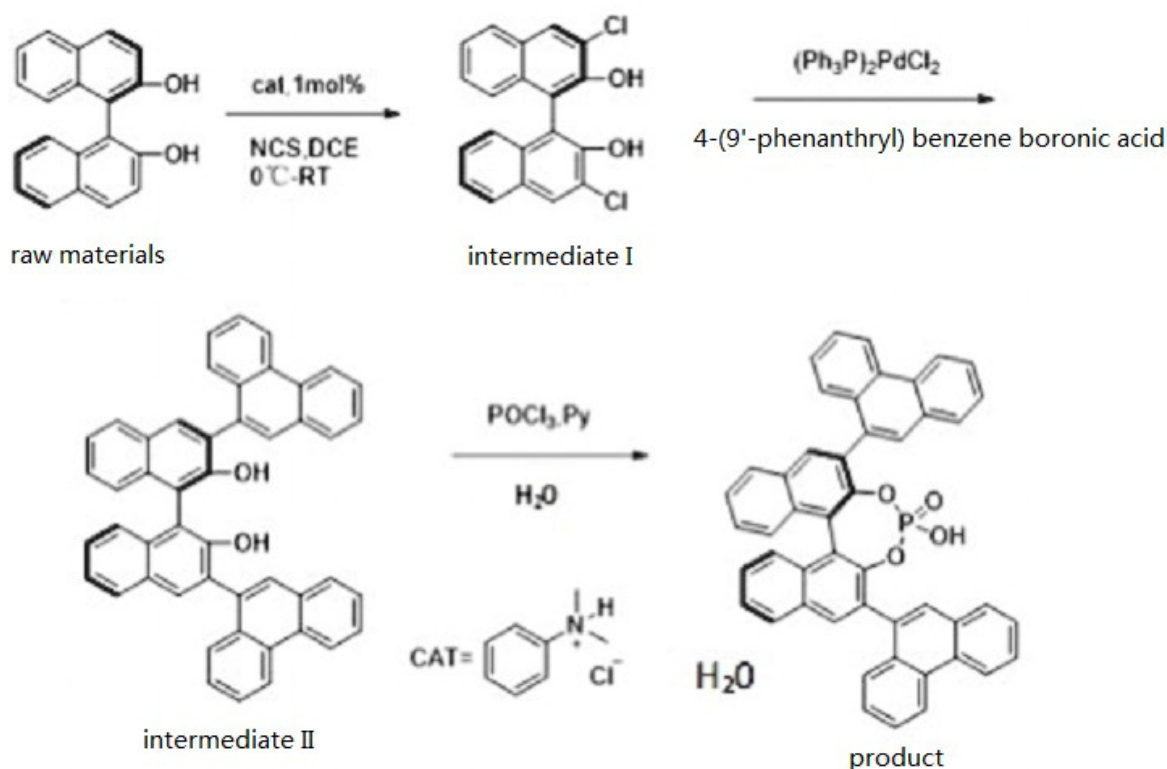
**[0048]** where TCL developing solvent: a mixed solvent of petroleum ether/ethyl acetate at a volume ratio of 1:5.

**[0049] Example 2**

**[0050]** A chiral phosphoric acid catalyst with the following structure formula was provided:



**[0051]** The above chiral phosphoric acid catalyst was synthesized as follows:



[0052] The specific steps of the above reaction included:

[0053] step S1, same as step S1 in Example 1;

[0054] step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the 4-(9'-phenanthryl) benzene boronic acid were used as raw materials, and the Suzuki coupling reaction was preformed under conditions of an alkaline environment (with  $\text{Na}_2\text{CO}_3$  as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.4 as the solvent, and a catalyst of palladium catalyst  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  at 90 °C for 6 h to obtain 2.1 g of intermediate II,  $[\alpha]_{\text{CHCl}_3} = 63.18^\circ$ ;

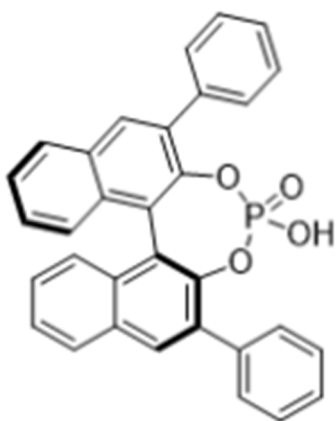
[0055] where the feeding ratio of the intermediate I, 4-(9'-phenanthryl) benzene boronic acid,  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ ,  $\text{Na}_2\text{CO}_3$  and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

[0056] step S3, same as step S3 in Example 1, and 1.22 g of crude chiral phosphate catalyst was obtained;

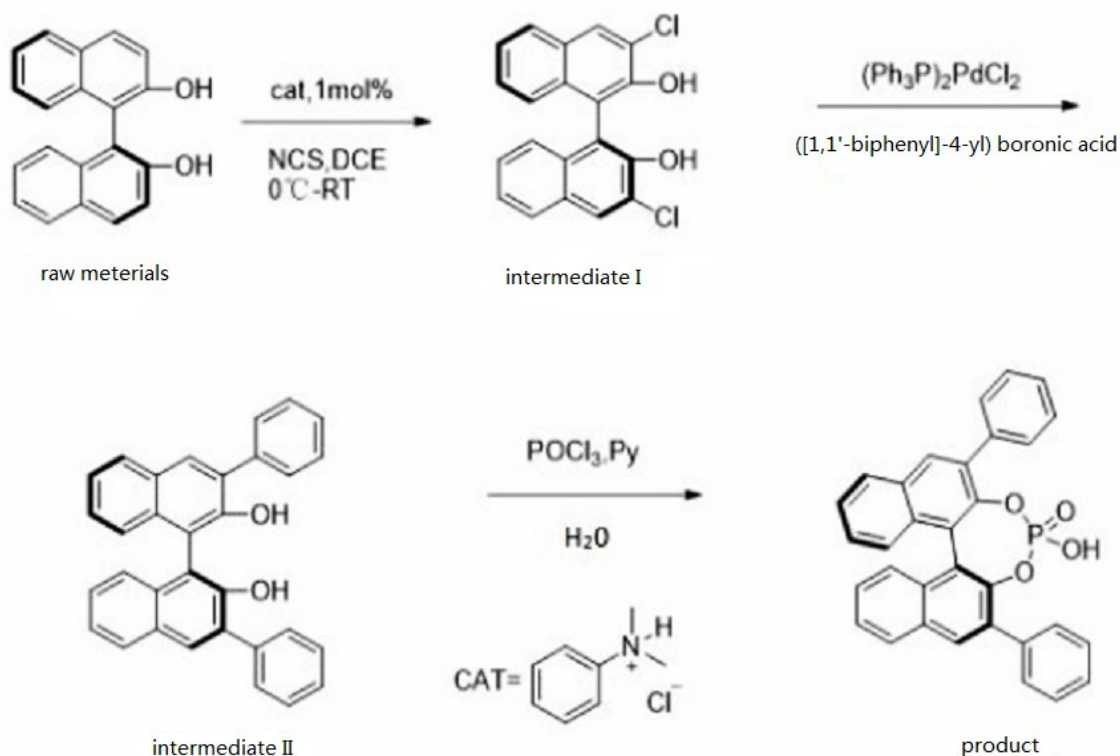
[0057] step S4, same as step S4 in Example 1, and 1.0 g of pure chiral phosphoric acid catalyst was obtained. The  $^1\text{H}$  NMR spectra was shown in FIG. 1, the HPLC detection diagram was shown in FIG. 9,  $[\alpha]_{\text{DMSO}} = -45.82^\circ$ , the yield was 91% and the purity was 98%.

### [0058] Example 3

[0059] A chiral phosphoric acid catalyst with the following structure formula was provided:



**[0060]** The above chiral phosphoric acid catalyst was synthesized as follows:



**[0061]** The specific steps of the above reaction included:

**[0062]** step S1, the difference from step S1 in Example 1 was that an equivalent amount of (S)-[1,1'-binaphthyl]-2,2'-diol was used to replace (R)-[1,1'-binaphthyl]-2,2'-diol, and 1.2 g of the intermediate I was obtained, [<sup>1</sup>H NMR (300MHz, CdCl<sub>3</sub>):δ8.06 (s, 2H), 7.80 (d, J = 8.1 Hz, 2H), 7.38 (t, J = 7.2 Hz, 2H), 7.28 (t, J = 7.1 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 5.56 (s, 2H)], [α] THF = -103.86°;

**[0063]** step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the ([1,1'-biphenyl]-4-yl) boronic acid were used as raw materials, and the Suzuki coupling reaction was

performed under conditions of an alkaline environment (with  $\text{Na}_2\text{CO}_3$  as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.65 as the solvent, and a catalyst of palladium catalyst  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  at 90 °C for 6 h, to obtain 1.4 g of the intermediate II;

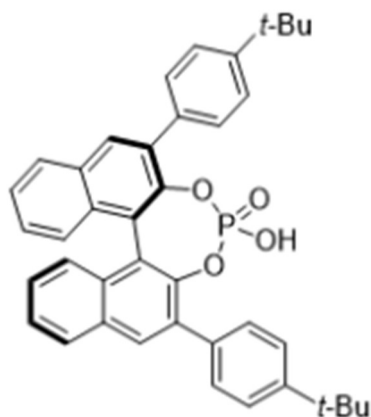
[0064] wherein the feeding ratio of the intermediate I, the ([1,1'-biphenyl]-4-yl) boronic acid, the  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , the  $\text{Na}_2\text{CO}_3$  and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

[0065] step S3, same as step S3 in Example 1, and 1.37 g of crude chiral phosphate catalyst was obtained;

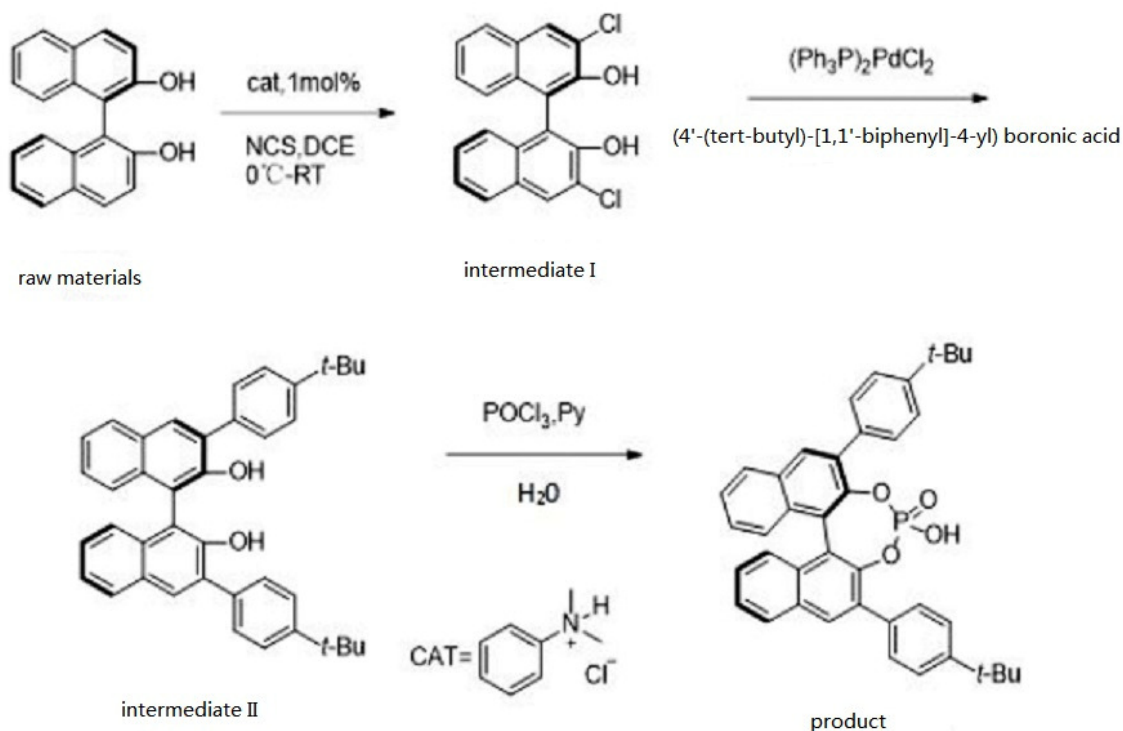
[0066] step S4, same as step S4 in Example 1, and 1.1 g of pure chiral phosphoric acid catalyst was obtained, the  $^1\text{H}$  NMR spectra was shown in FIG. 2, the HPLC detection diagram was shown in FIG. 10,  $[\alpha]_{\text{CHCl}_3} = 257.83^\circ$ , the yield was 96% and the purity was 98%.

[0067] **Example 4**

[0068] A chiral phosphoric acid catalyst with the following structure formula was provided:



[0069] The above chiral phosphoric acid catalyst was synthesized as follows:



[0070] The specific steps of the above reaction included:

[0071] step S1, same as step S1 in Example 1;

[0072] step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the (4'-(tert-butyl)-[1,1'-biphenyl]-4-yl) boronic acid were used as raw materials, and the Suzuki coupling reaction was performed under conditions of an alkaline environment (with  $\text{Na}_2\text{CO}_3$  as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.5 as the solvent, and a catalyst of palladium catalyst  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  at 90 °C for 6 h, and 1.8 g of the intermediate II was obtained,  $[\alpha]_{\text{CHCl}_3} = 34.72^\circ$ ;

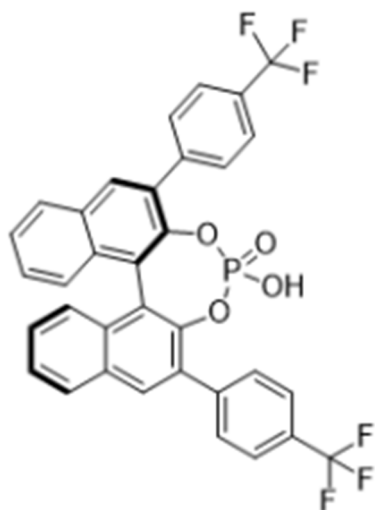
[0073] wherein the feeding ratio of the intermediate I, the (4'-(tert-butyl)-[1,1'-biphenyl]-4-yl) boronic acid, the  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , the  $\text{Na}_2\text{CO}_3$  and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

[0074] step S3, same as step S3 in Example 1, and 1.2 g of the crude chiral phosphate catalyst was obtained;

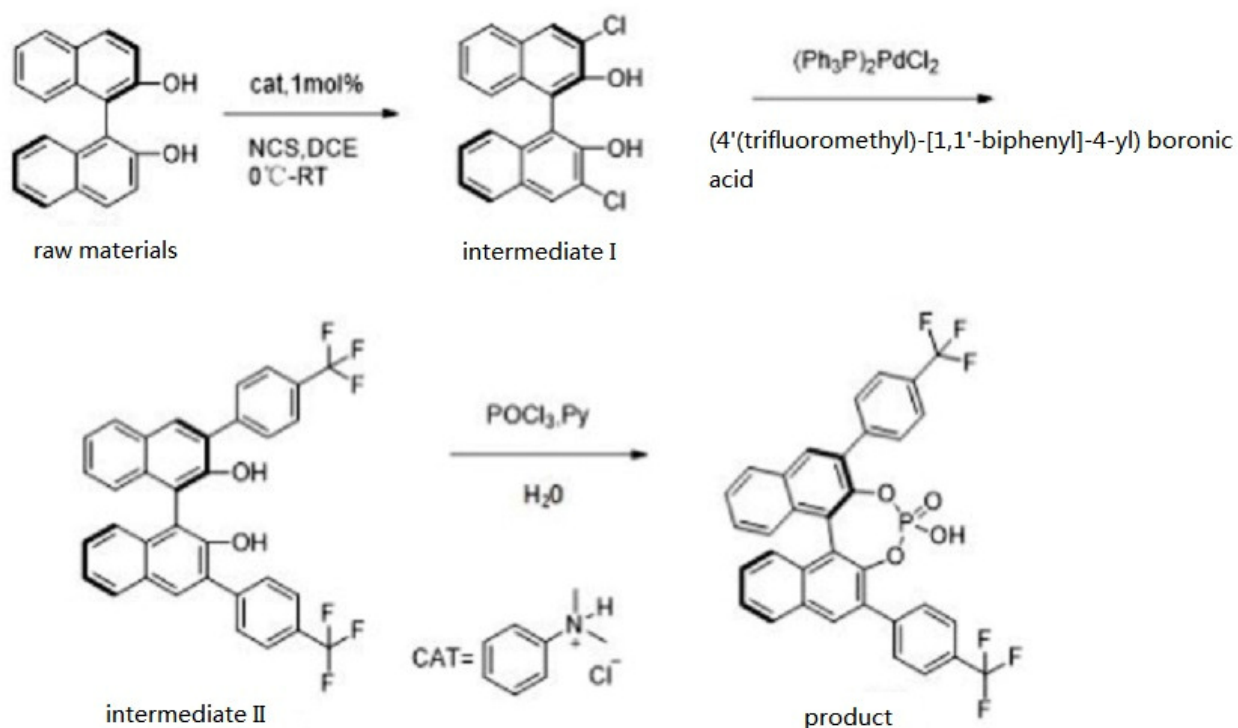
[0075] step S4, same as step S4 in Example 1, and 1.05 g of pure chiral phosphoric acid catalyst was obtained, the  $^1\text{H}$  NMR spectra was shown in FIG. 3, the HPLC detection diagram was shown in FIG. 11,  $[\alpha]_{\text{CHCl}_3} = 263.16^\circ$ , the yield was 94% and the purity was 98%.

#### [0076] Example 5

[0077] A chiral phosphoric acid catalyst with the following structure formula was provided:



[0078] The above chiral phosphoric acid catalyst was synthesized as follows:



[0079] The specific steps of the above reaction included:

[0080] step S1, same as step S1 in Example 1;

[0081] step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the (4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)boronic acid were used as raw materials, and the Suzuki coupling reaction was performed under conditions of an alkaline environment (with  $\text{Na}_2\text{CO}_3$  as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.5 as the solvent, and a catalyst of palladium catalyst  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  at 90 °C for 6 h, and 1.85 g of the intermediate II was

obtained,  $[\alpha]_{\text{CHCl}_3} = 52.42^\circ$ ;

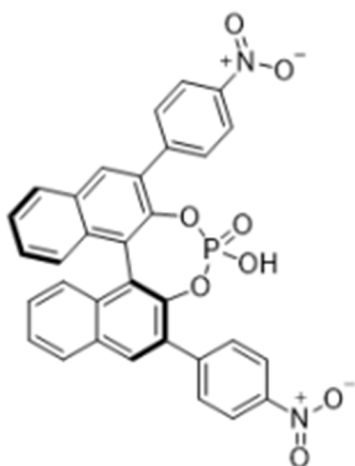
[0082] wherein the feeding ratio of the intermediate I, the (4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl) boronic acid, the  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , the  $\text{Na}_2\text{CO}_3$  and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

[0083] step S3, same as step S3 in Example 1, and 1.2 g of the crude chiral phosphate catalyst was obtained;

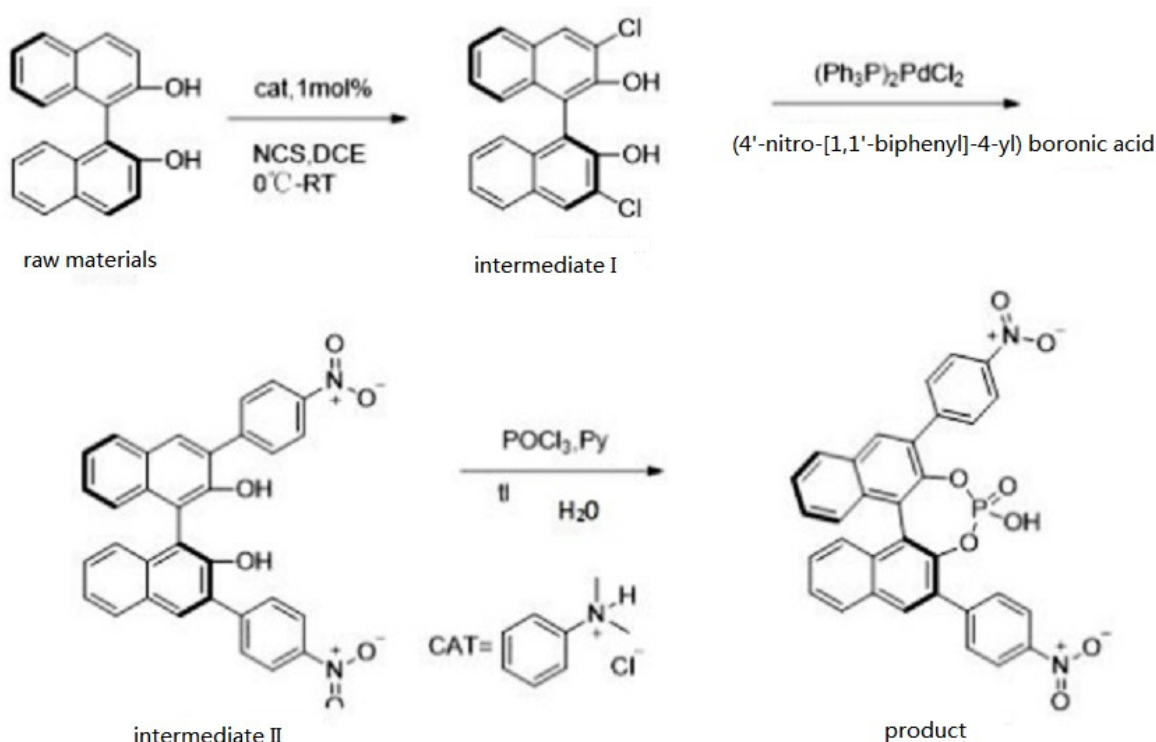
[0084] step S4, same as step S4 in Example 1, and 1.05 g of pure chiral phosphoric acid catalyst was obtained, the  $^1\text{H}$  NMR spectra was shown in FIG. 4, the HPLC detection diagram was shown in FIG. 12,  $[\alpha]_{\text{DMF}} = -356.04^\circ$ , the yield was 97% and the purity was 98%.

[0085] **Example 6**

[0086] A chiral phosphoric acid catalyst with the following structure formula was provided:



[0087] The above chiral phosphoric acid catalyst was synthesized as follows:



[0088] The specific steps of the above reaction included:

[0089] step S1, same as step S1 in Example 3;

[0090] step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the (4'-nitro-[1,1'-biphenyl]-4-yl) boronic acid were used as raw materials, and the Suzuki coupling reaction was performed under conditions of an alkaline environment (with Na<sub>2</sub>CO<sub>3</sub> as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.5 as the solvent, and a catalyst of palladium catalyst (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> at 90 °C for 6 h, and 1.7 g of the intermediate II was obtained, [α]<sub>D</sub><sup>20</sup> = 189.60°;

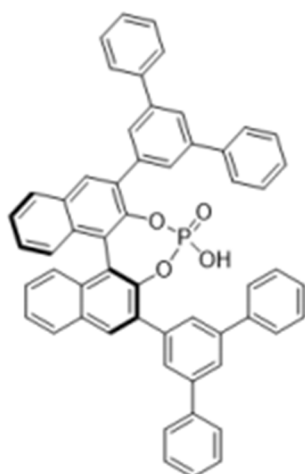
[0091] wherein the feeding ratio of the intermediate I, the (4'-nitro-[1,1'-biphenyl]-4-yl) boronic acid, the (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, the Na<sub>2</sub>CO<sub>3</sub> and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

[0092] step S3, same as step S3 in Example 1, and 1.21 g of the crude chiral phosphate catalyst was obtained;

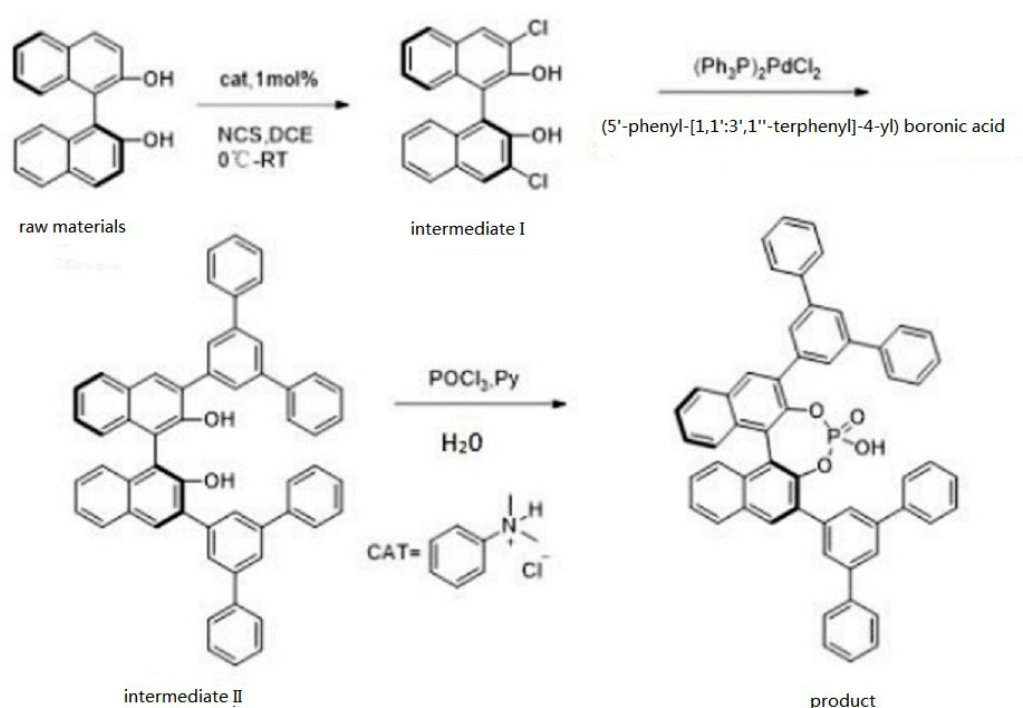
[0093] step S4, same as step S4 in Example 1, and 1.06 g of pure chiral phosphoric acid catalyst was obtained, the <sup>1</sup>H NMR spectra was shown in FIG. 5, the HPLC detection diagram was shown in FIG. 13, [α]<sub>D</sub><sup>20</sup> = -342.18°, the yield was 95% and the purity was 98%.

[0094] **Example 7**

[0095] A chiral phosphoric acid catalyst with the following structure formula was provided:



[0096] The above chiral phosphoric acid catalyst was synthesized as follows:



[0097] The specific steps of the above reaction included:

[0098] step S1, same as step S1 in Example 3;

[0099] step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the (5'-phenyl-[1,1':3',1''-terphenyl]-4-yl) boronic acid were used as raw materials, and the Suzuki coupling reaction was performed under conditions of an alkaline environment (with Na<sub>2</sub>CO<sub>3</sub> as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.5 as the solvent, and a catalyst of palladium catalyst (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> at 90 °C for 6 h, and 2.48 g of the intermediate II was obtained, [α]<sub>D</sub> DMF = 49.31°;

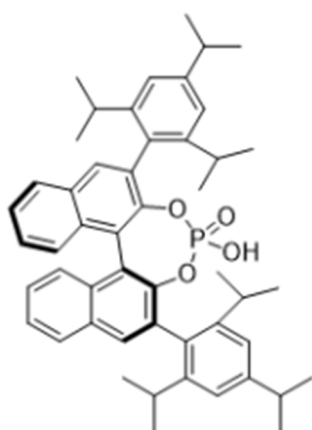
[00100] wherein the feeding ratio of the intermediate I, the (5'-phenyl-[1,1':3',1''-terphenyl]-4-yl)

boronic acid, the  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ , the  $\text{Na}_2\text{CO}_3$  and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;  
**[00101]** step S3, same as step S3 in Example 1, and 1.2 g of the crude chiral phosphate catalyst was obtained;

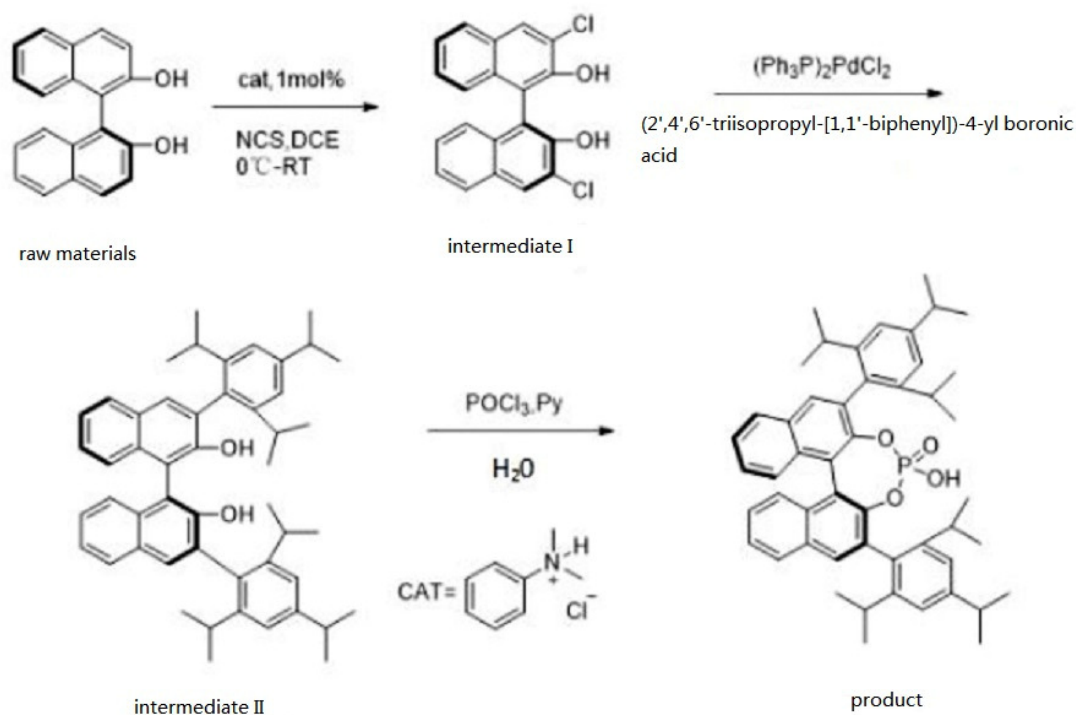
**[00102]** step S4, same as step S4 in Example 1, and 1.04 g of pure chiral phosphoric acid catalyst was obtained, the  $^1\text{H}$  NMR spectra was shown in FIG. 6, the HPLC detection diagram was shown in FIG. 14,  $[\alpha]_{\text{CHCl}_3} = 272.34^\circ$ , the yield was 96% and the purity was 98%.

**[00103] Example 8**

**[00104]** A chiral phosphoric acid catalyst with the following structure formula was provided:



**[00105]** The above chiral phosphoric acid catalyst was synthesized as follows:



**[00106]** The specific steps of the above reaction included:

[00107] step S1, same as step S1 in Example 3;

[00108] step S2, after termination of the reaction was monitored by TLC, the intermediate I was subjected to Suzuki coupling reaction by the following steps: the intermediate I and the (2',4',6'-triisopropyl-[1,1'-biphenyl] -4-yl) boronic acid were used as raw materials, and the Suzuki coupling reaction was performed under conditions of an alkaline environment (with Na<sub>2</sub>CO<sub>3</sub> as the alkali), a mixed solution of DMF and water at a weight ratio of 1:0.5 as the solvent, and a catalyst of palladium catalyst (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub> at 90 °C for 6 h, and the intermediate II was obtained in 2.2 g, [α]<sub>tetrahydrofuran</sub> = -84.49°;

[00109] wherein the feeding ratio of the intermediate I, the (2',4',6'-triisopropyl-[1,1'-biphenyl] -4-yl) boronic acid, the (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>, the Na<sub>2</sub>CO<sub>3</sub> and the solvent was 1 g:0.5 g:0.04 g:0.01 g:15 ml;

[00110] step S3, same as step S3 in Example 1, and 1.2 g of the crude chiral phosphate catalyst was obtained;

[00111] step S4, same as step S4 in Example 1, and 1.04 g of pure chiral phosphoric acid catalyst was obtained, the <sup>1</sup>H NMR spectra was shown in FIG. 7, the HPLC detection diagram was shown in FIG. 15, [α]<sub>CHCl<sub>3</sub></sub> = 62.92°, the yield was 95% and the purity was 98%.

#### [00112] Examples 9 to 12

[00113] A chiral phosphoric acid catalyst was provided, differing from Example 1 in that, in step S1, the feeding ratios of the [1,1'-binaphthyl]-2,2'-diol, the N-chlorosuccinimide, and the N,N-dimethylaniline hydrochloride was different, as shown in Table 1.

Table 1 Components in step S1 in Examples 1, 9 to 12 and their amounts (kg)

| Items<br>Component                        | Example 1 | Example 9 | Example 10 | Example 11 | Example 12 |
|-------------------------------------------|-----------|-----------|------------|------------|------------|
| [1,1'-binaphthyl]-2,2'-diol<br>(kg)       | 1         | 1         | 1          | 1          | 1          |
| N-chlorosuccinimide<br>(kg)               | 0.56      | 0.45      | 0.5        | 0.6        | 0.7        |
| N,N-dimethylaniline<br>hydrochloride (kg) | 0.02      | 0.005     | 0.01       | 0.02       | 0.03       |
| Dichloroethane<br>(L)                     | 5         | 5         | 5          | 5          | 5          |

#### [00114] Example 13

**[00115]** A chiral phosphoric acid catalyst was provided, differing from Example 1 in that the catalyst was used differently in step S1, using an equivalent amount of N,N-diethylaniline hydrochloride to replace N,N-dimethylaniline hydrochloride.

**[00116] Example 14**

**[00117]** A chiral phosphoric acid catalyst was provided, differing from Example 1 in that the catalyst was used differently in step S1, using an equivalent amount of a mixture of triethylamine hydrochloride and N,N-diethylaniline hydrochloride with a weight ratio of 1:1.

**[00118] Examples 15 to 16**

**[00119]** A chiral phosphoric acid catalyst was provided, differing from Example 1 in that in step S2, the feeding ratio of the intermediate I, the 4-tolyboronic acid, the  $(\text{Ph}_3\text{P})_2\text{PdCl}_2$  and the  $\text{Na}_2\text{CO}_3$  was different, as shown in Table 2.

Table 2 Components of step S2 in Examples 1, 15 to 16 and their amounts

| Item<br>Component                      | Example 1 | Example 15 | Example 16 |
|----------------------------------------|-----------|------------|------------|
| intermediate I                         | 1         | 1          | 1          |
| 4-tolyboronic acid                     | 0.5       | 0.4        | 0.65       |
| $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ | 0.04      | 0.005      | 0.05       |
| $\text{Na}_2\text{CO}_3$               | 0.01      | 0.01       | 0.05       |

**[00120]** The yield and purity of product of Examples 1 to 16 are shown in Table 3.

Table 3 Yield and purity of product of Examples 1 to 16

| Item<br>Component | Yield | Purity |
|-------------------|-------|--------|
| Example 1         | 97    | 99     |
| Example 2         | 91    | 98     |
| Example 3         | 96    | 98     |
| Example 4         | 94    | 98     |
| Example 5         | 97    | 98     |
| Example 6         | 95    | 98     |

|            |    |    |
|------------|----|----|
| Example 7  | 96 | 98 |
| Example 8  | 95 | 98 |
| Example 9  | 93 | 96 |
| Example 10 | 95 | 98 |
| Example 11 | 94 | 97 |
| Example 12 | 92 | 96 |
| Example 13 | 89 | 94 |
| Example 14 | 90 | 95 |
| Example 15 | 89 | 95 |
| Example 16 | 90 | 95 |

**[00121]** The synthesis method of chiral phosphoric acid catalyst of the present application is described below in combination with Examples 1 to 16 and the data in Table 3.

**[00122]** The process route of the present application is as follows: for parallel screening of the catalysts, the halogen atoms are selectively introduced to naphthol, which is coupled and phosphorylated subsequently to produce the chiral phosphoric acid catalyst. Since the reaction process does not require the use of precious metal catalysts or hydrocarbon activation, the synthesis cost is reduced greatly; and the catalytic and coupling reactions can be combined in fewer steps, become a concise and efficient synthesis route, and the yield and purity of the product chiral phosphoric acid catalysts are high. The purity of the products in Examples 1 to 16 was above 94% and up to 99%, and the yield was above 89% and up to 97%, which can satisfy large-scale production industry.

**[00123]** It should be noted that in other embodiments, the solvent in step S1 may also use trichloromethane, which does not impose a large influence on the synthesis route of chiral phosphoric acid catalyst. In the present application, dichloroethane is merely briefly described as an example of the solvent.

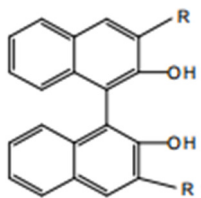
**[00124]** Similarly, in step S2, the weight ratio of DMF and water in the solvent can be selected in the range of 1:(0.4-0.65).

**[00125]** The above are the preferred embodiments of the present application, which are not intended to limit the protection scope of the present application. Therefore, all equivalent changes made according to the structure, shape and principle of the present application should be covered within the protection scope of the present application.



## WHAT IS CLAIMED IS:

1. A synthesis method of chiral phosphoric acid catalyst, comprising the follow steps:  
halogenation reaction, performed by using a [1,1'-binaphthyl]-2,2'-diol and a halogenating agent as raw materials to obtain an intermediate I;  
Suzuki coupling reaction, performed by using the intermediate I and a boronic acid compound as raw materials to obtain an intermediate II, wherein the intermediate II is represented as general formula (I);



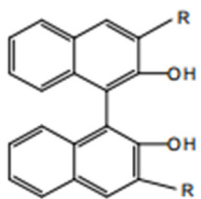
general formula (I):

- where, in the general formula (I), R is selected from phenylmethyl, phenanthryl, phenyl, tert-butyl phenyl, trifluoromethyl phenyl, nitrophenyl, and triisopropyl phenyl; and  
phosphorylation of the intermediate II, to obtain a crude chiral phosphate catalyst.

2. The synthesis method of chiral phosphoric acid catalyst according to claim 1, comprising the follow steps:

step S1, halogenation reaction, performed by using a [1,1'-binaphthyl]-2,2'-diol and a halogenating agent as raw materials to obtain an intermediate I;

step S2, Suzuki coupling reaction, performed by using the intermediate I and a boronic acid compound as raw materials to obtain an intermediate II, wherein the intermediate II is represented as general formula (I);



general formula (I):

where, in the general formula (I), R is selected from phenylmethyl, phenanthryl, phenyl, tert-butyl phenyl, trifluoromethyl phenyl, nitrophenyl, and triisopropyl phenyl;

step S3, phosphorylation of the intermediate II to obtain a crude chiral phosphate catalyst;  
and

step S4, chromatographing and eluting of the crude phosphate acid catalyst in silica gel column to obtain the chiral phosphoric acid catalyst.

3. The synthesis method of chiral phosphoric acid catalyst according to claim 2, wherein the halogenation reaction comprises:

stirring and mixing [1,1'-binaphthyl]-2,2'-diol and a halogenating agent as raw materials, a solvent and a catalyst to obtain the intermediate I,

wherein a feeding ratio of the [1,1'-binaphthyl]-2,2'-diol, the halogenating agent, and the catalyst is 1 g:(0.45-0.7) g:(0.005-0.03) g.

4. The synthesis method of chiral phosphoric acid catalyst according to claim 3, wherein the catalyst is an ammonium salt.

5. The synthesis method of chiral phosphoric acid catalyst according to claim 3, wherein the halogenating agent is a N-chlorosuccinimide.

6. The synthesis method of chiral phosphoric acid catalyst according to claim 3, wherein the [1,1'-binaphthyl]-2,2'-diol is one of R-type and S-type.

7. The synthesis method of chiral phosphoric acid catalyst according to claim 2, wherein the Suzuki coupling reaction comprises:

stirring and mixing the intermediate I and the boronic acid compound as raw materials, palladium catalyst and  $\text{Na}_2\text{CO}_3$  as an alkali in a solvent to obtain the Intermediate II represented as general formula (I);

wherein the feeding ratio of the Intermediate I, the boronic acid compound, the palladium catalyst, and the  $\text{Na}_2\text{CO}_3$  is 1 g:(0.4-0.65) g:(0.005-0.05) g:(0.01- 0.05) g.

8. The synthesis method of chiral phosphoric acid catalyst according to claim 7, wherein the boronic acid compound is one of aryl boronic acid, 4-(9'-phenanthryl) benzene boronic acid, ([1,1'-biphenyl]-4-yl) boronic acid, (4'-(tert-butyl)-[1,1'-biphenyl]-4-yl) boronic acid, (4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl) boronic acid, (4'-nitro-[1,1'-biphenyl]-4-yl) boronic acid, (5'-phenyl-[1,1':3,1''-terphenyl]-4-yl) boronic acid, (2',4',6'-triisopropyl-[1,1'-biphenyl] -4-yl) boronic acid.

9. The synthesis method of chiral phosphoric acid catalyst according to claim 7, wherein the solvent is a mixed solution of DMF and water at a weight ratio of 1:(0.4-0.65).