(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
09 January 2020 (09.01.2020)

WIPO | PCT

(10) International Publication Number
WO 2020/007017 A1

(51) International Patent Classification:
C07D 403/14 (2006.01) *C07D 487/04* (2006.01)
C07D 401/14 (2006.01) *C07D 491/048* (2006.01)
C07D 211/22 (2006.01)

(21) International Application Number:
PCT/CN2019/000044

(22) International Filing Date:
05 March 2019 (05.03.2019)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201810728197.9 05 July 2018 (05.07.2018) CN

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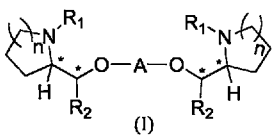
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2020/007017 A1

(54) Title: CHIRAL BISAMINO-ETHER COMPOUNDS, AND METHOD OF PREPARATION AND USE THEREOF



(I)

(57) Abstract: The present invention provides novel chiral bisamino-ether compounds, and method of preparation and use thereof. The chiral bisamino-ether compounds have the structure of formula (I). The method of preparation includes: using chiral aminomethanol compounds as starting materials to react with halogenated aryl compounds in the presence of a base to give a variety of chiral bisamino-ether compounds. The novel chiral bisamino-ether compounds can be used for asymmetric fluorocyclization of unsaturated heterocyclic compounds with excellent enantioselectivity and great potentials for industrial applications.

CHIRAL BISAMINO-ETHER COMPOUNDS, AND METHOD OF PREPARATION AND USE THEREOF

FIELD OF THE INVENTION

The present invention relates to novel chiral bisamino-ether compounds, and method of preparation and use thereof. Specifically, chiral aminomethanol compounds are used as starting materials to react with halogenated aryl compounds in the presence of a base to give a variety of chiral bisamino-ether compounds. The novel chiral bisamino-ether compounds can be used for asymmetric fluorocyclization of unsaturated heterocyclic compounds with excellent enantioselectivity and great potentials for industrial applications.

BACKGROUND OF THE INVENTION

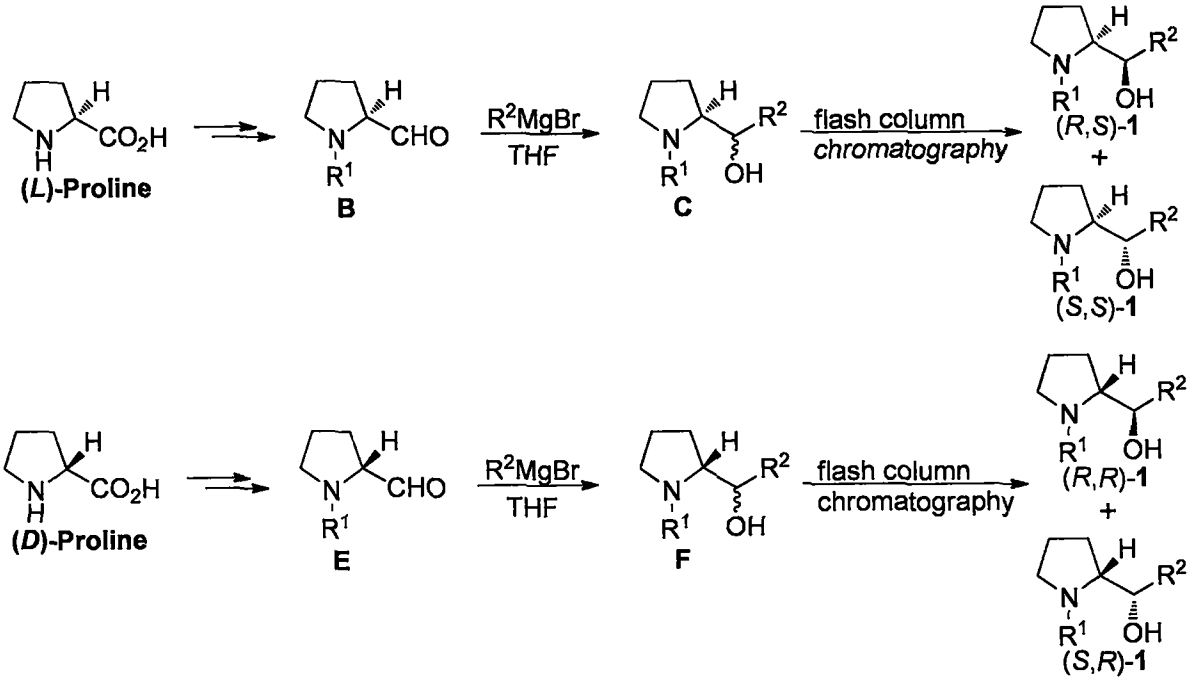
In the past few decades, natural bis-quinine or bis-quinidine has been used as a catalyst or reactant in a variety of asymmetric reactions to prepare important chiral compounds (Behrens, C.H.; Sharpless, K.B. Aldrichimica Acta 1983, 16, 67; Kolb, H.C.; van Nieuwenhze, M.S.; Sharlpless, K.B. Chem. Rev. 1994, 94, 2483; Li, G. G.; Chang, H. T.; Sharpless, K. B. Angew. Chem. Int. Ed. Engl. 1996, 35, 451; Jaganathan, A.; Garzan, A.; Whitehead, D. C.; Staples, R. J.; Borhan, B. Angew. Chem. Int. Ed. Engl. 2011, 50, 2593; Whitehead, D. C.; Yousefi, R.; Jaganathan, A.; Borhan, B. J. Am. Chem. Soc. 2010, 132, 3298; Lozano, O.; Blessley, G.; del Campo, T. M.; Thompson, A. L.; Giuffredi, G. T.; Bettati, M.; Walker, M.; Borman, R.; Gouverneur, V. Angew. Chem. Int. Ed. Engl. 2011, 50, 8105; Yu, P. A. Handbook of Reagents for Organic Synthesis: Catalytic Oxidation Reagents 2013, 483).

In the past, the materials of such bis-quinine or bis-quinidine compounds were derived from the natural product of quinine or quinidine. However, the quinine or quinidine, as a natural product, has a single structure rather than being a pair of mirror-image of enantiomers. Consequently, the compounds are difficult to be structurally modified, and thus that the *R* and *S* enantiomeric products cannot be ensured to have the same ee value.

SUMMARY OF THE INVENTION

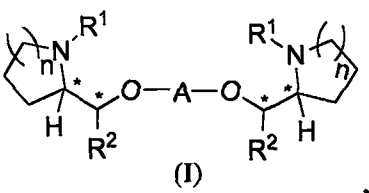
To overcome the above disadvantages of the natural products of quinine or quinidine, the present invention provided synthesis of various of chiral aminomethanol intermediates **1** using *D* or *L* type amino acids as starting materials (Jiang, X.; Tan, CK; Zhou, L.; Yeung, Y.-Y. Angew. Chem. Int. Ed. Engl. 2012, 51, 7771). For example, the natural *L*-proline or *D*-proline, which is inexpensive and readily available, was used as a starting material to carry out oxidation and Grignard reaction to give the compound C or F each having two chiral centers, and then through

column chromatography purification, four chiral aminomethanol compounds **1** having different stereo configurations can be obtained (as shown in the scheme below) as the raw materials in the present invention. The variability of the groups R_1 and R_2 allows the final product chiral bisamino-ether compound (**I**) of the present invention to have multiple tunable sites to form a variable spatial structure for the needs of different reactions, and the presence of *D* and *L* types of amino acids shall ensure that both *R* and *S* enantiomeric products with the same ee value can be obtained. It is indicated that the chiral bisamino-ether compounds (**I**) of the present invention have broad industrial utilities.



Therefore, in order to solve the problems associated with the natural bis-quinine or bis-quinidine compounds, the present invention provides novel chiral bisamino-ether compounds, and method of preparation and use thereof. The novel chiral bisamino-ether compounds can be used for asymmetric fluorocyclization of unsaturated heterocyclic compounds with excellent enantioselectivity for broad industrial applications.

In one aspect, the present invention provides a chiral bisamino-ether compound having the structure of formula (**I**):

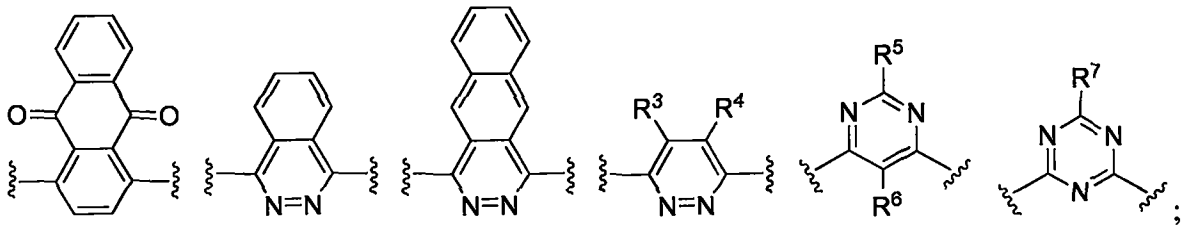


(I)

,

wherein:

n = 1 or 2; chiral center * has (*R*) or (*S*) configuration; and $\{\!\!-\!\!A\!\!-\!\!\}$ is one of the following moieties:



R^1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, haloalkyl, C_1-C_8 alkoxyl, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxyl substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxyl substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, and C_2-C_8 acyloxyl substituted phenyl;

R^2 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, haloalkyl, C_1-C_8 alkoxyl, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxyl substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxyl substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, C_2-C_8 acyloxyl substituted phenyl, naphthyl, pyridyl, quinolyl, isoquinolinyl, furyl, and thienyl;

R^3, R^4, R^5, R^6 and R^7 may be the same or different, and are each independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, haloalkyl, C_1-C_8 alkoxyl, C_1-C_8 acyl, C_2-C_8 acyloxyl, C_2-C_8 ester group, (C_1-C_8 acyl)amino, di(C_1-C_8 alkyl)amino, halogen, amino, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxyl substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxyl substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, C_2-C_8 acyloxyl substituted phenyl, naphthyl, pyridyl, quinolyl, isoquinolinyl, furyl and thienyl.

In the chiral bisamino-ether compound (I):

the C_1-C_8 alkyl is methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl , isoamyl, neopentyl, sec-pentyl, tert-amyl, cyclopentyl, n-hexyl, isohexyl, neohexyl, sec-hexyl, tert-hexyl, cyclohexyl, n-heptyl, isoheptyl, neoheptyl , n-heptyl, tert-heptyl, cycloheptyl, n-octyl, isooctyl, neooctyl, sec-octyl, tert-octyl, or cyclooctyl;

the C_1-C_9 unsaturated alkyl is allyl, 2-methylpropyl, cis-n-butenyl, trans-2-butenyl, 3,3-dimethylallyl, cis-2-pentenyl, trans-2-pentenyl, propargyl, benzyl, or 1-phenyl-1-propenyl;

the haloalkyl is halogenated alkyl with halogen being fluorine, chlorine, bromine or iodine;

the C_1-C_8 alkoxy is methoxyl, ethoxyl, n-propoxyl, isopropoxyl, cyclopropoxyl, n-butoxyl, iso-butoxyl, sec-butoxyl, tert-butoxyl, cyclobutoxyl, n-pentyloxyl, iso-pentyloxyl, neo-pentyloxyl, sec-pentyloxyl, tert-pentyloxyl, cyclopentyloxyl, n-hexyloxyl, iso-hexyloxyl, neo-hexyloxyl, sec-hexyloxyl, tert-hexyloxyl, cyclohexyloxyl, n-heptyloxyl, iso-heptyloxyl, neo-heptyloxyl,

sec-heptyloxyl, tert-heptyloxyl, cycloheptyloxyl, n-octyloxyl, iso-octyloxyl, neo-octyloxyl, sec-octyloxyl, tert-octyloxyl, or cyclooctyloxyl;

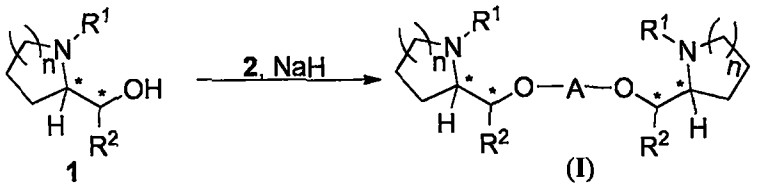
the C_1-C_8 acyl is formyl, acetyl, propionyl, n-butyryl, iso-butyryl, n-valeryl, iso-valeryl, neo-valeryl, sec-valeryl, n-hexanoyl, iso-hexanoyl, neo-hexanoyl , sec-hexanoyl, n-heptanoyl, iso-heptanoyl, neo-heptanoyl, sec-heptanoyl, n-octanoyl, iso-octanoyl, neo-octanoyl, sec-octanoyl, 1-cyclopropylformyl, 1-cyclobutylformyl, 1-cyclopentylformyl, 1-cyclohexylformyl, or 1-cycloheptylcarbonyl;

the C_2-C_8 acyloxyl is acetoxyl, propionyloxyl, n-butyryloxyl, iso-butyryloxyl, n-pentanoyloxyl, iso-valeryloxyl, sec-pentanoyloxyl, neo- pentanoyloxyl, n-hexanoyloxyl, iso-hexanoyloxyl, sec-hexanoyloxyl, neo-hexanoyloxyl, n-heptanoyloxyl, iso-heptanoyloxyl, sec-heptanoyloxyl, neo-heptanoyloxyl, n-octanoyloxyl, iso-octanoyloxyl, sec-octanoyloxyl, neo-octanoyloxyl, 1-cyclopropylcarbonyloxyl, 1-cyclobutylcarbonyloxyl, 1-cyclopentylcarbonyl, 1-cyclohexylcarbonyloxyl, or 1-cycloheptylcarbonyl;

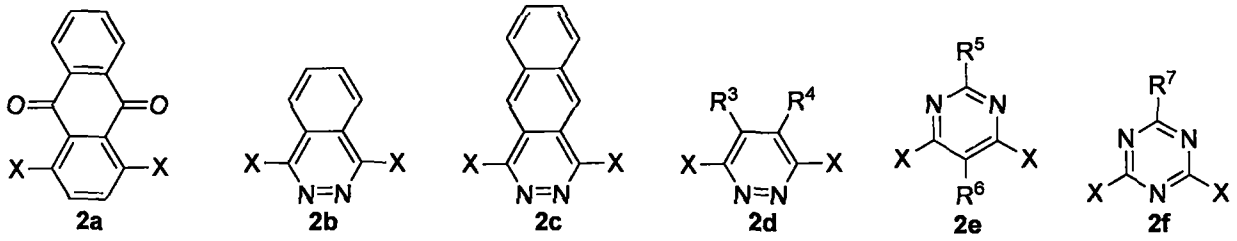
the C_2-C_8 ester group is methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, iso-butoxycarbonyl, n-pentyloxycarbonyl, iso-pentyloxycarbonyl, neo-pentyloxycarbonyl, sec-pentyloxycarbonyl, tert-pentyloxycarbonyl, cyclopentyloxycarbonyl, n-hexyloxycarbonyl, iso-hexyloxycarbonyl, sec-hexyloxycarbonyl, neo-hexyloxycarbonyl, tert-hexyloxycarbonyl, cyclohexyloxycarbonyl, n-heptyloxycarbonyl, iso-heptyloxycarbonyl, neo-heptyloxycarbonyl, sec-heptyloxycarbonyl, tert-heptyloxycarbonyl, or cycloheptyloxycarbonyl.

The chiral bisamino-ether compound (**I**), as described herein, comprises a racemate, dextroisomer and laevoisomer having same chemical formula but different stereo structures and optical rotation properties.

In another aspect, the present invention provides a method of preparation of the chiral bisamino-ether compound, and the method comprises: chiral amino-methanol compound **1** (2 mmol) being reacted with a base (2-4 mmol) in an organic solvent for 5-30 minutes, and then further reacted with halogenated aryl compound **2** (1-2 mmol) at 0-160 °C for 2-96 hours to give a chiral bisamino-ether compound (**I**) with different substituent groups:



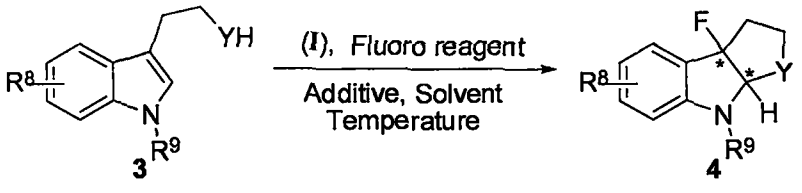
wherein: n = 1 or 2; R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are defined as in formula (**I**); the halogenated aryl compound **2** is selected from the group consisting of:



In some embodiments, the organic solvent is dimethylformamide, dichloromethane, dichloroethane, tetrahydrofuran, 1,4-dioxane, toluene, xylene, trimethylbenzene, chlorobenzene, dichlorobenzene, or any combination thereof.

In some embodiments, the base is sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or any combination thereof.

In yet another aspect, the present invention provides a use of the chiral bisamino-ether compound, wherein the use comprises: using the chiral bisamino-ether compound **I** in asymmetric fluorocyclization of unsaturated heterocyclic compound **3**:



wherein: R^8 and R^9 may be the same or different, and are each independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, halogen, haloalkyl, C_1-C_8 alkoxyl, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxy substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxy substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, C_2-C_8 acyloxy substituted phenyl, or naphthyl; the fluoro reagent is bis(tetrafluoroborate) salt of 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane or N-fluorobisbenzenesulfonamide; and the position marked by asterisk (*) is a chiral center.

In particular, in the use, the reaction is carried out by adding the chiral bisamino-ether compound (**I**) and the substrate **3** into a round bottom flask, adding an additive and a solvent, adding the fluoro reagent, and then stirring the reaction at a specified temperature until the completion of the reaction.

In the use, the reaction conditions include: the solvent is acetone, acetonitrile, ethyl acetate, tetrahydrofuran, 1,4-dioxane, toluene, dichloromethane, 1,2-dichloroethane, chloroform, or a combination thereof; the chiral bisamino-ether compound (**I**) is in an amount of 10-120 mol%; *the substrate* **3** *is in a concentration of 0.01-10 M; the additive is* sodium hydrogencarbonate, potassium hydrogencarbonate, cesium carbonate, sodium carbonate, potassium carbonate, or a

combination thereof; the reaction temperature is -78 to 40°C; the reaction time is 2-96 hours.

In the present invention, a chiral aminomethanol compound **1** is used as a starting material to react with a halogenated aryl compound **2** in the presence of a base to obtain a substituent-containing chiral bisamino-ether compound (**I**). The novel chiral bisamino-ether compound (I) can be used for the asymmetric fluorocyclization of the unsaturated heterocyclic compound **3**. The compounds of the invention showed some advantageous features, which include: having excellent effects with a wide range of substrates for a series of unsaturated heterocyclic compounds; having high tolerance to functional groups; having high enantioselectivity; and being able to obtain both *R* and *S* enantiomeric products with the same ee value. The above features indicate that the novel chiral bisamino-ether compound of the invention is superior over the previous bis-quinine or bis- quinidine compounds and can find broad applications in industry.

DETAILED DESCRIPTION OF EMBODIMENTS

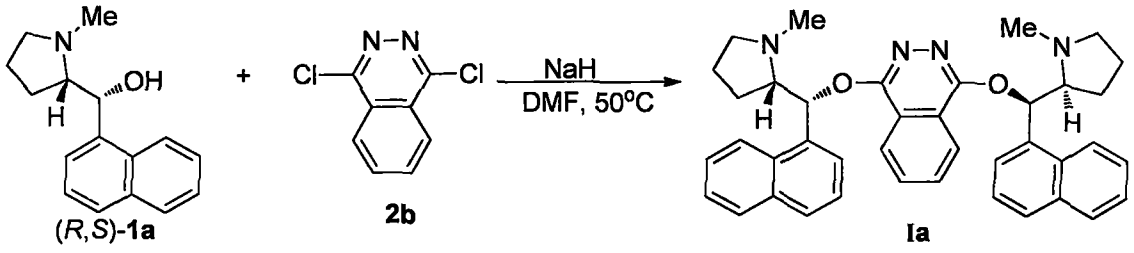
The invention will be further understood through the following examples, which should not be construed as limiting the scope of the invention. It should be understood that all of the techniques implemented based on the above teachings of the present invention are within the scope of the present invention.

It should be noted that the abbreviations used in the examples have the following meanings: Me refers to methyl, Et refers to ethyl, Allyl refers to allyl, Ph refers to phenyl, Mes refers to 2,4,6-trimethylphenyl, Bn refers to benzyl, Ts refers to p-toluenesulfonyl, Boc refers to tert-butoxycarbonyl, NMR refers to nuclear magnetic resonance, HRMS refers to high resolution mass spectrometry, chiral HPLC refers to high performance liquid chromatography with a chiral column, ee value refers to enantiomer excess value, Selectfluor refers to 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane bis(tetrafluoroborate) salt, and NFSI refers to N-fluorobis benzene sulfonamide.

Example 1: Preparation of the chiral bisamino-ether compounds

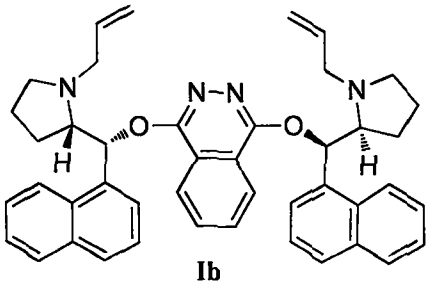
In this example, the compounds obtained by the synthesis described herein are all prepared with the same process, and thus, for the sake of brevity, only the process for preparing the compound **Ia** is specifically described below, while the process for other subsequently listed compounds is omitted.

1,4-Bis((*R*)-((*S*)-1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Ia**):



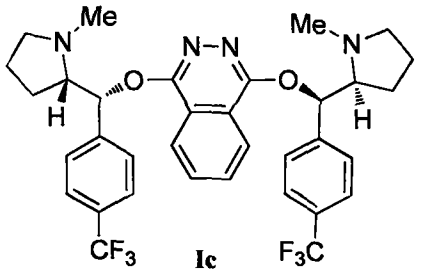
The chiral aminomethanol compound (*R,S*)-**1a** (482 mg, 2 mmol) was dissolved in dimethylformamide (6 mL), and then added with 60% sodium hydride (120 mg, 3 mmol) at room temperature for 15 min. Then, halogenated aryl compound **2b** (239 mg, 1.2 mmol) was added, and the reaction was run at 50 °C in an oil bath for 24 hours. After the reaction being completed, the reaction mixture was concentrated and cooled to room temperature, and added with water (6 mL), and then was extracted with ethyl acetate (15 mL×3). The organic phase was combined and dried over anhydrous sodium sulfate, and then filtrated. The filtrate was concentrated via rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 2:1, v/v) to give a light yellow solid 438 mg; mp 90-91°C; yield 72%. $[\alpha]_D^{25}$= 15.5 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.45-7.33 (m, 20H), 3.15-3.10 (m, 2H), 3.03-2.98 (m, 2H), 2.51 (s, 6H), 2.45-2.24 (m, 4H), 2.02-1.93 (m, 2H), 1.78-1.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 135.6, 133.8, 131.9, 130.6, 128.8, 127.9, 125.9, 125.5, 125.3, 123.5, 123.2, 123.1, 122.9; HRMS (TOF^+) calcd. for $C_{40}H_{40}N_4O_2$ $[M+H]^+$ 609.3579, found 609.3577。

1,4- Bis((*R*)-((*S*)-1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Ib**):



449 mg, yield 68%, light yellow solid; mp 94-95 °C; $[\alpha]_D^{25}$=18.6 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.93-7.48 (m, 16H), 6.15-6.02(m, 2H), 5.69 (s, broad, 2H), 5.42-5.25 (m, 4H), 3.83-3.77 (m, 2H), 3.29-3.10 (m, 6H), 2.48-2.39 (m, 2H), 1.81-1.60 (m, 8H), 1.19-1.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.7, 135.6, 133.6, 130.1, 129.0, 127.4, 125.7, 125.6, 125.3, 123.3, 122.6, 117.6, 67.3, 67.1, 57.0, 54.8, 24.4, 23.4; HRMS (TOF^+) calcd. for $C_{44}H_{44}N_4O_2$ $[M+H]^+$ 661.3534, found 661.3537.

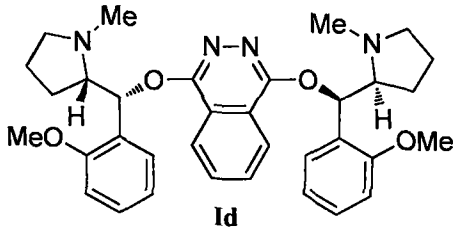
1,4-Bis((*R*)-((*S*)-1-methyl-2-pyrrolyl)(4-trifluoromethylphenyl)methoxy)phthalazine (**Ic**):



Ic

405 mg, yield 63%, light yellow solid; mp 86-87 °C; $[\alpha]_D^{25}$= 24.9 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.32-6.51 (m, 14H), 3.12-3.06 (m, 2H), 2.36 (s, 6H), 2.33-2.26 (m, 2H), 2.22-2.15 (m, 2H), 1.88-1.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.8, 143.8, 132.1, 129.8, 129.3, 127.0, 125.2 (q, J = 3.8 Hz), 123.1, 122.8, 76.1, 70.6, 57.5, 41.6, 25.9, 23.5; HRMS (TOF^+) calcd. for $C_{34}H_{34}F_6N_4O_2$ $[M+H]^+$ 645.3755, found 645.3764.

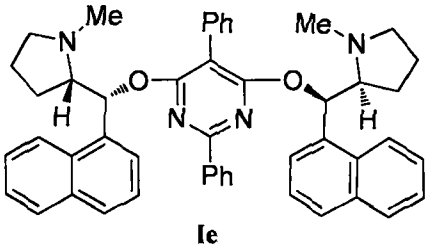
1,4-Bis((*R*)-(2-methoxyphenyl)((*S*)-1-methyl-2-pyrrolyl)methoxy)phthalazine (**Id**):



Id

364 mg, yield 64%, light yellow solid; mp 82-83°C; $[\alpha]_D^{25}$= 25.8 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.39-6.72 (m, 14H), 3.90 (s, 6H), 3.15-3.12 (m, 2H), 3.35-3.33 (m, 2H), 2.26 (s, 6H), 1.88-1.63 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 156.6, 131.6, 128.6, 128.2, 127.2, 123.2, 122.8, 120.4, 110.7, 74.9, 68.4, 58.6, 55.6, 43.6, 28.3, 24.1; HRMS (TOF^+) calcd. for $C_{34}H_{40}N_4O_4$ $[M+H]^+$ 569.6761, found 569.6759.

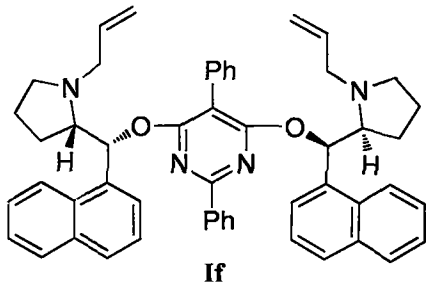
4,6-Bis((*R*)-((*S*)- 1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Ie**):



Ie

426 mg, yield 60%, light yellow solid; mp 137-138°C; $[\alpha]_D^{25}$= 17.1 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.33-7.07 (m, 26H), 3.11-3.06 (m, 2H), 2.94-2.91 (m, 2H), 2.40 (s, 6H), 2.33-2.24 (m, 2H), 2.16-2.08 (m, 2H), 1.76-1.59 (m, 6H), ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 160.6, 137.3, 136.2, 133.7, 131.8, 131.2, 130.7, 129.9, 129.0, 128.9, 128.0, 127.9, 127.6, 127.3, 126.0, 125.4, 124.1, 123.2, 104.7, 74.1, 69.3, 57.7, 41.5, 26.0, 23.1; HRMS (TOF^+) calcd. for $C_{48}H_{46}N_4O_2$ $[M+H]^+$ 711.4181, found 711.4183.

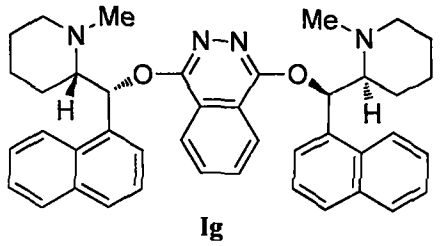
4,6-Bis((*R*)-((*S*)- 1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**If**):



If

465.4 mg, yield 61%, light yellow solid; mp 149-150°C; $[\alpha]_D^{25}$= 17.4 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.39-7.09 (m, 26H), 5.73-5.60 (m, 2H), 5.05-4.95 (m 4H), 3.25-3.19 (m, 4H), 3.08-3.04 (m, 2H), 2.95-2.88 (m, 2H), 2.40-2.32 (m, 2H), 2.11-2.04 (m, 2H), 1.75-1.59 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.8, 153.5, 130.2, 129.3, 126.6, 124.0, 123.9, 122.9, 121.7, 120.9, 120.7, 120.6, 120.2, 118.6, 118.3, 118.2, 117.4, 116.8, 109.2, 97.5, 68.7, 59.7, 50.8, 47.5, 19.7, 16.3; HRMS (TOF^+) calcd. for $C_{52}H_{50}N_4O_2$ $[M+H]^+$ 763.4007, found 763.4039.

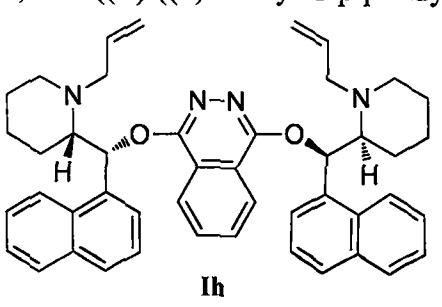
1,4-Bis((*R*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)phthalazine (**Ig**):



Ig

509 mg, yield 80%, light yellow solid; mp 91-92°C; $[\alpha]_D^{25}$= 15.4 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.53-7.28 (m, 20H), 3.01-2.88 (m, 3H), 2.66 (s, 6H), 2.57-2.53 (m, 2H), 2.19-2.12 (m, 2H), 2.05-1.95 (m, 1H), 1.78-1.54 (m, 6H), 1.10-0.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 134.9, 133.9, 132.0, 128.9, 127.9, 125.9, 125.5, 125.0, 123.8, 123.6, 123.5, 123.1, 71.7, 62.3, 58.2, 43.7, 25.8, 24.7, 24.5; HRMS (TOF^+) calcd. for $C_{42}H_{44}N_4O_2$ $[M+H]^+$ 637.5579, found 637.5590.

1,4-Bis((*R*)-((*S*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)phthalazine (**Ih**):

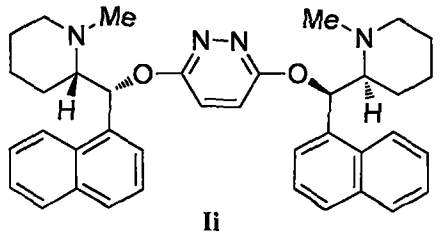


Ih

530.4 mg, yield 77%, light yellow solid; mp 96-97°C; $[\alpha]_D^{25}$= 22.7 (c 1.0, $CHCl_3$); ^1H NMR

($CDCl_3$, 300 MHz): δ 8.53-7.36 (m, 20H), 5.80-5.67 (m, 2H), 5.12-4.92 (m 4H), 3.92-3.86 (m, 2H), 3.26-2.94 (m, 6H), 2.26-2.20 (m, 2H), 2.05-1.97 (m, 2H), 1.82-1.78 (m, 2H), 1.66-1.49 (m, 6H), 1.22-1.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 135.4, 133.9, 131.9, 130.6, 128.8, 127.9, 125.9, 125.5, 125.0, 124.1, 124.0, 123.5, 123.1, 117.6, 72.4, 64.0, 56.9, 52.3, 25.2, 24.9, 24.2; HRMS (TOF^+) calcd. for $C_{46}H_{48}N_4O_2$ $[M+H]^+$ 689.6225, found 689.6237.

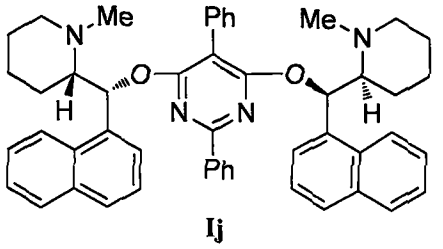
3,6-Bis((*R*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)pyridazine (**Ii**):



Ii

433.9 mg, yield 74%, light yellow solid; mp 85-86°C; $[\alpha]_D^{25}$= 10.0 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12-7.28 (m, 20H), 3.73-3.65 (m, 1H), 3.17-3.13 (m, 2H), 2.75 (s, 6H), 2.61-2.58 (m, 2H), 2.32-2.24 (m, 2H), 1.94-1.86 (m, 2H), 1.77-1.47 (m, 8H), 1.10-0.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.6, 151.2, 133.9, 133.2, 130.8, 130.3, 129.1, 128.4, 126.5, 124.9, 124.1, 122.8, 121.2, 72.8, 66.8, 53.1, 43.1, 25.3, 24.4, 24.1; HRMS (TOF^+) calcd. for $C_{38}H_{42}N_4O_2$ $[M+H]^+$ 587.7352, found 587.7361.

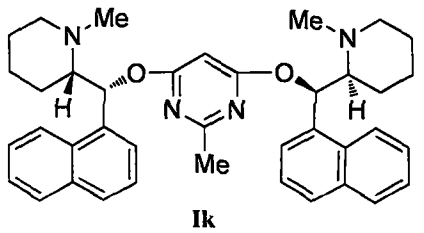
4,6-Bis((*R*)-((*S*)-1-methyl-2-piperidyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Ij**):



Ij

450 mg, yield 61%, light yellow solid; mp 150-151°C; $[\alpha]_D^{25}$= 24.3 (c 1.0, $CHCl_3$); ^1H NMR (*$CDCl_3$, 300 MHz*): δ 8.32-7.02 (m, 27H), 3.05-3.01 (m, 2H), 2.64-2.61 (m, 2H), 2.39-2.27 (m, 2H), 1.78-1.47 (m, 10H), 1.11-0.96 (m, 2H), ; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.1, 166.6, 160.6, 136.9, 135.0, 133.7, 131.4, 130.3, 130.1, 129.1, 127.9, 127.8, 127.6, 126.3, 125.5, 125.1, 124.6, 122.9, 104.9, 72.7, 66.0, 56.9, 24.6, 23.7, 23.3, 22.6; HRMS (TOF^+) calcd. for $C_{50}H_{50}N_4O_2$ $[M+H]^+$ 739.4007, found 739.3988.

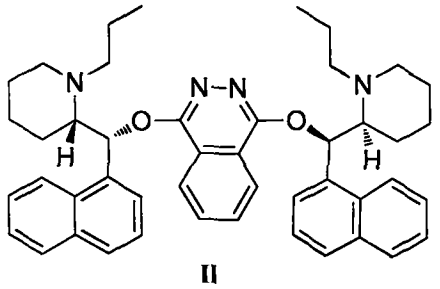
2-Methyl-4,6-bis((*R*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)pyrimidine (**Ik**):



Ik

456 mg, yield 76%, light yellow solid; mp 85-86°C; $[\alpha]_D^{25}$= 16.3 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.12-7.38 (m, 16H), 6.32 (s, 1H), 3.04-2.97 (m, 2H), 2.67 (s, 6H), 2.22-2.12 (m, 2H), 2.04 (s, 3H), 1.90-1.52 (m, 7H), 1.40-1.36 (m, 2H), 1.01-0.92 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.3, 166.9, 134.7, 133.7, 130.2, 129.0, 127.8, 126.1, 125.4, 126.3, 124.7, 123.0, 90.6, 71.4, 66.7, 58.2, 43.2, 25.8, 24.6, 24.3; HRMS (TOF^+) calcd. for $C_{39}H_{44}N_4O_2$ $[M+H]^+$ 601.3537, found 601.3530.

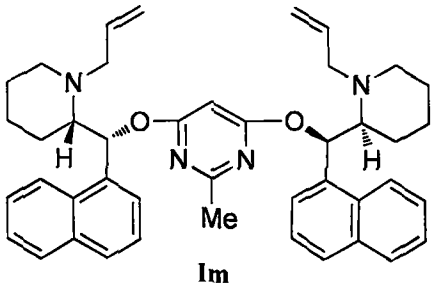
1,4-Bis((*R*)-(1-naphthyl)((*S*)-1-propyl-2-piperidyl)methoxy)phthalazine (**II**):



II

505 mg, yield 73%, light yellow solid; mp 100-101°C; $[\alpha]_D^{25}$= 21.4 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.50-7.33 (m, 20H), 3.19-3.07 (m, 4H), 2.90-2.87 (m, 2H), 2.47-2.38 (m, 2H), 2.18-1.94 (m, 4H), 1.81-1.75 (m, 2H), 1.64-1.50 (m, 6H), 1.42-1.08 (m, 4H), 0.52 (t, J = 9.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.6, 135.6, 133.9, 131.9, 130.6, 128.8, 127.7, 125.8, 125.4, 125.0, 124.1, 124.0, 123.0, 72.6, 64.4, 55.3, 52.5, 25.1, 24.8, 24.1, 20.0, 11.6; HRMS (TOF^+) calcd. for $C_{46}H_{52}N_4O_2$ $[M+H]^+$ 693.6384, found 693.6391.

4,6-Bis((*R*)-((*S*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)-2-methylpyrimidine (**Im**):

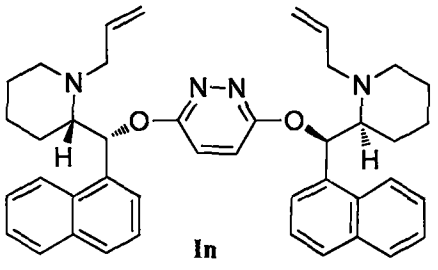


Im

515 mg, yield 79%, light yellow solid; mp 97-98°C; $[\alpha]_D^{25}$= 18.6 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.23-7.43 (m, 16H), 6.20-6.06 (m, 2H), 5.44-5.30 (m 4H), 3.81-3.75 (m,

2H), 3.50-3.42 (m, 2H), 3.14-3.10 (m, 2H), 2.83-2.79 (m, 2H), 2.41-2.33 (m, 2H), 2.15 (s, 3H), 1.92-1.61 (m, 8H), 1.39-1.32 (m, 3H), 1.10-0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 167.0, 135.2, 133.7, 130.5, 128.9, 127.8, 125.9, 125.4, 125.3, 125.0, 123.5, 118.2, 90.8, 71.8, 63.0, 57.1, 53.4, 25.9, 25.6, 25.3, 24.3; HRMS (TOF$^+$) calcd. for $C_{43}H_{48}N_4O_2$ $[M+H]^+$ 653.4977, found 653.4980.

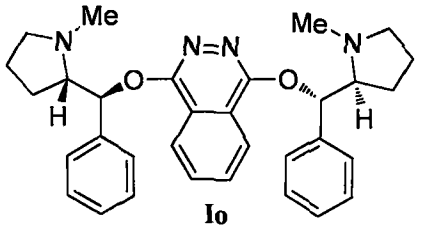
3,6-Bis((*R*)-((*S*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)pyridazine (**In**):



In

440 mg, yield 69%, brown oil; $[\alpha]_D^{25}$= 42.7 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.21-7.23 (m, 16H), 6.15-6.02 (m, 2H), 5.46-5.31 (m 4H), 3.86-3.79 (m, 2H), 3.48-3.41 (m, 2H), 3.16-3.12 (m, 2H), 2.89-2.85 (m, 2H), 2.41-2.32 (m, 2H), 21.90-1.61 (m, 9H), 1.48-1.43 (m, 3H), 1.13-1.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.7, 151.1, 133.8, 130.7, 130.6, 131.0, 129.0, 128.2, 126.2, 125.7, 124.9, 124.3, 123.3, 121.1, 73.4, 63.1, 57.2, 53.5, 25.4, 25.1, 24.1; HRMS (TOF$^+$) calcd. for $C_{42}H_{46}N_4O_2$ $[M+H]^+$ 639.5690, found 639.5692.

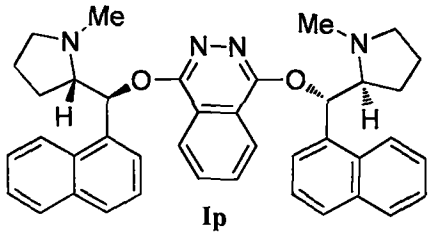
1,4-Bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(phenyl)methoxy)phthalazine (**Io**):



Io

396 mg, yield 78%, light yellow solid; mp 81-82°C; $[\alpha]_D^{25}$= –40.6 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.29-6.37 (m, 16H), 3.12-3.02 (m, 4H), 2.52 (s, 6H), 2.40-2.32 (m, 2H), 1.71-1.64 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.5, 139.5, 131.7, 127.9, 127.6, 123.0, 122.8, 80.0, 69.2, 58.1, 43.1, 28.3, 23.4; HRMS (TOF$^+$) calcd. for $C_{32}H_{36}N_4O_2$ $[M+H]^+$ 509.4573, found 509.4576.

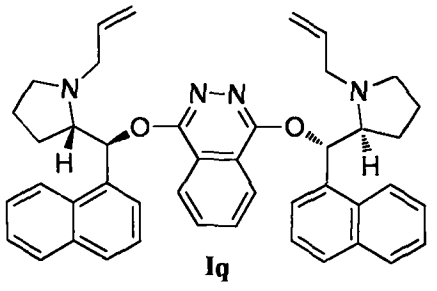
1,4-Bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Ip**):



Ip

389 mg, yield 64%, light yellow solid; mp 89-90°C; $[\alpha]_D^{25}$= –32.1 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.54-6.99 (m, 20H), 3.35-3.28 (m, 2H), 3.13-3.08 (m, 2H), 2.36-2.30 (m, 6H), 2.27 (s, 6H), 1.86-1.69 (m, 2H), 1.64-1.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.7, 135.9, 133.9, 131.7, 131.3, 128.7, 128.1, 125.8, 125.6, 125.3, 125.2, 124.7, 123.1, 122.8, 79.1, 69.0, 58.5, 43.6, 29.2, 23.9; HRMS (TOF^+) calcd. for $C_{40}H_{40}N_4O_2$ $[M+H]^+$ 609.3579, found 609.3576.

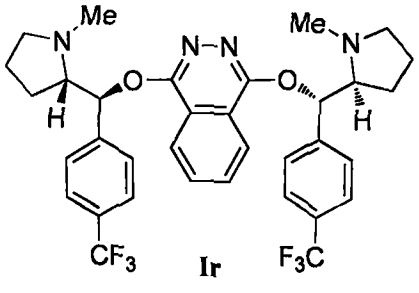
1,4-Bis((*S*)-((*S*)-1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Iq**):



Iq

437 mg, yield 66%, light yellow solid; mp. 93-94°C; $[\alpha]_D^{25}$= –20.7 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.47-7.28 (m, 16H), 5.81-5.68 (m, 2H), 4.99-4.93(m, 4H), 3.77-3.62 (m, 2H), 3.1-3.24 (m, 4H), 3.01-2.95 (m, 2H), 2.57-2.45 (m, 2H), 1.82-1.64 (m, 10H), 1.30-1.26 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 133.7, 131.9, 131.0, 128.6, 128.2, 125.8, 125.3, 125.2, 124.4, 123.2, 122.8, 66.7, 59.1, 54.5, 29.7, 28.9, 24.2; HRMS (TOF^+) calcd. for $C_{44}H_{44}N_4O_2$ $[M+H]^+$ 661.3534, found 661.3532.

1,4-Bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(4-trifluoromethylphenyl)methoxy)phthalazine (**Ir**):

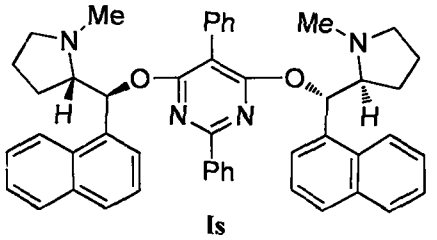


Ir

418.6 mg, yield 65%, light yellow solid; mp 88-89°C; $[\alpha]_D^{25}$= –19.3 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.31-6.39 (m, 14H), 3.09-3.00 (m, 4H), 2.51 (s, 6H), 2.37-2.29 (m, 2H), 1.77-1.49 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.5, 143.3, 132.1, 130.2, 129.8, 129.3, 128.9, 127.8, 124.8, 122.9, 122.6, 124.8 (q, J = 3.8 Hz), 122.9, 122.6, 79.3, 68.9, 57.9, 42.9, 27.9, 23.6;

HRMS (TOF$^+$) calcd. for $C_{34}H_{34}F_6N_4O_2$ [M+H]$^+$ 645.3755, found 645.3761.

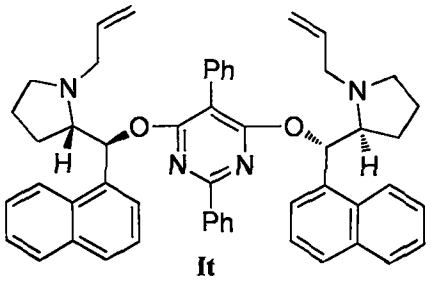
4,6-bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Is**):



Is

433 mg, yield 61%, light yellow solid; mp 136-137°C; $[\alpha]_D^{25}$= –23.6 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.50-6.76 (m, 26H), 3.22-3.08 (m, 2H), 2.38-2.30 (m, 2H), 2.26 (s, 6H), 1.86-1.77 (m, 2H), 1.65-1.53 (m, 4H), 1.43-1.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.0, 162.7, 159.3, 136.1, 133.9, 132.5, 131.3, 131.0, 130.2, 129.0, 128.7, 128.5, 128.4, 128.3, 128.1, 126.2, 125.3, 124.5, 118.9, 81.6, 69.5, 58.4, 43.2, 28.6, 23.5; HRMS (TOF$^+$) calcd. for $C_{48}H_{46}N_4O_2$ [M+H]$^+$ 711.4181, found 711.4186.

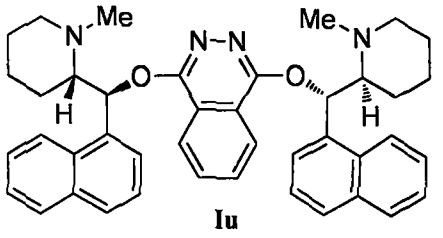
4,6-bis((*S*)-((*S*)-1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**It**):



It

480 mg, yield 63%, light yellow solid; mp 147-148°C; $[\alpha]_D^{25}$= –65.3 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.58-6.71 (m, 26H), 5.84-5.70 (m, 2H), 5.04-4.96 (m 4H), 3.44-3.33 (m, 4H), 3.11-3.06 (m, 2H), 2.93-2.86 (m, 2H), 2.44-2.36 (m, 2H), 1.79-1.69 (m, 2H), 1.60-1.40 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8, 161.2, 137.6, 137.1, 136.2, 133.9, 132.4, 131.6, 131.0, 129.0, 128.3, 128.0, 127.6, 125.8, 125.3, 124.9, 116.4, 104.6, 80.5, 66.8, 59.1, 54.5, 28.5, 24.0; HRMS (TOF$^+$) calcd. for $C_{52}H_{50}N_4O_2$ [M+H]$^+$ 763.4007, found 763.4038.

1,4-Bis((*S*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)phthalazine (**Iu**):

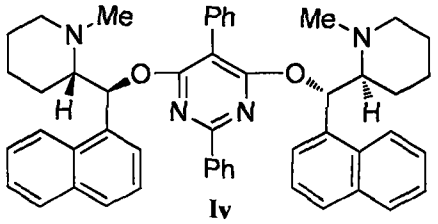


Iu

477 mg, yield 75%, light yellow solid; mp. 93-94°C; $[\alpha]_D^{25}$= –36.9 (c 1.0, $CHCl_3$); ^1H NMR

($CDCl_3$, 300 MHz): δ 8.66-7.11 (m, 20H), 3.41-3.35 (m, 2H), 2.95-2.91 (m, 2H), 2.43 (s, 6H), 2.49-2.39 (m, 2H), 1.56-1.51 (m, 6H), 1.18-1.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.1, 135.7, 134.0, 131.8, 131.6, 128.7, 128.4, 127.1, 125.9, 125.4, 125.3, 123.1, 122.8, 78.4, 66.3, 55.6, 42.9, 27.3, 24.2, 23.5; HRMS (TOF^+) calcd. for $C_{42}H_{44}N_4O_2$ $[M+H]^+$ 637.5579, found 637.5584.

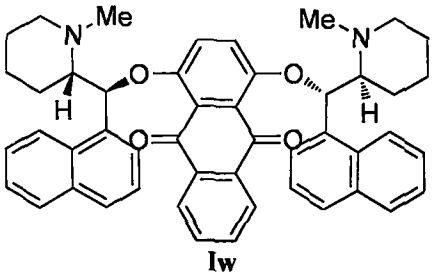
4,6-Bis((*S*)-((*S*)-1-methyl-2-piperidyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Iv**):



Iv

472 mg, yield 64%, light yellow solid; mp 150-151°C; $[\alpha]_D^{25}$= −17.0 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.40-7.10 (m, 26H), 3.67-3.56 (m, 1H), 3.06-2.88 (m, 3H), 3.00 (s, 3H), 2.94 (s, 3H), 2.42-2.30 (m, 2H), 1.67-1.48 (m, 5H), 1.28-0.86 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.5, 164.3, 162.7, 154.7, 133.7, 132.4, 132.0, 131.3, 131.0, 130.8, 130.4, 128.9, 128.8, 128.5, 128.1, 128.0, 127.9, 127.6, 127.3, 126.2, 125.7, 125.3, 124.9, 105.9, 67.4, 56.9, 43.9, 36.5, 31.5, 27.8, 24.5, 23.6; HRMS (TOF^+) calcd. for $C_{50}H_{50}N_4O_2$ $[M+H]^+$ 739.4007, found 739.4005.

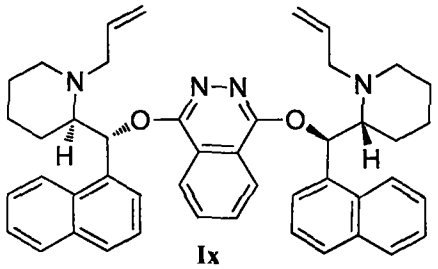
1,4-Bis((*S*)-((*S*)-1-methyl-2-piperidyl)(1-naphthyl)methoxy)-9,10-nonanedione (**Iw**):



Iw

407 mg, yield 57%, brown solid; mp 149-148°C; $[\alpha]_D^{25}$= −39.1 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 8.66-6.80 (m, 22H), 3.63-3.55 (m, 2H), 3.29-3.25 (m, 1H), 2.80-2.70 (m, 2H), 2.06 (s, 6H), 1.92-1.37 (m, 8H), 1.21-0.95 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 182.6, 182.1, 176.8, 155.8, 138.5, 134.2, 134.0, 133.9, 133.6, 133.0, 131.5, 131.4, 129.6, 129.1, 127.3, 126.8, 126.4, 126.3, 125.5, 123.9, 123.8, 120.7, 69.2, 57.6, 43.8, 27.5, 23.9, 23.4, 22.9; HRMS (TOF^+) calcd. for $C_{48}H_{46}N_2O_4$ $[M+H]^+$ 715.5179, found 715.5172.

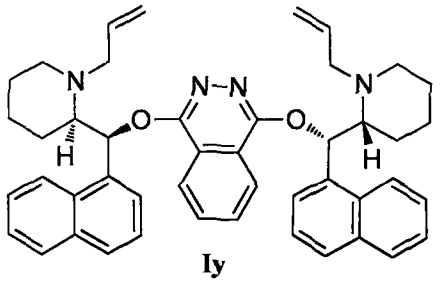
1,4-Bis((*R*)-((*R*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)phthalazine (**Ix**):



Ix

523.6 mg, yield 76%, light yellow solid; mp 97-98°C; $[\alpha]_D^{25}$= –23.9 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.53-7.32 (m, 20H), 6.09-5.99 (m, 2H), 5.42-5.25 (m 4H), 3.98-3.93 (m, 2H), 3.53-3.50 (m, 2H), 3.20-3.04 (m, 4H), 2.41-2.35 (m, 2H), 2.13-2.05 (m, 2H), 1.86-1.82 (m, 2H), 1.64-1.59 (m, 4H), 1.21-1.12 (m, 3H), 0.91-0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 156.5, 133.9, 131.9, 131.8, 130.7, 128.8, 128.0, 126.0, 125.5, 125.0, 124.1, 123.8, 123.5, 123.2, 122.8, 122.6, 72.2, 63.7, 62.8, 56.9, 53.0, 24.9, 24.1; HRMS (TOF^+) calcd. for $C_{46}H_{48}N_4O_2$ $[M+H]^+$ 689.6225, found 689.6231.

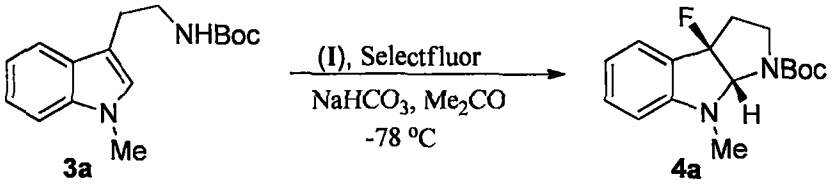
1,4-Bis((*S*)-((*R*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)phthalazine (**Iy**):



Iy

523.6 mg, yield 76%, light yellow solid; mp 96-97°C; $[\alpha]_D^{25}$= 45.3 (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.53-7.32 (m, 20H), 6.09-5.99 (m, 2H), 5.42-5.25 (m 4H), 3.98-3.93 (m, 2H), 3.53-3.50 (m, 2H), 3.20-3.04 (m, 4H), 2.41-2.35 (m, 2H), 2.13-2.05 (m, 2H), 1.86-1.82 (m, 2H), 1.64-1.59 (m, 4H), 1.21-1.12 (m, 3H), 0.91-0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.8, 156.5, 133.9, 131.9, 131.8, 130.7, 128.8, 128.0, 126.0, 125.5, 125.0, 124.1, 123.8, 123.5, 123.2, 122.8, 122.6, 72.2, 63.7, 62.8, 56.9, 53.0, 24.9, 24.1; HRMS (TOF^+) calcd. for $C_{46}H_{48}N_4O_2$ $[M+H]^+$ 689.6225, found 689.6231.

Example 2: Different Chiral Bisamino-ether Compounds Used for Asymmetric Fluorocyclization of **3a**



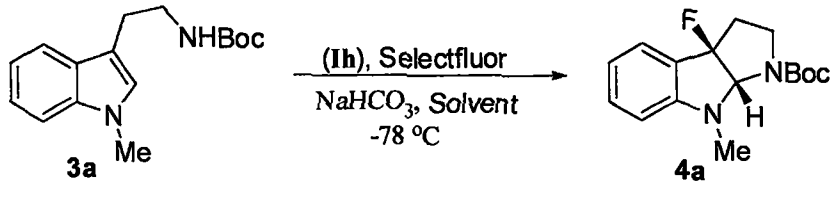
In a 10 mL round-bottom flask were added **3a** (27.6 mg, 0.1 mmol), sodium bicarbonate ($NaHCO_3$, 10.1 mg, 0.12 mmol), chiral bisamino-ether compound **I** (0.12 mmol) and 2.5 mL of

acetone, and the mixture was stirred at -78 °C for 15 minutes. Then, a bis(tetrafluoroborate) salt of l-4-fluoro-1,4-diazabicyclo[2.2.2]octane (Selectfluor, 42.5 mg, 0.12 mmol) was added. After the reaction being completed, the reaction mixture was concentrated by rotary evaporation at room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give **4a**. The ee value was analyzed by chiral HPLC, and the experimental results are shown in Table 1.

Table 1: Different Chiral Bisamino-ether Compounds Used for Asymmetric Fluorocyclization of **3a**

I	Reaction time (h)	Yield (%)	ee value (%)
Ia	48	59	13
Ig	48	75	86
Iu	48	46	-22
Ih	48	80	93
If	72	55	14
Il	48	65	79
In	48	60	19
Ik	48	55	26

Example 3: Different Solvents Used for Asymmetric Fluorocyclization of **3a**

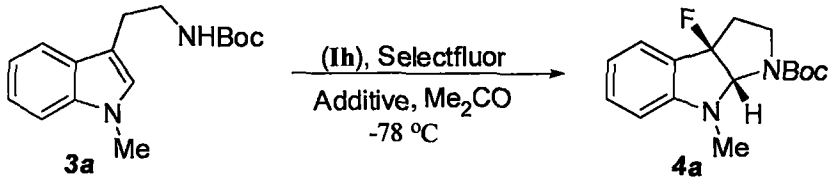


In a 10 mL round-bottom flask were added **3a** (27.6 mg, 0.1 mmol), $NaHCO_3$ (10.1 mg, 0.12 mmol), chiral bisamino-ether compound **Ih** (82.6 mg, 0.12 mmol) and a solvent (2.5 mL), and the mixture was stirred at -78 °C for 15 minutes. Then, Selectfluor (42.5 mg, 0.12 mmol) was added. After the reaction being completed, the reaction mixture was concentrated by rotary evaporation at room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give **4a**. The ee value was analyzed by chiral HPLC, and the experimental results are shown in Table 2.

Table 2: Different Solvents for Asymmetric Fluorocyclization of **3a**

Solvent	Reaction time (h)	Yield (%)	ee value (%)
Me_2CO	48	80	93
MeOH	48	55	33
PhMe	96	<5	-
MeCN	48	47	51
EtOAc	96	<5	-
THF	72	50	48
CH_2Cl_2	96	<5	-

Example 4: Different Additives for Asymmetric Fluorocyclization of **3a**

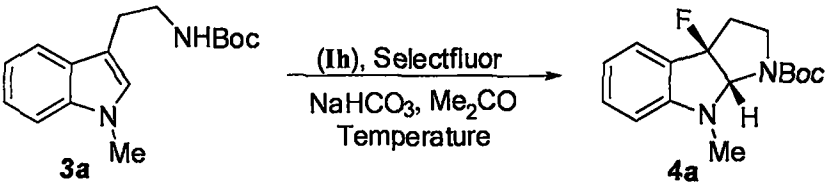


In a 10 mL round-bottom flask were added **3a** (27.6 mg, 0.1 mmol), an additive (0.12 mmol), chiral bisamino-ether compound **Ih** (82.6 mg, 0.12 mmol), and acetone (2.5 mL), and the mixture was stirred at -78 °C for 15 minutes. Then, Selectfluor (42.5 mg, 0.12 mmol) was added. After the reaction being completed, the reaction mixture was concentrated by rotary evaporation room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give **4a**. The ee value was analyzed by chiral HPLC, and the experimental results are shown in Table 3.

Table 3: Different Additives for Asymmetric Fluorocyclization of **3a**

Additive	Reaction time (h)	Yield (%)	ee value (%)
$NaHCO_3$	48	80	93
$KHCO_3$	48	76	88
Na_2CO_3	48	71	87
K_2CO_3	48	64	83
Cs_2CO_3	48	57	79

Example 5: Different Temperatures for Asymmetric fluorocyclization of **3a**

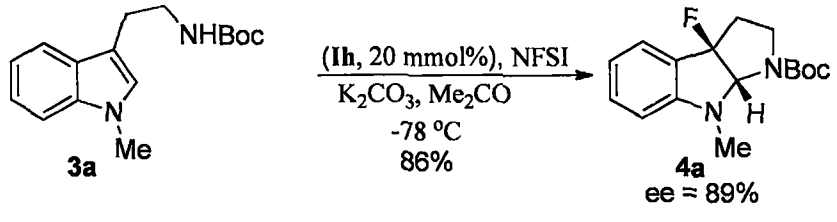


In a 10 mL round-bottom flask were added **3a** (27.6 mg, 0.1 mmol), $NaHCO_3$ (10.1 mg, 0.12 mmol), chiral bisamino-ether compound **Ih** (82.6 mg, 0.12 mmol), and acetone (2.5 mL), and the mixture was stirred at different temperatures for 15 minutes. Then, Selectfluor (42.5 mg, 0.12 mmol) was added. After the reaction being completed, the reaction mixture was concentrated by rotary evaporation at room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give **4a**. The ee value was analyzed by chiral HPLC, and the experimental results are shown in Table 4:

Table 4: Different Temperatures for Asymmetric Fluorocyclization of **3a**

Temperature (°C)	Reaction time (h)	Yield (%)	ee value (%)
-78	48	80	93
-40	24	65	45
-20	24	54	37
0	12	55	30

Example 6: Chiral Bisamino-ether Compound **Ih** for Catalytic Enantioselective Fluorocyclization of **3a**



In a 10 mL round-bottom flask were added **3a** (27.6 mg, 0.1 mmol), K_2CO_3 (20.7 mg, 0.15 mmol), chiral bisamino-ether compound **Ih** (13.8 mg, 0.02 mmol) and acetone (1 mL), and the mixture was stirred at -78 °C for 15 minutes. Then, N-fluorobisbenzenesulfonamide (NFSI, 37.8 mg, 0.12 mmol) was added and reacted for 72 hours. The reaction mixture was concentrated by rotary evaporation at room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give 25.1 mg of **4a**, with yield of 86% and ee value of 89% as analyzed with chiral HPLC.

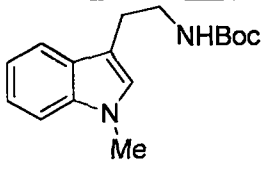
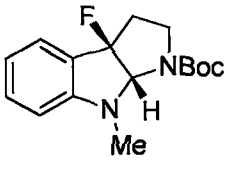
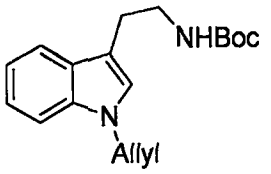
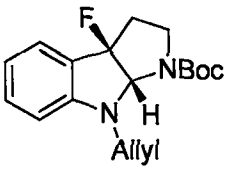
Example 7: Asymmetric Fluorocyclization of the Substrate **3a-s**

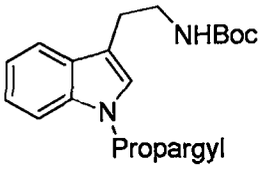
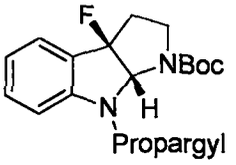
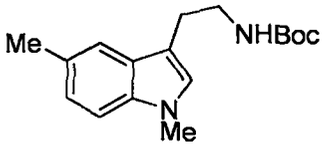
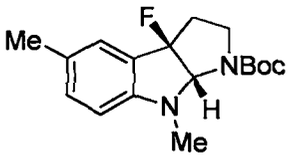
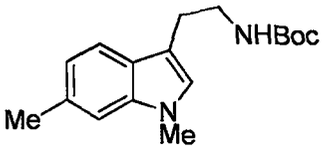
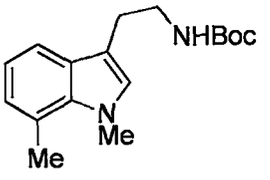
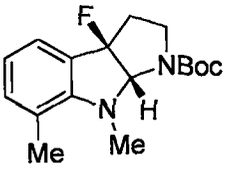
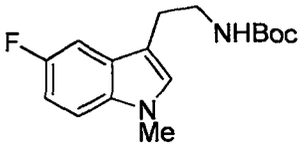
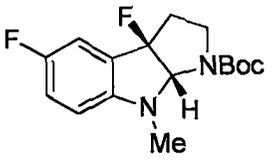
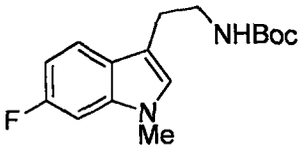
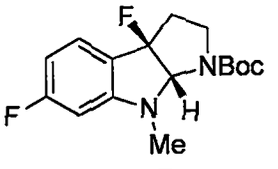
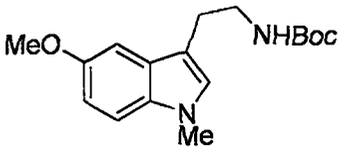
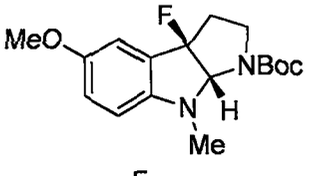
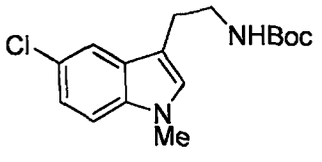
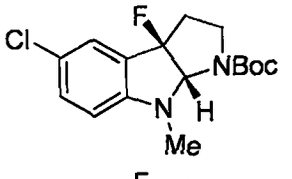
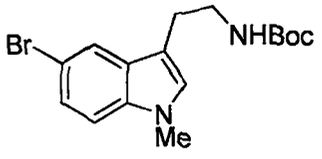
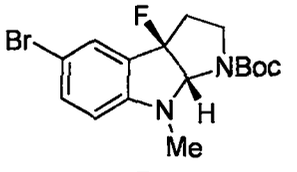
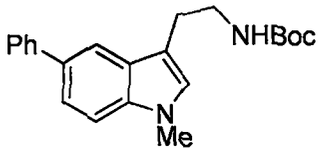
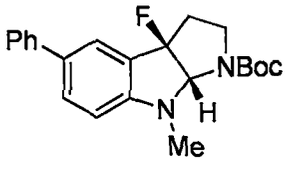
In a 10 mL round-bottom flask were added **3** (0.1 mmol), sodium bicarbonate ($NaHCO_3$, 10.1 mg, 0.12 mmol), chiral bisamino-ether compound **Ih** (82.6 mg, 0.12 mmol) and acetone (2.5 mL), and the mixture was stirred at -78 °C for 15 minutes. Then a bis(tetrafluoroborate) salt of 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane (Selectfluor, 42.5 mg, 0.12 mmol) was added. After the reaction being completed, the reaction mixture was concentrated by rotary evaporation at room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give **4**. The ee value was analyzed by chiral HPLC, and the experimental results are shown in Table 7.

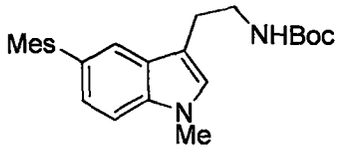
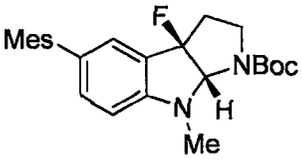
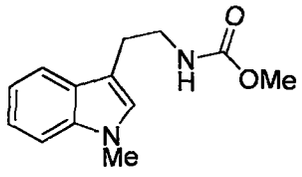
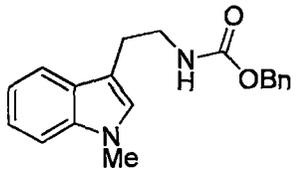
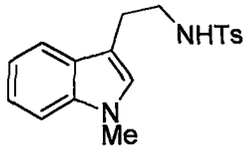
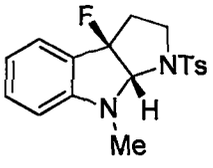
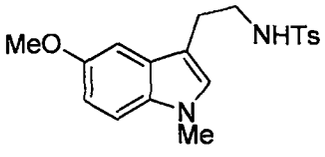
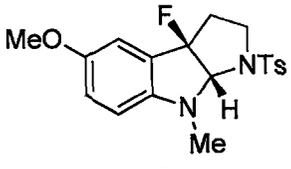
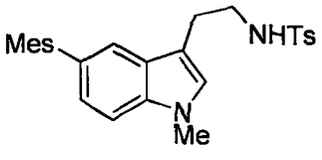
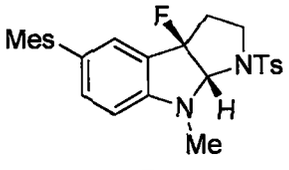
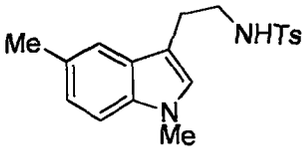
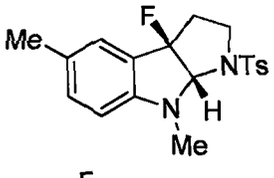
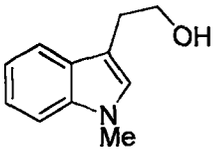
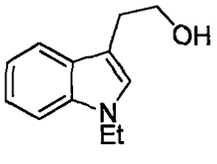
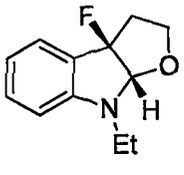
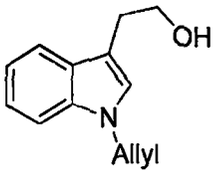
Example 8: Asymmetric fluorocyclization of the Substrate **3aa-an**

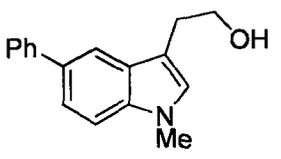
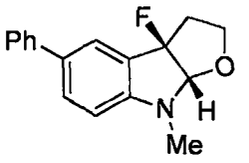
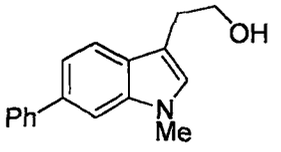
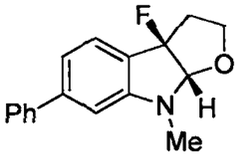
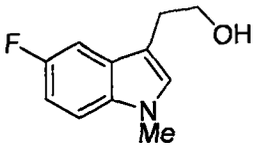
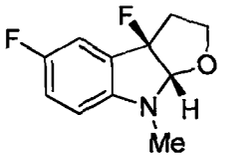
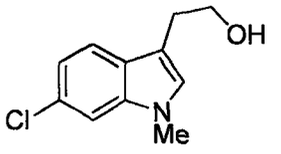
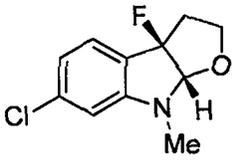
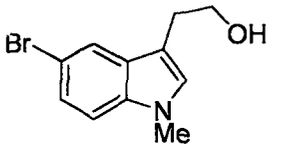
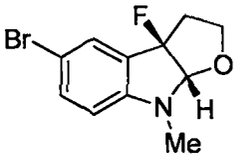
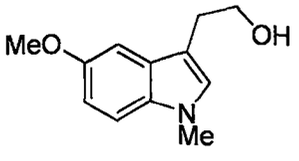
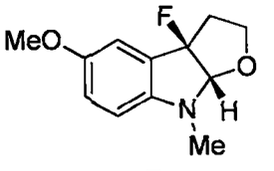
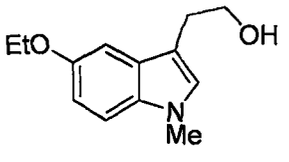
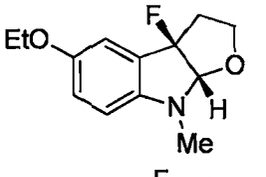
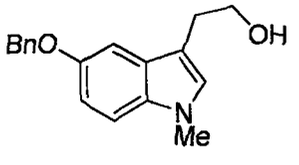
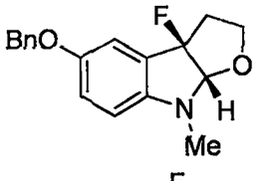
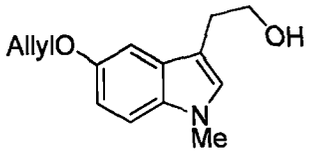
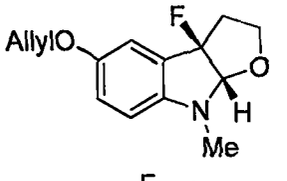
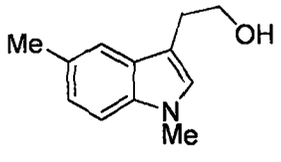
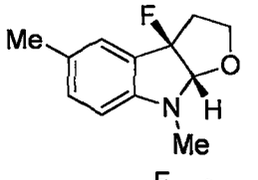
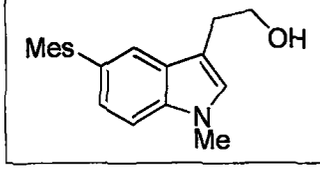
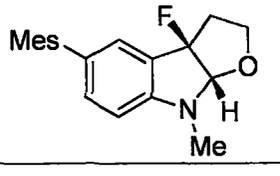
In a 10 mL round-bottom flask were added **3** (0.1 mmol), sodium bicarbonate ($NaHCO_3$, 10.1 mg, 0.12 mmol), chiral bisamino-ether compound **Ig** (76.3 mg, 0.12 mmol) and acetone (2.5 mL), and the mixture was stirred at -78 °C for 15 minutes. Then a bis(tetrafluoroborate) salt of 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane (Selectfluor, 42.5 mg, 0.12 mmol) was added. After the reaction being completed, the reaction mixture was concentrated by rotary evaporation at room temperature, and then water (1 mL) was added. The mixture was extracted with ethyl acetate (5 mL×3), and the organic phases were combined and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated by rotary evaporation to remove solvent. The residue was separated with silica gel column chromatography (petroleum ether/ethyl acetate = 6:1, v/v) to give **4**. The ee value was analyzed by chiral HPLC, and the experimental results are shown in Table 7.

Table 7: Results of Asymmetric Fluorocyclization for Substrate **3**

Substrate **3**		Product **4**		Reaction time (h)	Yield (%)	ee value (%)
	**3a**		**4a**	48	80	93
	**3b**		**4b**	48	40	55

	**3c**		**4c**	72	31	54
	**3d**		**3d**	48	80	95
	**3e**		**4e**	48	76	81
	**3f**		**4f**	48	77	85
	**3g**		**4g**	72	69	82
	**3h**		**4h**	48	61	80
	**3i**		**4i**	48	39	81
	**3j**		**4j**	48	64	90
	**3k**		**4k**	48	59	90
	**3l**		**4l**	72	60	86

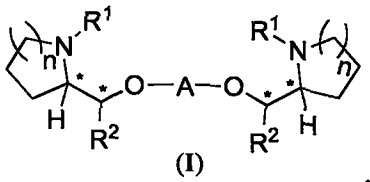
	**3m**		**4m**	72	63	86
	**3n**		**4n**	48	65	80
	**3o**		**4o**	72	69	86
	**3p**		**4p**	72	75	77
	**3q**		**4q**	72	67	89
	**3r**		**4r**	72	63	93
	**3s**		**4s**	72	68	84
	**3aa**		**4aa**	48	72	91
	**3ab**		**4ab**	48	68	86
	**3ac**		**4ac**	48	64	77

	**3ad**		**4ad**	72	67	92
	**3ae**		**4ae**	72	70	86
	**3af**		**4af**	48	62	88
	**3ag**		**4ag**	72	63	85
	**3ah**		**4ah**	72	60	64
	**3ai**		**4ai**	48	61	94
	**3aj**		**4aj**	48	70	96
	**3ak**		**4ak**	72	68	96
	**3al**		**4al**	48	69	94
	**3am**		**4am**	48	70	91
	**3an**		**4an**	72	65	99

Although particular embodiments and examples have been herein described in detail, the above description has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the invention. In particular, it is contemplated by the inventor that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as claimed.

CLAIMS

1. A chiral bisamino-ether compound, having a structure of formula (I):

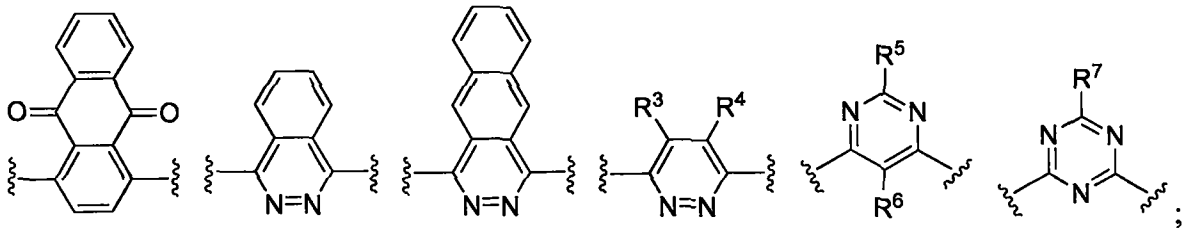


(I)

,

wherein:

n = 1 or 2; chiral center * has (*R*) or (*S*) configuration; and is one of the following moieties:



;

R^1 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, haloalkyl, C_1-C_8 alkoxyl, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxyl substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxyl substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, and C_2-C_8 acyloxyl substituted phenyl;

R^2 is selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, haloalkyl, C_1-C_8 alkoxyl, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxyl substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxyl substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, C_2-C_8 acyloxyl substituted phenyl, naphthyl, pyridyl, quinolyl, isoquinolinyl, furyl, and thienyl;

R^3, R^4, R^5, R^6 and R^7 may be the same or different, and are each independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, haloalkyl, C_1-C_8 alkoxyl, C_1-C_8 acyl, C_2-C_8 acyloxyl, C_2-C_8 ester group, (C_1-C_8 acyl)amino, di(C_1-C_8 alkyl)amino, halogen, amino, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxyl substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxyl substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, C_2-C_8 acyloxyl substituted phenyl, naphthyl, pyridyl, quinolyl, isoquinolinyl, furyl and thienyl.

2. The chiral bisamino-ether compound of claim 1, wherein:

the C_1-C_8 alkyl is methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl , isoamyl, neopentyl, sec-pentyl, tert-amyl, cyclopentyl, n-hexyl, isohexyl, neohexyl, sec-hexyl, tert-hexyl, cyclohexyl, n-heptyl, isoheptyl, neoheptyl , n-heptyl, tert-heptyl, cycloheptyl, n-octyl, isooctyl, neooctyl, sec-octyl, tert-octyl, or cyclooctyl;

the C_1-C_9 unsaturated alkyl is allyl, 2-methylpropyl, cis-n-butenyl, trans-2-butenyl, 3,3-dimethylallyl, cis-2-pentenyl, trans-2-pentenyl, propargyl, benzyl, or 1-phenyl-1-propenyl;

the haloalkyl is halogenated alkyl with halogen being fluorine, chlorine, bromine or iodine;

the C_1-C_8 alkoxy is methoxyl, ethoxyl, n-propoxyl, isopropoxyl, cyclopropoxyl, n-butoxyl, iso-butoxyl, sec-butoxyl, tert-butoxyl, cyclobutoxyl, n-pentyloxyl, iso-pentyloxyl, neo-pentyloxyl, sec-pentyloxyl, tert-pentyloxyl, cyclopentyloxyl, n-hexyloxyl, iso-hexyloxyl, neo-hexyloxyl, sec-hexyloxyl, tert-hexyloxyl, cyclohexyloxyl, n-heptyloxyl, iso-heptyloxyl, neo-heptyloxyl, sec-heptyloxyl, tert-heptyloxyl, cycloheptyloxyl, n-octyloxyl, iso-octyloxyl, neo-octyloxyl, sec-octyloxyl, tert-octyloxyl, or cyclooctyloxyl;

the C_1-C_8 acyl is formyl, acetyl, propionyl, n-butyryl, iso-butyryl, n-valeryl, iso-valeryl, neo-valeryl, sec-valeryl, n-hexanoyl, iso-hexanoyl, neo-hexanoyl , sec-hexanoyl, n-heptanoyl, iso-heptanoyl, neo-heptanoyl, sec-heptanoyl, n-octanoyl, iso-octanoyl, neo-octanoyl, sec-octanoyl, 1-cyclopropylformyl, 1-cyclobutylformyl, 1-cyclopentylformyl, 1-cyclohexylformyl, or 1-cycloheptylcarbonyl;

the C_2-C_8 acyloxyl is acetoxyl, propionyloxyl, n-butyryloxyl, iso-butyryloxyl, n-pentanoyloxyl, iso-valeryloxyl, sec-pentanoyloxyl, neo- pentanoyloxyl, n-hexanoyloxyl, iso-hexanoyloxyl, sec-hexanoyloxyl, neo-hexanoyloxyl, n-heptanoyloxyl, iso-heptanoyloxyl, sec-heptanoyloxyl, neo-heptanoyloxyl, n-octanoyloxyl, iso-octanoyloxyl, sec-octanoyloxyl, neo-octanoyloxyl, 1-cyclopropylcarbonyloxyl, 1-cyclobutylcarbonyloxyl, 1-cyclopentylcarbonyl, 1-cyclohexylcarbonyloxyl, or 1-cycloheptylcarbonyl;

the C_2-C_8 ester group is methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, iso-butoxycarbonyl, n-pentyloxycarbonyl, iso-pentyloxycarbonyl, neo-pentyloxycarbonyl, sec-pentyloxycarbonyl, tert-pentyloxycarbonyl, cyclopentyloxycarbonyl, n-hexyloxycarbonyl, iso-hexyloxycarbonyl, sec-hexyloxycarbonyl, neo-hexyloxycarbonyl, tert-hexyloxycarbonyl, cyclohexyloxycarbonyl, n-heptyloxycarbonyl, iso-heptyloxycarbonyl, neo-heptyloxycarbonyl, sec-heptyloxycarbonyl, tert-heptyloxycarbonyl, or cycloheptyloxycarbonyl.

3. The chiral bisamino-ether compound of claim 1, comprising a racemate, dextroisomer and laevoisomer having same chemical formula but different stereo structures and optical rotation properties.

4. The chiral bisamino-ether compound of claim 1, the compound being selected form the group consisting of:

1,4-Bis((*R*)-((*S*)-1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Ia**);

1,4- Bis((*R*)-((*S*)-1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Ib**);

1,4-Bis((*R*)-((*S*)-1-methyl-2-pyrrolyl)(4-trifluoromethylphenyl)methoxy)phthalazine (**Ic**);

1,4-Bis((*R*)-(2-methoxyphenyl)((*S*)-1-methyl-2-pyrrolyl)methoxy)phthalazine (**Id**);

4,6-Bis((*R*)-((*S*)- 1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Ie**);

4,6-Bis((*R*)-((*S*)- 1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**If**);

1,4-Bis((*R*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)phthalazine (**Ig**);

1,4-Bis((*R*)-((*S*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)phthalazine (**Ih**);

3,6-Bis((*R*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)pyridazine (**Ii**);

4,6-Bis((*R*)-((*S*)-1-methyl-2-piperidyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Ij**);

2-Methyl-4,6-bis((*R*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)pyrimidine (**Ik**);

1,4-Bis((*R*)-(1-naphthyl)((*S*)-1-propyl-2-piperidyl)methoxy)phthalazine (**Il**);

4,6-Bis((*R*)-((*S*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)-2-methylpyrimidine (**Im**);

3,6-Bis((*R*)-((*S*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)pyridazine (**In**);

1,4-Bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(phenyl)methoxy)phthalazine (**Io**);

1,4-Bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Ip**);

1,4-Bis((*S*)-((*S*)-1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)phthalazine (**Iq**);

1,4-Bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(4-trifluoromethylphenyl)methoxy)phthalazine (**Ir**);

4,6-bis((*S*)-((*S*)-1-methyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Is**);

4,6-bis((*S*)-((*S*)-1-allyl-2-pyrrolyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**It**);

1,4-Bis((*S*)-((*S*)-1-methyl-2-piperidinyl)(1-naphthyl)methoxy)phthalazine (**Iu**);

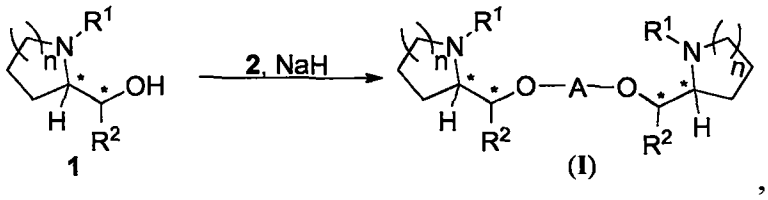
4,6-Bis((*S*)-((*S*)-1-methyl-2-piperidyl)(1-naphthyl)methoxy)-2,5-diphenylpyrimidine (**Iv**);

1,4-Bis((*S*)-((*S*)-1-methyl-2-piperidyl)(1-naphthyl)methoxy)-9,10-nonanedione (**Iw**);

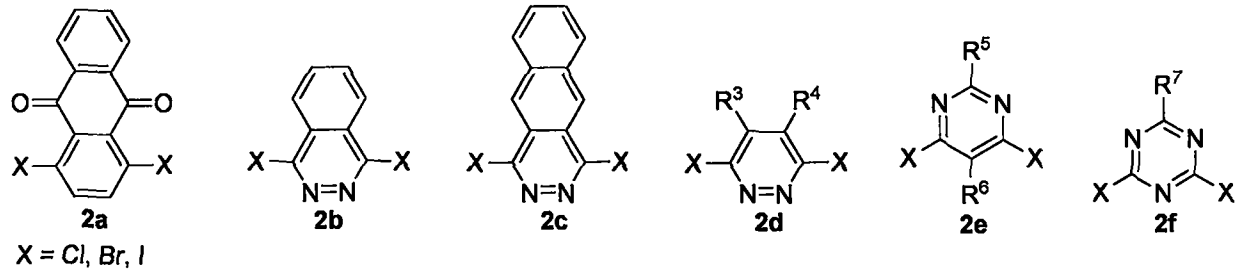
1,4-Bis((*R*)-((*R*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)phthalazine (**Ix**); and

1,4-Bis((*S*)-((*R*)-1-allyl-2-piperidyl)(1-naphthyl)methoxy)phthalazine (**Iy**).

5. A method of preparation of the chiral bisamino-ether compound of claim 1, the method comprising: chiral amino-methanol compound **1**, 2 mmol, being reacted with a base, 2-4 mmol, in an organic solvent for 5-30 minutes, and then further reacted with halogenated aryl compound **2**, 1-2 mmol, at 0-160 °C for 2-96 hours to give a chiral bisamino-ether compound (**I**) with different substituent groups:



wherein: n = 1 or 2; R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are defined as in claim 1; the halogenated aryl compound **2** is selected from the group consisting of:

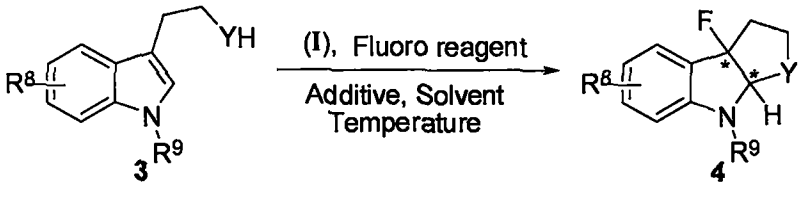


X = Cl, Br, I

6. The method of claim 5, wherein the organic solvent is dimethylformamide, dichloromethane, dichloroethane, tetrahydrofuran, 1,4-dioxane, toluene, xylene, trimethylbenzene, chlorobenzene, dichlorobenzene, or any combination thereof.

7. The method of claim 5, wherein the base is sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, or any combination thereof.

8. A use of the chiral bisamino-ether compound of claim 1, wherein the use comprises: using the chiral bisamino-ether compound **I** in asymmetric fluorocyclization of unsaturated heterocyclic compound **3**:



YH = NHBoc, NHTs, NHCOOBn, NHCOOMe, OH

wherein: R^8 and R^9 may be the same or different, and are each independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, C_1-C_9 unsaturated alkyl, halogen, haloalkyl, C_1-C_8 alkoxyl, phenyl, C_1-C_8 alkyl substituted phenyl, halophenyl, hydroxy substituted phenyl, amino substituted phenyl, di(C_1-C_8 alkyl)amino substituted phenyl, C_1-C_8 alkoxy substituted phenyl, C_1-C_8 acyl substituted phenyl, (C_1-C_8 acyl)amino substituted phenyl, C_2-C_8 ester group-substituted phenyl, C_2-C_8 acyloxy substituted phenyl, or naphthyl; the fluoro reagent is bis(tetrafluoroborate) salt of 1-chloromethyl-4-fluoro-1,4-diazabicyclo[2.2.2]octane or

N-fluorobisbenzenesulfonamide; and the position marked by asterisk (*) is a chiral center.

9. The use of claim 8, wherein reaction being carried out by adding the chiral bisamino-ether compound (**I**) and the substrate **3** into a round bottom flask, adding an additive and a solvent, adding the fluoro reagent, and then stirring the reaction at a specified temperature until the completion of the reaction.

10. The use of claim 8, wherein reaction conditions comprising: the solvent is acetone, acetonitrile, ethyl acetate, tetrahydrofuran, 1,4-dioxane, toluene, dichloromethane, 1,2-dichloroethane, chloroform, or a combination thereof; the chiral bisamino-ether compound (**I**) is in an amount of 10-120 mol%; the substrate **3** is in a concentration of 0.01-10 M; the additive is sodium hydrogencarbonate, potassium hydrogencarbonate, cesium carbonate, sodium carbonate, potassium carbonate, or a combination thereof; the reaction temperature is -78 to 40°C; the reaction time is 2-96 hours.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/000044

A. CLASSIFICATION OF SUBJECT MATTER

C07D 403/14(2006.01)i; C07D 401/14(2006.01)i; C07D 211/22(2006.01)i; C07D 487/04(2006.01)i; C07D 491/048(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

CNKI,CNPAT,WPI,EPODOC,STN,jinan university, the chinese university of hong kong, jiang xiaojian, yang yingyang, bisamino-ether, bisamino ether, amino diether, amino-diether, amino ether, fluorocycli+, fluor+ s cycli+

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	CN 108997321 A (JINAN UNIVERSITY ET AL.) 14 December 2018 (2018-12-14) Claims 1-10	1-10
A	LOZANO,O.et al. "Organocatalyzed Enantioselective Fluorocyclizations" *Angew. Chem. Int. Ed.*, Vol. 50, 12 July 2011 (2011-07-12), ISSN: 1433-7851, pages 8105-8109	1-10
A	LIANG,X.W.et al. "Asymmetric fluorinative dearomatization of tryptamine derivatives" *Chem. Commun.*, Vol. 53, 24 April 2017 (2017-04-24), ISSN: 1539-7345, pages 5531-5534	1-10
A	Cai,Q.et al. "Chiral-Amine-Catalyzed Asymmetric Bromocyclization of Tryptamine Derivatives" *Asian J. Org. Chem.*, Vol. 3, 02 October 2013 (2013-10-02), ISSN: 2193-5815, pages 408-411	1-10

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

* Special categories of cited documents:

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

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2019	**29 May 2019**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **LI,Lei** Telephone No. **86-(10)-53962154**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/000044

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	AFONSO,C.A.M. et al. "Synthesis of 2，4，6-Tri-substituted-1，3，5-Triazines" *Molecules,* Vol. 11, 31 January 2006 (2006-01-31), ISSN: 1420-3049, pages 81-102	1-7
A	FUJIWARA,T. et al. "Synthesis of 10b-fluorinated analogues of protubonine A and its 11a-epimer via fluorocyclisation of tryptophan-containing dipeptides" *RSC Adv.,* Vol. 5, 08 December 2014 (2014-12-08), ISSN: 2046-2069, pages 5464-5473	1-10
A	FUJIWARA,T. et al. "Useful procedures for fluorocyclization of tryptamine and tryptophol derivatives to 3a-fluoropyrrolo[2，3-b]indoles and 3a-fluorofuro[2，3-b]indoles" *Journal of Fluorine Chemistry,* Vol. 165, 04 June 2014 (2014-06-04), ISSN: 0022-1139, pages 7-13	1-10
A	WO 2014068341 A2 (ISIS INNOVATION LIMITED) 08 May 2014 (2014-05-08)	1-10

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/000044

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
CN	108997321	A	14 December 2018	None			
WO	2014068341	A2	26 June 2014	GB	201219820	D0	19 December 2012
				WO	2014068341	A4	14 August 2014
				WO	2014068341	A2	08 May 2014
				EP	2914582	A2	09 September 2015
				US	2015284401	A1	08 October 2015
				US	9701684	B2	11 July 2017