

METHODS FOR PRODUCING INTERMEDIATES OF ELACESTRANT

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to Italian Application No. 102023000021471, filed on October 16, 2023, which is hereby incorporated by reference in its entirety.

BACKGROUND

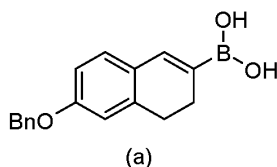
[0002] Breast cancer is the second leading cause of cancer-related death in women, with an estimated 246,660 newly diagnosed cases and 40,450 deaths in the United States alone in 2016. Breast cancer is a heterogeneous disease divided into three subtypes based on expression of three receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2). Overexpression of ERs is found in many breast cancer patients. ER-positive (ER+) breast cancers comprise two-thirds of all breast cancers. Other than breast cancer, estrogen and ERs are associated with ovarian cancer, colon cancer, prostate cancer, and endometrial cancer, among others.

[0003] Elacestrant is an oral nonsteroidal small molecule that acts as a selective estrogen receptor (ER) degrader (SERD). Elacestrant has been approved by the Food and Drug Administration (FDA) for treating postmenopausal women or adult men with ER-positive, HER2-negative, estrogen receptor gene α (ESR1)-mutated advanced or metastatic breast cancer with disease progression following at least one line of endocrine therapy.

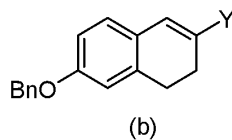
[0004] Thus, improved commercial-scale methods of synthesizing elacestrant, and intermediates thereof, would be highly advantageous.

SUMMARY

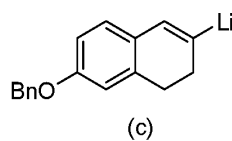
[0005] In one aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a process of preparing a compound of Formula (a):



the process comprising: reacting a compound of Formula (b):



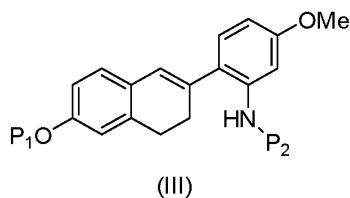
with a lithiation reagent to form a compound of Formula (c):



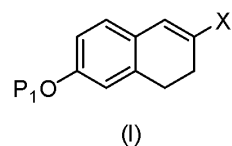
[0006] wherein the compound of Formula (c) is reacted with a borate ester and is hydrolyzed to form the compound of Formula (a), wherein Y is Br, Cl, or I.

[0007] In some embodiments, the lithiation reagent is *n*-butyl lithium. In some embodiments, the borate ester is triisopropyl borate. In some embodiments, the process is carried out in continuous flow mode or in batch mode. In some embodiments, the process is carried out in continuous flow mode.

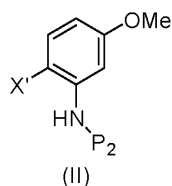
[0008] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a process of preparing a compound of Formula (III):



the process comprising reacting a compound of Formula (I):



with a compound of Formula (II):

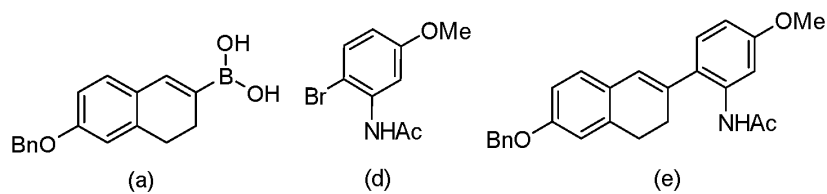


in the presence of a transition metal catalyst, a base, and a solvent, wherein P_1 is H or a phenol protecting group; P_2 is H, Et, or an amino protecting group; X is a halogen or $B(OH)_2$; and X' is a halogen or $B(OH)_2$; wherein X and X' are suitable for cross-coupling of Formula (I) with Formula (II).

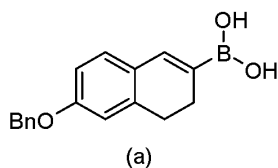
[0009] In some embodiments, X is $B(OH)_2$. In some embodiments, P_1 is H or a phenol protecting group selected from $(C=O)-C_1-C_8$ alkyl, $(C=O)-aryl$, $(C=O)-heteroaryl$, $Si(C_1-C_5 alkyl)_3$, $Si(aryl)_2(C_1-C_5 alkyl)$ and CH_2-aryl ; P_2 is H, Et, or an amino protecting group selected from $(C=O)-C_1-C_8$ alkyl, $(C=O)-aryl$, $(C=O)-heteroaryl$, $(C=O)-O-C_1-C_8 alkylaryl$, or $(C=O)-(CH_2)_n-C=O$ - wherein n is 2 or 3; X is Cl, Br, I, or $B(OH)_2$; and X' is Cl, Br, I, or $B(OH)_2$, wherein when X is $B(OH)_2$, X' is Cl, Br, or I. In some embodiments, P_1 is CH_2-aryl ; P_2 is $(C=O)-C_1$ alkyl; X is $B(OH)_2$; and X' is Cl, Br, or I.

[0010] In some embodiments, the transition metal catalyst is a palladium-containing catalyst. In some embodiments, the transition metal catalyst contains Pd(0). In some embodiments, the transition metal catalyst comprises or consists of Pd/C. In some embodiments, the base is an inorganic base, an organic base, or a combination thereof. In some embodiments, the base is selected from K_2CO_3 , KOtBu, CS_2CO_3 , Na_3PO_4 , K_3PO_4 , KOH, NaOH, CsOH, LiOH, NEt_3 , and combinations thereof. In some embodiments, the base is Na_3PO_4 .

[0011] In some embodiments, the compounds of Formulas (I), (II), and (III) are (a), (d) and (e):

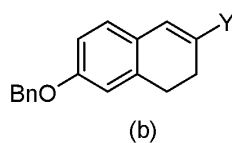


[0012] In some embodiments, the compound of Formula (I) is a compound of Formula (a):

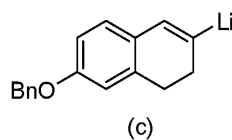


wherein the compound of Formula (a) is prepared by a process comprising:

reacting a compound of Formula (b):



with a lithiation reagent to form a compound of Formula (c):

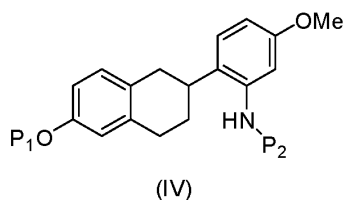


wherein the compound of Formula (c) is reacted with a borate ester and is hydrolyzed to form the compound of Formula (a), wherein Y is Br, Cl, or I.

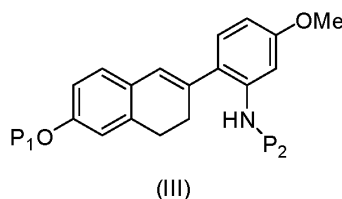
[0013] In some embodiments, the lithiation reagent is *n*-butyl lithium. In some embodiments, the borate ester is triisopropyl borate.

[0014] In some embodiments, the process of preparing the compound of Formula (a) is carried out in continuous-flow mode or in batch mode. In some embodiments, the process of preparing the compound of Formula (a) is carried out in continuous-flow mode.

[0015] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a process of preparing a compound of Formula (IV):



the process comprising reduction of a compound of Formula (III):

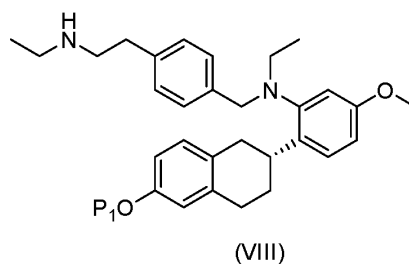


in the presence of a transition metal catalyst comprising Pd(0), wherein P₁ is H or a phenol protecting group and P₂ is H, Et, or an amino protecting group.

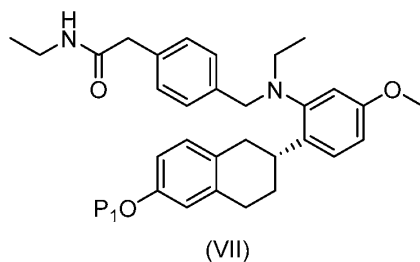
[0016] In some embodiments, P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, or (C=O)-(CH₂)_n-C=O)- wherein n is 2 or 3. In some embodiments, P₁ is CH₂-aryl and P₂ is (C=O)-C₁ alkyl.

[0017] In some embodiments, the transition metal catalyst comprises Pd/C. In some embodiments, the reduction is conducted in the presence of H₂. In some embodiments, the process is carried out using continuous-flow mode or batch-mode. In some embodiments, the process is carried out using continuous-flow mode.

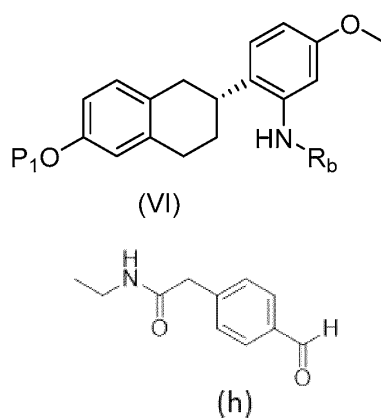
[0018] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a process of preparing a compound of Formula (VIII):



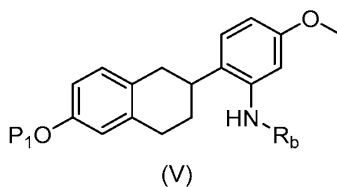
the process comprising reducing a compound of Formula (VII):



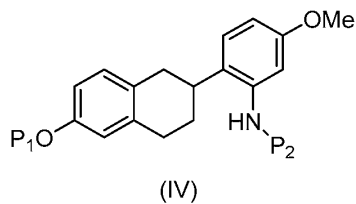
wherein the compound of Formula (VII) is prepared by reductive amination of a compound of Formula (VI) in the presence of a compound of Formula (h):



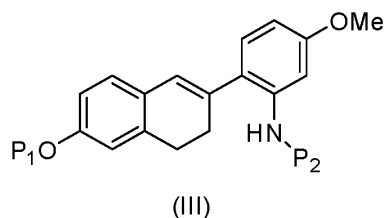
wherein the compound of Formula (VI) is prepared by reacting a compound of Formula (V)



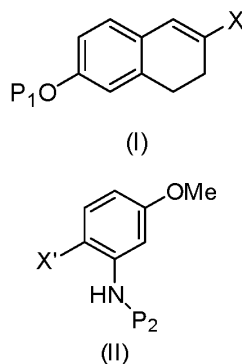
with a chiral acid to form an enantiomerically enriched salt, crystallizing the enantiomerically enriched salt, and freeing the compound of Formula (VI), wherein the compound of Formula (V) is prepared by treating a compound of Formula (IV) with a deprotecting agent:



wherein the compound of Formula (IV) is prepared by reduction of a compound of Formula (III):



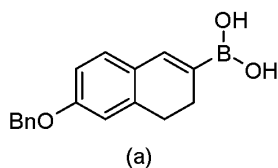
wherein reduction of the compound of Formula (III) is carried out using a Pd(0) catalyst; wherein the compound of Formula (III) is prepared by coupling a compound of Formula (I) with a compound of Formula (II):



and wherein P₁ is H or a phenol protecting group; R_b is H or Et; P₂ is (C=O)-C₁ alkyl; X is a halogen or a boronic acid; X' is a halogen or a boronic acid; and wherein X and X' are suitable for cross-coupling the compound of Formula (I) with the compound of Formula (II). In some embodiments, X is a boronic acid, and X' is a halogen. In some embodiments, X is a boronic acid, and X' is Br, Cl, or I.

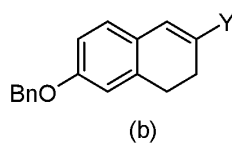
[0019] In some embodiments, reduction of the compound of Formula (III) is carried out using batch mode or continuous-flow mode. In some embodiments, reduction of the compound of Formula (III) is carried out using continuous-flow mode. In some embodiments, the compound of Formula (I) is the compound of Formula (a).

[0020] In some embodiments, the compound of Formula (I) is a compound of Formula (a):

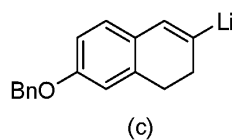


wherein the compound of Formula (a) is prepared by a process comprising:

reacting a compound of Formula (b):



with a lithiation reagent to form a compound of Formula (c):



wherein the compound of Formula (c) is reacted with a borate ester and is hydrolyzed to form the compound of Formula (a), wherein Y is Br, Cl, or I.

[0021] In some embodiments, the lithiation reagent is *n*-butyl lithium. In some embodiments, the borate ester is triisopropyl borate.

[0022] In some embodiments, the process of preparing the compound of Formula (a) is carried out in continuous-flow mode or in batch mode. In some embodiments, the process of preparing the compound of Formula (a) is carried out in continuous-flow mode.

[0023] Both the foregoing summary and the following detailed description are exemplary and explanatory. They are intended to provide further details of the disclosure, but are not to be construed as limiting. Other objects, advantages, and novel features will be readily apparent to those skilled in the art from the following detailed description of the disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] **FIG. 1** shows a schematic of a continuous-flow system for use in Step 1 of the process described herein.

[0025] FIG. 2 shows a schematic of a bubbling bed continuous-flow system that may be used in Step 3 of the process described herein.

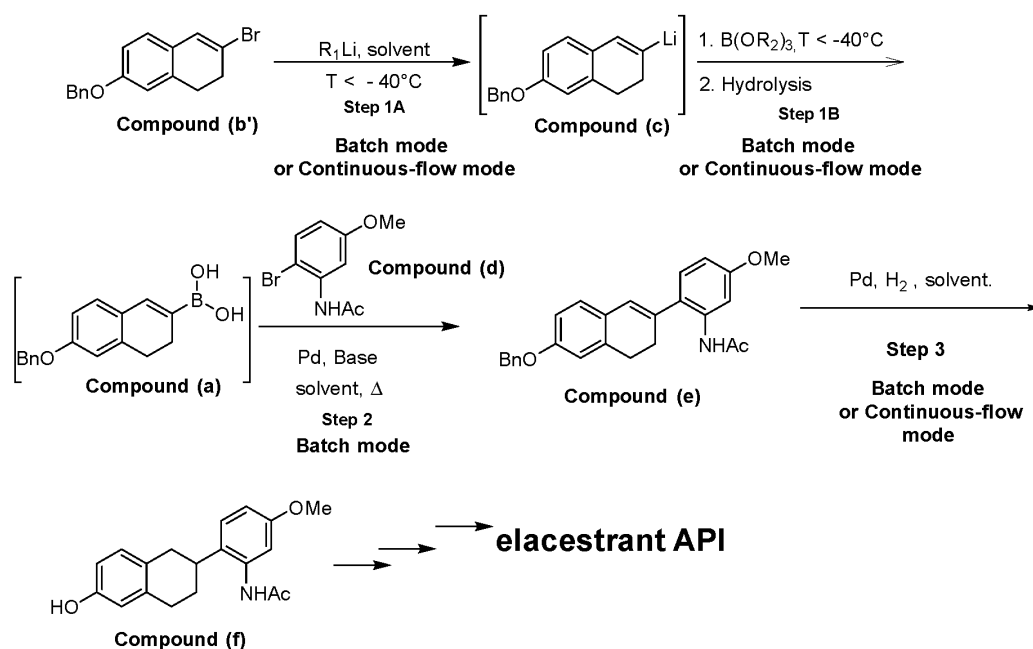
[0026] FIG. 3 shows a schematic for a trickle bed continuous-flow system that may be used in Step 3 of the process described herein.

DETAILED DESCRIPTION

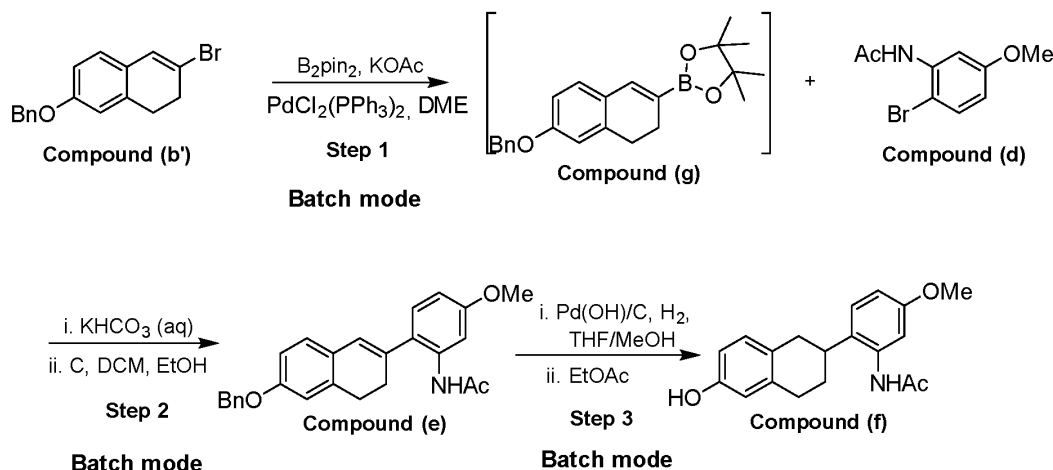
[0027] In one aspect, the present disclosure relates to a 3-step process for the preparation of N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (**Compound (f)**), and more in general to a 3-step process for the preparation of **Compound IV**, an intermediate of the active pharmaceutical ingredient (API) elacestrant, a novel oral SERD aimed to treat breast cancer (**Scheme 1**).

[0028] A previously reported synthesis of intermediate N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)acetamide is shown in **Scheme 2** (PCT/US2020/017777).

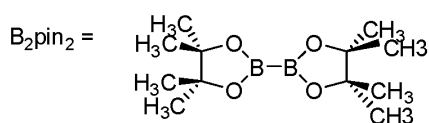
Scheme 1. Synthesis of N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (**Compound (f)**), according to one embodiment of the present disclosure.



Scheme 2. Previously reported synthesis of N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (**Compound (f)**).



→ **elacestrant**
→ **API**



[0029] Although the process shown in **Scheme 2** is a viable method for producing elacestrant, the present inventors endeavored to improve it for improved safety, reduced cost, and improved atom economy.

[0030] In particular, the inventors successfully improved: (1) Step 1 and Step 2, by reducing the quantity of palladium used, which in turn reduces costs and simplifies the purification steps required to separate the palladium from the intermediate **Compound (f)**. In particular, in the current process described in **Scheme 2**, at least two to three treatments with carbon are necessary in order to effectively purge palladium from intermediate **Compound (e)**; (2) Step 2, and in particular the atom economy in the preparation of intermediate **Compound (e)**; and (3) Step 3, by reducing its safety hazards and costs. In particular, in terms of safety, the reduction performed in Step 3 of **Scheme 2** is carried out under hydrogen pressure (~ 7 bar)

in batch mode using small, specialized equipment (a standard 3000-liter hydrogenation reactor), which presents safety risks and possible hydrogen leakage. Furthermore, the use of batch mode in **Scheme 2** allows the manufacture of 500 kg of elacestrant API, but only when: (i) an amount of about 2200 kg of **Compound (e)** is used, and (ii) after carrying out 15 runs of the Step 3 (meaning 15 hydrogenations). The overall production time of Step 3 performed according to **Scheme 2** is about 1200 hours. Advantageously, the use of a continuous-flow hydrogenation in Step 3 results in a substantial savings of production time (about 200 hours vs 1200 hours with the batch process) due to the fact that 500 kg of elacestrant can be produced in only one hydrogenation run (compared to 15 hydrogenations) for an amount of **Compound (e)** of about 2200 kg.

[0031] It should be understood that the known process shown in **Scheme 2** can be improved by replacing one or more of its Steps with one or more solutions disclosed herein for Steps 1, 2, and 3 so that one, some, or all the advantages above described can be achieved. Thus, improvements to any of Step 1, Step 2, or Step 3, alone or in combination, are intended to fall within the scope of this disclosure.

[0032] In particular, regarding (2), the use of bis(pinacolato)diboron (MW= 253.94) to produce the boronic ester (**Compound (g)**), though effective, offers an atom economy of approximately 50%, and no atoms of bis(pinacolato)diboron are finally incorporated in the reaction product, as the boronic ester moiety is a leaving group in the coupling reaction of Step 2 (**Scheme 2**). Additionally, bis(pinacolato)diboron is a high-cost raw material. Moreover, the preparation of boronic ester **Compound (g)** requires the use of a significant amount of a palladium catalyst (2 mol%, relative to **Compound (b')**), creating cost concerns and the need for extensive purification.

[0033] In one embodiment, a different boronic derivative (**Compound (a)**) is used in Step 2, reducing the amount of palladium used: 0.1 mol%, relative to **Compound (b')**, compared to 2 mol%, relative to **Compound (b')**, used in the process shown in **Scheme 2**.

[0034] The preparation of intermediate **Compound (a)** can be performed using either the traditional batch mode or continuous-flow mode.

[0035] Continuous-flow production offers several advantages over batch production: (1) the continuous-flow system has a small spatial footprint, and it is energetically economical due to the small cooled/heated reactor volumes; (2) the small reactor volumes offer improved safety; (3) the continuous-flow apparatus is a closed system which prevents environmental damage, worker exposure, and product contamination. In particular, the preparation of the novel intermediate **Compound (a)** in a continuous-flow mode enables a high level of control over reaction parameters (*e.g.*, reaction temperature, residence time, and stoichiometry) compared to batch mode. The continuous production affords a high and uniform product quality and facilitates industrial-scale production, due to facile scale-up using assessed strategies such as longer operating time, numbering-up, and enlargement of the flow channel. In addition, the continuous-flow technique is more efficient than batch-mode, potentially alleviating the requirements for cryogenic conditions, thereby decreasing the energy consumption.

[0036] Additionally, the use of the intermediate **Compound (a)** has unexpectedly significantly decreased the amount of the toxic palladium catalyst in the Suzuki coupling reaction (Step 2, **Scheme 1**): 0.1 mol%, compared to 2 mol%, relative to **Compound (b')** (**Scheme 2**). In addition to a significant cost savings for palladium, the downstream purification process for separating palladium from **Compound (f)** is much less burdensome due to the fact that, according to **Scheme 1**, **Compound (e)** is obtained with a reaction that is carried out with less palladium compared to that used in the process according to **Scheme 2**. In **Scheme 1**, purification based on absorption of palladium on carbon is realized in the work-up of Step 2. By eliminating use of palladium in Step 1, the amount of palladium used in the process is significantly reduced, and removal of palladium is much more efficient.

[0037] Additionally, the boronic acid derivative **Compound (a)** can be prepared using a relatively cheap raw material (*e.g.*, triisopropyl borate (MW=188.07)) with an overall greater atom economy. **Compound (a)** may be prepared without using palladium catalyst, and even if palladium is used Steps 2 and/or 3, eliminating its use in Step 1 facilitates less burdensome purification to reduce its concentration below acceptable limits in the API.

[0038] In one embodiment, Step 3 (the hydrogenation step, **Scheme 1**) can be performed in continuous-flow mode instead of batch mode.

[0039] The current batch hydrogenation process of **Compound (e)** (Step 3, **Scheme 2**) is relatively time- and energy-consuming, which greatly limits the amount of this intermediate (and consequently of elacestrant) that can be manufactured, resulting in an overall low/unsatisfactory productivity. The continuous-flow hydrogenation of **Compound (e)** in the present disclosure (Step 3, **Scheme 1**) has at least the following advantages over the batch process: (a) hydrogenation using a fixed-bed reactor eliminates the cumbersome operation of catalyst filtration in the batch-mode process; (b) the cycle-time and hence the industrial time occupancy is overall highly decreased; (c) the continuous-flow hydrogenation has significant safety benefits: the pressurized hydrogen and the catalyst are contained in a small, sealed volume, consequently avoiding handling of explosive gas and pyrophoric catalyst; (d) the continuous-flow system warrants high level of control over reaction parameters such as reaction temperature, residence time, and stoichiometry, compared to batch processes; and (e) the continuous production affords a uniformly high product quality and facilitates industrial-scale processing, due to facile scale-up using assessed strategies such as longer operating time, numbering-up, and enlargement of the flow-channel. Accordingly, the use of a continuous-flow hydrogenation improves efficiency and safety, relative to the batch hydrogenation of **Compound (e)**.

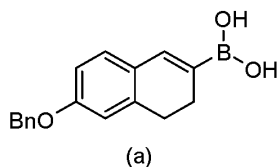
[0040] **FIG. 1** shows a schematic figure of a continuous-flow system that can be used for Step 1 of the processes described herein. As a non-limiting example, a solution of **Compound (b')** in THF and n-butyl lithium in hexane may be continuously pumped through a pre-cooling loop in the continuous-flow reactor (or plug flow reactor, PFR1). After about 30 seconds of reaction at $T = -50\text{ }^{\circ}\text{C} - -40\text{ }^{\circ}\text{C}$, the solution was added to a pre-cooled solution of triisopropyl borate in THF and continuously pumped in PFR2. After 35 seconds of reaction at $T = -50\text{ }^{\circ}\text{C} - -40\text{ }^{\circ}\text{C}$, the reaction mixture is quenched an aqueous solution in the CSTR (Continuous Stirred Tank Reactor) and pumped in a separator removing the aqueous waste. The organic solution flows into the receiving tank for work-up.

[0041] **FIG. 2** shows a schematic of an exemplary bubbling bed continuous-flow system that may be used in Step 3 of the process described herein. There are two feeding solutions: the hydrogen gas, which enters into the hydrogen buffer tank and is operated by a gas mass flowmeter; and a solution containing **Compound (e)**, which was prepared in advance and

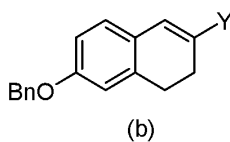
injected into the system using a plunger pump. Both the gas mass flowmeter and the plunger pump are controlled by PLC control system. The two feeding solutions are transported to the bottom of the bubbling bed and travel through the catalyst column (3% w/w Pd/Al₂O₃). The reaction is performed at 40–50°C under a hydrogen pressure of 1 MPa. The biphasic reaction mixture exits from the top of the bubbling bed into a gas-liquid separator. After removing excess gas, the reaction system flows into the receiving tank for work-up.

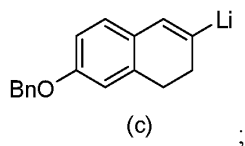
[0042] FIG. 3 shows a schematic for an exemplary trickle bed continuous-flow system that may be used in Step 3 of the process described herein. There are two feeding solutions: hydrogen gas, which enters the hydrogen buffer tank regulated by a gas mass flowmeter; and a solution containing **Compound (e)**, which was prepared in advance and injected into system by a plunger pump. Both gas mass flowmeter and plunger pump are controlled by a PLC control system, the two feeding solutions are transported to the head of the trickle bed and travel through the catalyst column (3% w/w Pd/Al₂O₃). The reaction is performed at 40–50°C under a hydrogen pressure of 1 MPa. The biphasic reaction mixture exits from the bottom of the trickle bed into the gas-liquid separator. After removing excess gas, the reaction system flows into the receiving tank for work-up.

[0043] In some embodiments, Step 1 comprises a process of preparing a compound of Formula (a):



[0044] The compound of Formula (a) may be preparing in two steps: (A) reacting a compound of Formula (b) with a lithiation agent to form a compound of Formula (c);





and (B) reacting compound of Formula (c) with a borate ester to form a boronic ester, followed by acid hydrolysis of the resulting boronic ester to form the compound of Formula (a). In some embodiments, Y is a halogen. In some embodiments, Y is Br, Cl, or I.

[0045] Examples of lithiation reagents include, but are not limited to, methyl lithium, ethyl lithium, propyl lithium, isopropyl lithium, sec-butyl lithium, n-butyl lithium, tert-butyl lithium, or pentyl lithium. In some embodiments, the lithiation reagent is *n*-butyl lithium.

[0046] Exemplary solvents that may be used in Step 1 include, but are not limited to, dimethoxyethane (DME), tetrahydrofuran (THF), DME/methyl tert-butyl ether (MTBE), 2-methyl THF (2-Me-THF)/DME, DME/THF, THF/MTBE, THF/2-Me-THF, or combinations thereof. In some embodiments, the solvent used in Step 1 comprises DME/MTBE.

[0047] Examples of borate esters that may be used in Step 1 include, but are not limited to, trimethyl borate, triethyl borate, tripropyl borate, triisopropyl borate, tributyl borate, or combinations thereof. In some embodiments, the borate ester comprises triisopropyl borate.

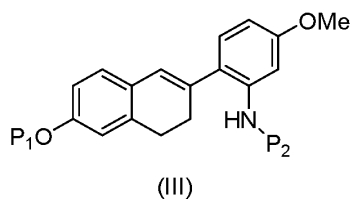
[0048] In some embodiments, Step 1 is carried out under cooling at a temperature from about 0°C to about -80 °C, about -20°C to about -80°C, about -40°C to -75°C; about -30°C to about -65°C, about -35°C to about -65°C, about -35°C to about -60°C, or any range or value therein between.

[0049] In some embodiments, the hydrolysis of the boronic ester is carried out using an aqueous inorganic acid. Non-limiting examples of the inorganic acid include H₂SO₄, HCl, HBr, HI, HNO₃, H₃PO₄, NH₄Cl, and HClO₄. In some embodiments, hydrolysis of the boronic ester may be performed using an inorganic base. Non-limiting examples an inorganic bases include, but are not limited to, Na₂CO₃, K₂CO₃, KOH, NaOH, and combinations thereof.

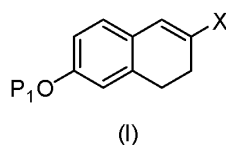
[0050] In some embodiments, the process is carried out in continuous flow mode or in batch mode. In some embodiments, the process is carried out in continuous flow mode.

[0051] In some embodiments, the compound of Formula (a) is used in Step 2 without isolation or purification. In some embodiments, the compound of Formula (a) is isolated and purified before being used in Step 2 of the process.

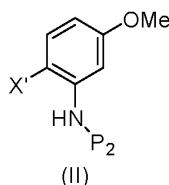
[0052] In some embodiments, Step 2 of the process includes preparing a compound of Formula (III)



comprising reacting a compound of Formula (I):



with a compound of Formula (II):



in the presence of a transition metal catalyst, a base, and a solvent, wherein P_1 is H or a phenol protecting group; P_2 is H, Et, or an amino protecting group; X is a halogen or $B(OH)_2$; and X' is a halogen or $B(OH)_2$; wherein said X and X' are suitable for cross-coupling of Formula (I) with Formula (II).

[0053] In some embodiments, X is $B(OH)_2$. In some embodiments:

- P_1 is H or a phenol protecting group selected from $(C=O)-C_1-C_8$ alkyl, $(C=O)$ -aryl, $(C=O)$ -heteroaryl, $Si(C_1-C_5 \text{ alkyl})_3$, $Si(aryl)_2(C_1-C_5 \text{ alkyl})$ and CH_2 -aryl;
- P_2 is H, Et, or an amino protecting group selected from $(C=O)-C_1-C_8$ alkyl, $(C=O)$ -aryl, $(C=O)$ -heteroaryl, $(C=O)-O-C_1-C_8$ alkylaryl, or $(C=O)-(CH_2)_n-C=O$ - wherein n is 2 or 3;

- X is Cl, Br, I, or B(OH)₂; and

- X' is Cl, Br, I, or B(OH)₂,

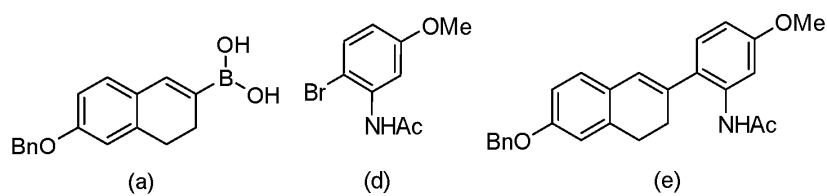
wherein when X is B(OH)₂, X' is Cl, Br, or I.

[0054] In some embodiments, P₁ is CH₂-aryl; P₂ is (C=O)-C₁ alkyl; X is B(OH)₂; and X' is Cl, Br, or I.

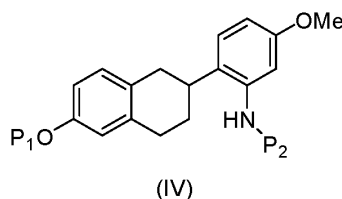
[0055] In some embodiments, the transition metal catalyst is a palladium-containing catalyst. In some embodiments, the transition metal catalyst is a copper-containing catalyst. In some embodiments, the transition metal catalyst is selected from the group consisting of Pd(OAc)₂, Pd(PPh₃)₄, PdCl₂(PPh₃)₂, Pd(dppf)Cl₂, Pd₂(dba)₃, Cu(0), Pd(PCy₃)₂, Pd/C, Pd/Al₂O₃, Pd/SiO₂, Pd/TiO₂, Pd/zeolites, Pd/CeO₂, Pd/organic polymers (such as polystyrene and copolymers), Pd/cyclodextrins, and a combination of two or more thereof. In some embodiments, the transition metal catalyst comprises Pd(0). In some embodiments, the transition metal catalyst is Pd/C. In some embodiments, a low amount of the transition metal catalyst is used. In some embodiments, the transition metal catalyst is used in an amount from about 0.0001 equivalents to about 0.004 equivalents. In some embodiments, the transition metal catalyst is used in an amount of about 0.001 equivalents.

[0056] In some embodiments, the base is an inorganic base, an organic base, or a combination thereof. In some embodiments, the base is selected from K₂CO₃, KO^tBu, Cs₂CO₃, Na₃PO₄, K₃PO₄, KOH, NaOH, CsOH, LiOH, NEt₃, and combinations thereof. In some embodiments, the base is Na₃PO₄.

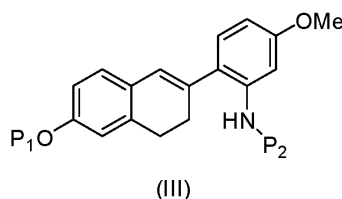
[0057] In some embodiments, the compounds of Formulas (I), (II), and (III) are (a), (d) and (e):



[0058] In some embodiments, Step 3 of the process comprises preparing a compound of Formula (IV)



comprising reduction of a compound of Formula (III):



in the presence of a transition metal catalyst, wherein P₁ is H or a phenol protecting group and P₂ is H, Et, or an amino protecting group.

[0059] In some embodiments:

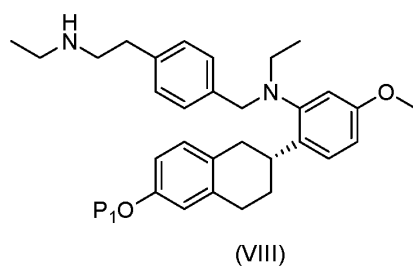
- P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and
- P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, or (C=O)-(CH₂)_n-C=O)- wherein n is 2 or 3.

[0060] In some embodiments, P₁ is CH₂-aryl and P₂ is (C=O)-C₁ alkyl.

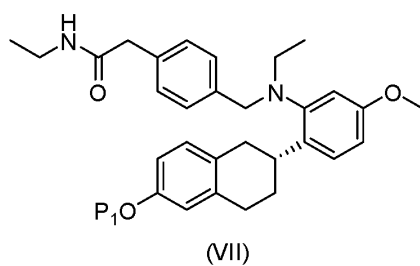
[0061] In some embodiments, the transition metal catalyst comprises a metal selected from Pd, Pt, Rh, Ru, Ni, Co, and a combination of two or more thereof, where the metal is supported on carbon, Al₂O₃, Al₂CO₃, CaCO₃, BaSO₄, SiO₂, TiO₂, zeolites, CeO₂, organic polymers (such as polystyrene and copolymers), cyclodextrins, or a combination of two or more thereof. In some embodiments, the transition metal catalyst comprises or consists of Pd(0). In some embodiments, the transition metal catalyst comprises or consists of Pd/C. In some embodiments, the reduction is conducted in the presence of H₂. In some embodiments, the reduction is carried out using continuous-flow mode or batch-mode. In some embodiments, the reduction is carried out using continuous-flow mode.

[0062] In some embodiments, the reduction in continuous-flow mode is performed using a bubbling bed or a trickle-bed configuration. In one preferred embodiment, the reduction in continuous-flow mode is performed using a bubbling bed configuration

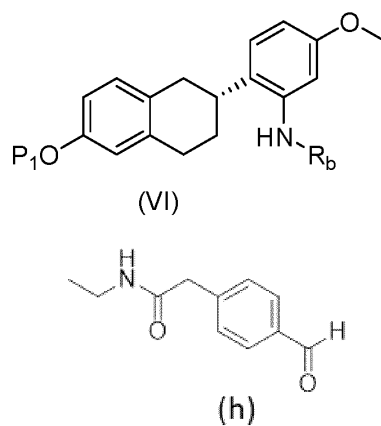
[0063] In some embodiments, a process of preparing a compound of Formula (VIII)



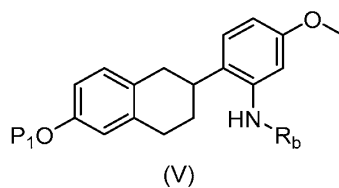
comprises reducing a compound of Formula (VII):



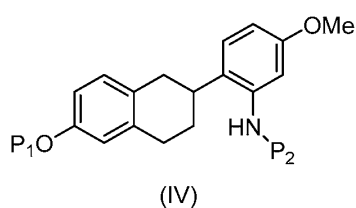
wherein the compound of Formula (VII) is prepared by reductive amination of a compound of Formula (VI) in the presence of a compound of Formula (h):



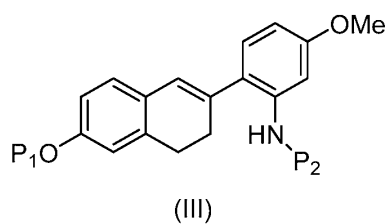
wherein the compound of Formula (VI) is prepared by reacting a compound of Formula (V)



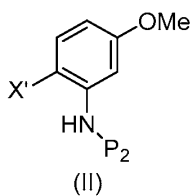
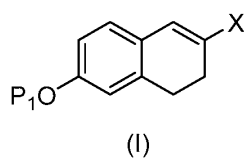
with a chiral acid to form an enantiomerically enriched salt, crystallizing the enantiomerically enriched salt, and freeing the compound of Formula (VI), wherein the compound of Formula (V) is prepared by treating a compound of Formula (IV) with a deprotecting agent:



wherein the compound of Formula (IV) is prepared by reducing a compound of Formula (III):



wherein reducing the compound of Formula (III) is performed using a Pd(0) catalyst; wherein the compound of Formula (III) is prepared by coupling a compound of Formula (I) with a compound of Formula (II):



and wherein P₁ is H or a phenol protecting group; R_b is H or Et; P₂ is (C=O)-C₁ alkyl; X is a halogen or a boronic acid; X' is a halogen or a boronic acid; and wherein X and X' are suitable for cross-coupling the compound of Formula (I) with the compound of Formula (II).

[0064] In some embodiments, the compound of Formula (I) is the compound of Formula (a) that can be prepared according to Step 1 as described in the previous paragraphs.

[0065] In some embodiments, reducing the compound of Formula (III) is performed using batch mode or continuous-flow mode. In some embodiments, reducing the compound of Formula (III) is carried out using continuous-flow mode.

[0066] As used herein, “about” will be understood by persons of ordinary skill in the art and will vary to some extent depending upon the context in which it is used. If there are uses of the term which are not clear to persons of ordinary skill in the art, given the context in which it is used, “about” will mean up to plus or minus 10% of the particular term.

[0067] The use of the terms “a” and “an” and “the” and similar referents in the context of describing the elements (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the embodiments and does not pose a limitation on the scope of the claims unless otherwise stated. No language in the specification should be construed as indicating any non-claimed element as essential.

[0068] Various embodiments are described hereinafter. It should be noted that the specific embodiments are not intended as an exhaustive description or as a limitation to the broader aspects discussed herein. One aspect described in conjunction with a particular embodiment is not necessarily limited to that embodiment and can be practiced with any other embodiment(s).

[0069] The present disclosure, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present disclosure.

EXAMPLES

[0070] While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the technology in its broader aspects as defined in the following claims.

Example 1. Step 1 in Batch Mode

[0071] Step 1 of the process described herein was carried out in batch-mode. Different solvent systems, lithiation reagents, borate reagents, and temperatures were tested to determine optimal conditions for carrying out Step 1 using batch-mode.

Table 1. Screening of Solvents

Entry	Solvent	Ratio	IPC results (%)			
			Compound (a)	Compound (b')	Impurity1	Impurity2
1	THF	N/A	75	N.D.	10	6
2	DME	N/A	85	3	9	1
3	MTBE	N/A	0.1	99.7	0.2	N.D.
4	2-MeTHF	N/A	36	43	3	N.D.
5	DME & MTBE	1:1	95	N.D.	4	N.D.
6	DME & MTBE	4:1	93	0.6	5	0.4
7	DME & 2-MeTHF	1:1	92	0.2	6	1
8	DME & THF	1:1	78	N.D.	7	4
9	THF & MTBE	1:1	66	2	16	1
10	THF & 2-MeTHF	1:1	80	N.D.	5	2

N.D. = not detected

[0072] DME/MTBE at ratios of 1:1 and 4:1 were determined to be the preferred solvent mixtures.

Table 2. Screening of Lithium Reagents and Borate Reagents

Entry	Lithium reagent	Borate ester	Quench condition	IPC results (%)		
				Compound (a)	Impurity1	Impurity2
1	LDA	B(O <i>i</i> Pr) ₃	15% H ₂ SO ₄	0.5	93	0.6
2	LiHMDS	B(O <i>i</i> Pr) ₃	15% H ₂ SO ₄	N.D.	100	N.D.
3	<i>n</i> -BuLi	B(O <i>i</i> Pr) ₃	15% H ₂ SO ₄	95	N.D.	4.5
4	<i>n</i> -BuLi	B(OEt) ₃	15% H ₂ SO ₄	95	0.7	4.2
5	<i>n</i> -BuLi	B(OMe) ₃	15% H ₂ SO ₄	29	0.3	29

N.D. = not detected

[0073] It was determined that *n*-BuLi and triisopropyl borate were the preferred lithiation reagent and borate reagent, respectively. Lithium diisopropylamide (LDA) and Lithium hexamethyl disilazide (LiHMDS), as lithiating agents, proved unsuitable to produce **Compound (a)**.

[0074] When Step 1 and Step 2 are carried out at temperatures above -35°C, the purity of **Compound (a)** decreases significantly (*i.e.*, the content of Impurity 1 increases). However, performing Step 1 between -35°C and -75°C provides the desired boronic acid **Compound (a)** in 92~95% HPLC yield.

Example 2. Step 1 in Continuous-flow Mode

[0075] Step 1 of the process described herein was also carried out in continuous-flow mode. Different solvent systems, residence times, and temperatures were tested to determine optimal conditions for carrying out Step 1 using continuous flow-mode.

[0076] When performing Step 1 under batch conditions using DME/MTBE as the solvent system, the reaction mixture was heterogeneous. In order to evaluate the feasibility of the continuous-flow process for this reaction in PFR, the solubility of starting material **Compound (b')** was evaluated in various solvents at different temperatures (**Table 3**). Based on the solubility results, it was found that THF and temperatures between -40°C and -60°C were the most suitable conditions for this reaction for the continuous-flow mode.

Table 3. Screening of Solvents and Reaction Temperatures

Solvent	Compound (b') Solubility (ml/g)	Temp. (°C)	Status
THF	5	-40	Homogeneous
	10	-50	
	15	-60	
2-Me-THF	10	-20	
	15	-30	
DME	10	20	Heterogeneous
	15	20	
MTBE	10	20	
	15	20	

[0077] The reactions were conducted in a plug flow reactor (PFR) in the presence of 1.3 equiv of *n*-BuLi at -78°C. IPC showed that the conversion increased with shortened residence time, and the purity of the lithiation intermediate was increased. (Entries 1-3, **Table 4**).

[0078] According to the previous conclusion, when shortening the residence time to 2.5 min and setting a high flow rate, such as 39.2g/min, IPC showed that most of starting material (**Compound (b')**) would be consumed, and the percentage of the key intermediate (**Compound (c)**) would reach to about 90% (Entry 4, **Table 4**). However, a high flow rate would result in a significant increase in the pulse of the plunger pump. When the injection pump was used to charge the material, IPC showed the similar results (Entry 5, **Table 4**). Based on these results, it was concluded that the injection pump could be used as charging pump for maintaining steady charging status and to evaluate the following experiments (Entry 5, **Table 4**). Under similar conditions, it was found that the residual starting material was significantly increased along with decreasing the residence time (5-7).

Table 4. Investigation of Residence Time

Entry	Flow rate (g/min)	Residence time (min)	IPC for step 1A (% , HPLC)				
			Imp. A (RT 3.6min)	Cmpd. (b')	Cmpd. (c)	Imp. 2	Imp. 3
1	-	30	0.7	18.9	55.1	6.3	11.2
2	-	15	0.4	23.3	69.3	0.3	3.8
3	-	10	0.7	4.4	81.4	1.5	6.1
4	39.2	2.5	0.5	1.0	90.3	1.1	3.0
5	39.2g	2.5	0.1	0.8	92.1	1.7	4.1
6	-	1.5	-	25.8	72.4	0.4	0.8
7	-	0.67	-	36.9	62.1	0.1	0.4

Table 5. Investigation of Reaction Temperature

Entry	Temp. (°C)	Solvent volume	Residence time	IPC for step 1A (% , HPLC)				
				Imp A (RT 3.6min)	Cmpd. (b')	Cmpd. (c)	Imp 2	Imp 3
1	-78	15V	40s	-	36.9	62.1	0.1	0.4
2	-65	15V	40s	-	13.3	85.7	-	1.0
3	-65	15V	50s	-	2.5	93.8	0.6	2.2
4	-55	15V	40s	0.2	1.5	94.4	0.9	2.5
5	-50	15V	35s	0.4	0.6	94.6	1.1	3.3
6	-50	15V	40s	0.3	0.4	93.8	0.9	3.2
7	-50	15V	30s	0.1	2.1	93.8	1.1	2.6

[0079] The preferred reaction temperature was found to be from about -50°C to about -60°C.

[0080] Analogous experiments were conducted using Cl- and I-containing analogues of **Compound (b')** – that is, Formula (b), where Y = Cl or I. The results from such experiments were comparable to those obtained for **Compound (b')**, in which Y=Br.

Example 3. Step 2 in Batch Mode

[0081] The use of the boronic acid **Compound (a)** has unexpectedly led to a significant decrease of the amount of the toxic and costly palladium catalyst in the Suzuki coupling reaction. A reduction of at least 10 times of palladium has been achieved: from the standard loading of 0.02 equivalents of Pd in the standard commercial process to 0.001 equivalents in the process described herein.

Table 6. Investigation of Catalyst Loading

Entry	Scale	Eq. of Pd Cat.	Time (h)	IPC tracking (HPLC method)			Weight	Isolated Compound (e)		
				Cmpd. (e)	Imp. 4	Imp. 5		Purity (%)	Assay (%)	Yield (%)
1	20g	0.02	13	93	Trace	1	23.52g	99.6	98.6	81.3
2	20g	0.004	13	95	Trace	1	23.44g	99.9	97.4	80.0
3	20g	0.002	13	95	N.D.	1	24.31g	99.9	99.1	84.5
4	20g	0.001	16	95	N.D.	1	23.27g	99.9	98.4	80.3

N.D. = not detected

Example 4. Step 3 in Continuous-flow Mode

[0082] Two different equipment configurations were tested: a “trickle-bed” configuration (as shown in **FIG. 2**) and a “bubbling-bed” configuration (as shown in **FIG. 3**).

Reaction procedure (“trickle-bed” and “bubbling-bed” configuration)

[0083] Fixed bed information: The length is 40 cm and the inner diameter is 0.8 cm. 5.0g of the palladium catalyst was added to the trickle bed/bubbling bed, the remaining space of the fixed bed is filled with 0.1 cm glass beads.

[0084] A solution containing **Compound (e)**, the Starting Material (SM), in 20 volumes of THF:MeOH = 1:1, was connected to the pumping system. After setting 40°C and 1.0 MPa hydrogen pressure, the flow reaction is started. The flow rate of SM solution was 0.2 g/min, and the flow rate of hydrogen gas was 10 ml/min. Samples were sent to HPLC during the reaction.

Table 7. Base Reaction Conditions for Hydrogenation Reaction in Fixed Bed (Trickle and Bubbling Modes)

Reaction condition	Temperature/°C	40
	Pressure/Mpa	1.0
	Liquid flow rate g/min	0.2
	Gas flow rate ml/min	10
	Solvent	THF/MeOH (20 v, 1:1)
	Catalysts	3% Pd/Al ₂ O ₃
Fixed bed information	Internal diameter mm	8
	Effective heating length/mm	20
	Catalyst loading quality/g	6

Table 8. Results from “Trickle-bed” Experiments

Entry	Reaction condition	IPC-purity%					
		RT	20.290	13.653	14.250	19.755	Yield
		RRT	1.486	1.000	1.044	1.447	
		duration h	Cmpd. (e)	Cmpd. (f)	Imp. 6 + Imp. 7	Imp. 8	
1	trickle bed 0.2g/min	4-8	90.72	0.33	0.06	8.78	N/A
2	trickle bed 0.1g/min	12-16	60.38	4.60	0.23	34.71	N/A

[0085] The trickle bed configuration was tested first. In entry 1 of **Table 8**, when the liquid flow rate was set as 0.2 g/min, a large amount of SM was detected, and almost no products were generated. When the feeding speed was reduced to 0.1g/min (entry 2, **Table 8**), there was still a large amount of **Compound (e)** remaining.

Table 9. Results from “Bubbling-bed” Experiments

Entry	Reaction condition	IPC-purity%					Yield
		RT	20.290	13.653	14.250	19.755	
		RRT	1.486	1.000	1.044	1.447	
		duration (h)	Cmpd. (e)	Cmpd.(f)	Imp. 6 + Imp. 7	Imp. 8	
1	bubbling bed 0.2g/min	13-29	0	97.04	0.12	0.53	N/A

[0086] With the same liquid flow rate of 0.2 g/min used in the trickle-bed experiment (entry 1, **Table 9**), the bubbling bed configuration showed excellent results. Most of the product purity is over 96% and conversion of **Compound (e)** was nearly 100%. These results indicated that the bubbling bed configuration was better than the trickle bed configuration and the further investigation of the continuous hydrogenation was performed using bubbling bed configuration.

[0087] In **Table 10**, the results of small-scale experiments aimed to find suitable reaction conditions (using the “bubbling-bed” set-up) are reported.

Reaction procedure

[0088] Fixed bed information: The length is 40 cm, and the inner diameter is 0.8 cm. 5.0g of the palladium catalyst was added to the bed, and the remaining space of the fixed bed was filled with 0.1-cm glass beads to form SM solution.

[0089] The solution of **Compound (e)** in 20 volumes of THF:MeOH = 1:1 was connected to the pumping system. After setting at a selected temperature (40°C, 50 °C, 55 °C or 60°C) and 1.0 MPa or 3 MPa hydrogen pressure, the flow reaction was started. The flow rate of **Compound (e)** solution was set at 0.2 g/min or 0.3 g/min, and the flow rate of hydrogen gas was set at 12 ml/min or 18 ml/min. Samples were sent to HPLC during the reaction.

Table 10. Small Scale Bubbling-bed Trials

Entry	Reaction condition	IPC-purity%					Yield
		RT	20.290	13.653	14.250	19.755	
		RRT	1.486	1.000	1.044	1.447	
		duration h	Compound (e)	Compound (f)	Imp. 6 + Imp. 7	Imp. 8	
4	T=40°C P=1.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	7	0.40	98.04	0.28	0.00	N/A
5	T=40°C P=1.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	21	0.00	97.51	0.12	0.38	N/A
6	T=40°C P=1.0MPa Liquid flow rate =0.3g/min Gas flow rate =18ml/min	4	0.24	89.99	1.09	7.23	N/A
7	T=40°C P=3.0MPa Liquid flow rate =0.3g/min Gas flow rate =18ml/min	5	0.32	86.95	0.88	10.53	N/A
8	T=40°C P=3.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	11	0.00	94.56	0.89	2.78	N/A

9 bis	T=40°C P=3.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	2	0.17	91.28	0.85	5.87	Catalyst performance gets worse
10 bis	T=45°C P=3.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	5	0.11	94.19	0.76	3.07	Temperature rise Improve the performance
11	T=45°C P=1.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	29	0.06	97.42	0.68	0.19	after 70 hrs in optimal flow condition the increase of temperature guarantee OPTIMAL performance
		7	0.06	96.38	1.78	0.80	after 100 hours there is still a worsening of performance
12	T=50°C P=1.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	26	0.05	97.52	1.28	0.17	a new temperature increase brings performance back to the desired levels
		8	0.02	96.42	1.26	1.07	Anyway, after few hours a new worsening in performances is seen
13	T=55°C P=1.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	11	0.08	96.97	1.08	0.7	a new temperature increase, after 155hrs, brings performance back to the desired levels, but the effect last for few hrs
		4	0.76	95.01	1.9	1.6	catalyst performance gets worse fast

14	T=60°C P=1.0MPa Liquid flow rate =0.2g/min Gas flow rate =12ml/min	176-195?	0.06	97.02	1.39	0.5	the subsequent temperature rise seems less effective
		196-202	0.13	94.82	1.69	2.32	

[0090] On the basis of the above results, the most advantageous reaction conditions were determined.

Example 5. Materials and Methods

Example 5A. Preparation of 6-(benzyloxy)-3,4-dihydronaphtalen-2-ylboronic acid (Compound (a)), batch mode

[0091] 7-Benzyloxy-3-bromo-1,2-dihydro-naphtalene (200 g, 0.63452 mol) was dissolved in a 1:1 mixture of DME/MTBE (2000 mL, 10 vol), cooled and thermostated at -75°C under an atmosphere of nitrogen. 2.0 M *n*-BuLi in cyclohexane (412.4mL, 0.82488 mol) was added dropwise and stirred for 30 min. Triisopropyl borate (190.4 mL, 0.82488 mol) was added and the mixture was stirred for 3 hours with cooling. The reaction was quenched with H₂SO₄ 15% (600 mL, 3 vol) at 0-5°C. The organic layer was separated and was extracted with Water (2 x 400 mL) at room temperature. The organic layer was cooled to 0-5°C in 1 hour, stirred for further 1 hour and filtered to get crude product as a solid. The crude solid was suspended in a 10:1 mixture of heptane:MTBE (400 mL, 2 vol.) and then filtered to obtain the intermediate 6-(benzyloxy)-3,4-dihydronaphtalen-2-ylboronic acid (154 g, purity 97.36%, assay 97.33%, yield 84.3%). ¹H-NMR (400 MHz, DMSO-d₆, 298K); δ (ppm^{*}): 2.23 (m, 2H), 2.61 (m, 2H), 5.09 (s, 2H), 6.77-6.84 (m, 2H), 7.00 (d, 1H), 7.06 (s, 1H), 7.29-7.47 (m, 5H), 7.56 (bs, 2H)**

[0092] *Chemical shifts (δ) were referenced on the residual proton of internal standard TMS (δ = 0.00 ppm).

Example 5B. Preparation of 6-(benzyloxy)-3,4-dihydronaphtalen-2-ylboronic acid (Compound (a)), batch mode

[0093] 7-Benzyloxy-3-bromo-1,2-dihydro-naphtalene (30 g, 0.09518 mol) was dissolved in a 1:1 mixture of DME:MTBE (300 mL, 10 vol.), cooled, and thermostated at -45°C under an

atmosphere of nitrogen. 2.0 M *n*-BuLi in cyclohexane (61.9 mL, 0.12373 mol) was added dropwise and stirred for 30 min. Triisopropyl borate (28.6 mL, 0.12373 mol) was added, and the mixture was stirred for 3 hours with cooling. The reaction was quenched with H₂SO₄ 15% (90 mL, 3 vol.) at 0-5°C. The organic layer was separated and was extracted with water (2 × 60 mL) at room temperature. The organic layer was cooled to 0-5°C in 1 hour, further stirred for 1 hour, and filtered to get crude product as a solid. The crude solid was suspended in a 10:1 mixture of heptane:MTBE (60 mL, 2 vol.) and then filtered to obtain the intermediate 6-(benzyloxy)-3,4-dihydronaphtalen-2-ylboronic acid (22.9 g, purity 99.5%, assay 95.7%, yield 82.1%).

Example 5C. Preparation of 6-(benzyloxy)-3,4-dihydronaphtalen-2-ylboronic acid (Compound (a)), batch mode, T = -75°C, scale-up

7-Benzyloxy-3-bromo-1,2-dihydro-naphtalene (100 g, 0.31726 mol) was dissolved in a 1:1 mixture of DME:MTBE (1000 mL, 10 vol.), cooled, and thermostated at -75°C under an atmosphere of nitrogen. 2.0 M *n*-BuLi in cyclohexane (206.2 mL, 0.41244 mol) was added dropwise and stirred for 30 min. Triisopropyl borate (95.2 mL, 0.41244 mol) was added, and the mixture was stirred for 3 hours with cooling. The reaction was quenched with H₂SO₄ 15% (300 mL, 3 vol.) at 0-5°C. The organic layer was separated and was extracted with water (2 × 200 mL) at room temperature. The organic layer was cooled to 0-5°C in 1 hour, further stirred for 1 hour, and filtered to get crude product as a solid. The crude solid was suspended in a 10:1 mixture of heptane:MTBE (200 mL, 2 vol.) and then filtered to obtain the intermediate 6-(benzyloxy)-3,4-dihydronaphtalen-2-ylboronic acid (77.5 g, purity 99.9%, assay 94.6%, yield 82.4%).

[0094] On the basis of the results of Examples 5 A-C, the target product **Compound (a)** can be obtained with adequate purity and yield in the explored range of temperatures (*e.g.*, -45°C – -75°C).

Example 5D. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (e)), batch mode, 0.02 equiv. Pd catalyst

[0095] 6-(benzyloxy)-3,4-dihydronaphthalen-2-ylboronic acid (20.0 g, 0.0714 mol) was dissolved in 140 ml of DME at room temperature, and 20% KHCO_3 (2.8 eq.) and N-(2-bromo-5-methoxyphenyl)acetamide (17.43 g, 0.0714 mol) were added to the reaction mixture. After degassing the mixture, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.02 eq., 1.0 g, 0.00143 mol) was added, and the mixture was heated to 78–82°C for 13 hours. The mixture was cooled to 50–60°C and filtered. The solid cake was washed with 20 ml of DME, and the aqueous layer was separated. The organic phase was cooled to 15–25°C and 180 ml of water were added. After 2 hours of stirring, the precipitated solid was collected by filtration and washed with 60 ml of water. The solid was dissolved in 200 ml of dichloromethane, then treated with 5 g of carbon at 35–45°C for 6–8 hours. After cooling to room temperature, the suspension was filtered and, after a solvent switch to 6 volumes (120 ml) of ethanol, the precipitated solid was collected by filtration and dried at $T \leq 45^\circ\text{C}$ under vacuum until residual DCM and EtOH were both below 1.0%. N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained (23.52 g, purity 99.60%, assay 98.59%, yield 81.31%). $^1\text{H-NMR}$ (400 MHz, DMSO-d_6 , 298K); δ (ppm^{*}): 1.99 (s, 3H), 2.45 (m, 2H), 2.83 (m, 2H), 3.74 (s, 3H), 5.10 (s, 2H), 6.44 (s, 1H), 6.76 (dd, 1H), 6.81 (dd, 1H), 6.87 (d, 1H), 7.04 (d, 1H), 7.09 (d, 1H), 7.29–7.48 (m, 5H), 9.21 (s, 1H)

[0096] *Chemical shifts (δ) were referenced on the residual proton of internal standard TMS ($\delta = 0.00$ ppm).

Example 5E. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound(e)), batch mode, 0.004 equiv. Pd catalyst

[0097] 6-(benzyloxy)-3,4-dihydronaphthalen-2-ylboronic acid (20.0 g, 0.0714 mol) was dissolved in 140 ml of DME at room temperature, and 20% KHCO_3 (2.8 eq.) and N-(2-bromo-5-methoxyphenyl)acetamide (17.43 g, 0.0714 mol) were added to the reaction mixture. After degassing the mixture, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.004 eq., 0.25 g, 0.000286 mol) was added, and the mixture was heated to 78–82°C for 13 hours. The mixture was cooled to 50–60°C and filtered. The solid cake was washed with 20 ml of DME, and the aqueous layer was

separated. The organic phase was cooled to 15–25°C and 180 ml of water was added. After 2 hours of stirring, the precipitated solid was collected by filtration and washed with 60 ml of water. The solid was dissolved in 200 ml of dichloromethane, then treated with 5 g of carbon at 35–45°C for 6–8 hours. After cooling to room temperature, the suspension was filtered and, after a solvent switch to 6 volumes (120 ml) of ethanol, the precipitated solid was collected by filtration and dried at $T \leq 45^\circ\text{C}$ under vacuum until residual DCM and EtOH were both below 1.0%. N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained (23.44 g, purity 99.96%, assay 97.39%, yield 80.04%).

Example 5F. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (e)), batch mode, 0.002 equiv. Pd catalyst

[0098] 6-(benzyloxy)-3,4-dihydronaphthalen-2-ylboronic acid (20.0 g, 0.0714 mol) was dissolved in 140 ml of DME at room temperature, and 20% KHCO_3 (2.8 eq.) and N-(2-bromo-5-methoxyphenyl)acetamide (17.43 g, 0.0714 mol) were added to the reaction mixture. After degassing the mixture, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.002 eq., 0.1 g, 0.000143 mol) was added, and the mixture was heated to 78–82°C for 13 hours. The mixture was cooled to 50–60°C and filtered. The solid cake was washed with 20 ml of DME, and the aqueous layer was separated. The organic phase was cooled to 15–25°C, and 180 ml of water were added. After 2 hours of stirring, the precipitated solid was collected by filtration and washed with 60 ml of water. The solid was dissolved in 200 ml of dichloromethane, treated with 5 g of carbon at 35–45°C for 6–8 hours. After cooling to room temperature, the suspension was filtered, and after a solvent switch to 6 volumes (120 ml) of ethanol, the precipitated solid was collected by filtration and dried at $T \leq 45^\circ\text{C}$ under vacuum until residual DCM and EtOH were both below 1.0%. N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained (24.31 g, purity 99.97%, Assay 99.07%, Yield 84.46%).

Example 5G. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (e)), batch mode, 0.001 equiv. Pd catalyst

[0099] 6-(benzyloxy)-3,4-dihydronaphthalen-2-ylboronic acid (20.0 g, 0.0714 mol) was dissolved in 140 ml of DME at room temperature, and 20% KHCO_3 (2.8 eq.) and N-(2-

bromo-5-methoxyphenyl)acetamide (17.43 g, 0.0714 mol) were added to the reaction mixture. After degassing the mixture, Pd(PPh₃)₂Cl₂ (0.001 eq., 0.05 g, 0.0000715 mol) was added, and the mixture was heated to 78–82°C for 16 hours. The mixture was cooled to 50–60°C and filtered. The solid cake was washed with 20 ml of DME, and the aqueous layer was separated. The organic phase was cooled to 15–25°C, and 180 ml of water was added. After 2 hours of stirring, the precipitated solid was collected by filtration and washed with 60 ml of water. The solid was dissolved in 200 ml of dichloromethane, then treated with 5 g of carbon at 35–45°C for 6–8 hours. After cooling to room temperature, the suspension was filtered, and after a solvent switch to 6 volumes (120 ml) of ethanol, the precipitated solid was collected by filtration and dried at T ≤ 45°C under vacuum until residual DCM and EtOH were both below 1.0%. 23.27 g of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained (23.27 g, purity 99.93%, assay 98.43%, yield 80.31%).

Example 5H. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (Compound(e)), telescoping mode, 0.004 equiv. Pd catalyst

[00100] 7-Benzyloxy-3-bromo-1,2-dihydro-naphthalene (30 g, 0.095 mol) was dissolved in a 4:1 mixture of DME:MTBE (300 mL, 10 vol.), cooled, and thermostated at -65°C under an atmosphere of nitrogen. 2.0 M *n*-BuLi in cyclohexane (61.8 mL, 0.1235 mol) was added dropwise and stirred for 30 min. Triisopropyl borate (28.56 mL, 0.1235 mol) was added, and the mixture was stirred for 3 hours with cooling. The reaction was quenched with 15% H₂SO₄ at 0–5°C, and the pH of the aqueous phase was adjusted until pH ≥ 6 by adding 15% H₂SO₄. The vessel was charged with KHCO₃ (20% wt., 3.0 eq, based on pH) and N-(2-bromo-5-methoxyphenyl)acetamide (23.3 g, 0.095 mol) at 15–30°C. The mixture was purged with N₂ until oxygen was ≤ 1000 ppm. After degassing the mixture, Pd(PPh₃)₂Cl₂ (0.004 eq., 2.66 g, 0.0038 mol) was added, and the mixture was heated to 78–82°C for 15 hours. The mixture was cooled to 50–60°C and filtered. The solid cake was washed with 30 ml of DME, and the aqueous layer was separated. The organic phase was cooled to 15–25°C, and 270 ml of water was added. After 2 hours of stirring, the precipitated solid was collected by filtration and washed with 90 ml of water. The solid was dissolved in 300 ml of dichloromethane, treated with 7.5 g of carbon at 35–45°C for 6–8 hours. After cooling to room temperature, the

suspension was filtered and, after a solvent switch to 6 volumes (180 ml) of ethanol, the precipitated solid was collected by filtration and dried at $T \leq 45^{\circ}\text{C}$ under vacuum until residual DCM and EtOH were both below 1.0%. N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained (27.4 g, purity 99.64%, assay 96.68%, yield 69.7%).

[00101] On the basis of the results of examples 5 D-H, the target product **Compound(e)**, can be obtained with adequate purity, assay, and yield in the explored range of palladium catalyst amount (i.e. 0.001 eq – 0.02 eq.).

Example 5I. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (e)), 0.01 equiv. Pd/C catalyst

[00102] 6-(benzyloxy)-3,4-dihydronaphthalen-2-ylboronic acid (5.0 g, 0.018 mol) was dissolved, under nitrogen, in 35 ml of dry THF and 35 ml of NaOH 1M (2.0 eq.) previously degassed, followed by the addition of N-(2-bromo-5-methoxyphenyl)acetamide (7 g, 0.029 mol, 1.6 eq.). Pd/C (10%, 50% wet) (0.01 eq., 0.4 g, 1.8×10^{-4} mol) was added, and the mixture was heated to $66\text{--}68^{\circ}\text{C}$ for 4.5 hours. The mixture was cooled to $25\text{--}30^{\circ}\text{C}$, diluted with 25 ml of THF, and filtered. The solid cake was washed with 50 ml of THF, the filtrate was collected, and the solvent was evaporated under vacuum until dryness. The residue was dissolved in 250 ml of DCM, and the organic solution was washed with 100 ml of H_2O . The organic phase was then washed with 100 ml of brine and evaporated to dryness. 6 g of crude N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained; the solid was suspended in 48 ml of absolute EtOH and 6 ml of DCM. After dissolution at reflux, the solution was cooled to 10°C and filtered. The solid was washed twice with 10 ml of EtOH and then dried under vacuum at 45°C . 4.70 g of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide was obtained (purity 99.9 %, assay 99.2 %, yield 65 %).

[00103] On the basis of the results of Example 5I, the **Compound (e)**, can be obtained with adequate purity, assay, and yield using palladium on carbon as catalyst.

Example 5J. Preparation of N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (Compound (f)), continuous flow hydrogenation mode

[00104] A stainless steel, high-pressure reactor (bubbling bed reactor, inner diameter 30 mm, length 150 mm) was filled with 220 g of a 3% palladium/alumina catalyst. In a 100L container separately prepared, N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (3.5 Kg, 8.76 mol) was dissolved in a mixture of THF (35 L, 31.1 kg) and MeOH (35 L, 27.7 kg) to prepare a reaction solution having a concentration of 5 wt.%. Hydrogen was fed at a flow rate of 500 mL/min, and the reaction solution was fed at a flow rate of 0.82 g/min into the high pressure reactor filled with the catalyst, and continuous hydrogenation was performed at a reactor inner temperature 40-45°C, inside pressure 1.0 MPa (10 bar). Continuously-discharged hydrogen gas was separated from the reaction mixture, and the reaction mixture discharged from the reactor outlet was recovered for 100 hours in total. Under reduced pressure, the volume of the reaction mixture was concentrated to 6-10 mL at not more than 45°C. 20 L of ethyl acetate was added to the residual mixture, which was concentrated to 6-10 mL at not more than 45°C. The operation was repeated until residual THF and MeOH were less than 2.0%. At not more than 25°C, 10 L of ethyl acetate was added, and the mixture was stirred for 1 hr. The precipitated solid was collected by filtration and washed with ethyl acetate (10 L). The solid was dried under reduced pressure at 50°C until a constant weight was reached to give N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (2.6 kg, yield 95.8%, purity 99.7%, assay 99.9%). ¹H-NMR (400 MHz, DMSO-d₆, 298K); δ (ppm^{*}): 1.66-1.89 (m, 2H), 2.01 (s, 3H), 2.60 (m, 1H), 2.68-2.86 (m, 3H), 2.99-3.12 (m, 1H), 3.71 (s, 3H), 6.46-6.55 (m, 2H), 6.76 (dd, 1H), 6.84 (d, 1H), 6.94 (d, 1H), 7.21 (d, 1H), 9.00 (s, 1H), 9.33 (s, 1H)

[00105] *Chemical shifts (δ) were referenced on the residual proton of internal standard TMS (δ = 0.00 ppm).

Example 5K. Preparation of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl)acetamide (Compound (e)), continuous flow and telescoping mode

[00106] In a bottle A, 7-benzyloxy-3-bromo-1,2-dihydro-naphtalene (30 g, 0.095 mol) was dissolved in THF (300 mL, 10 vol.) to obtain solution A. To a bottle B was added *n*-BuLi (2.5M in hexane solution, 1.3 equiv., 0.124 mol, 49.5 mL) to obtain solution B. A bottle C

was charged with triisopropyl borate (1.3eq., 0.124 mol, 23.3 g; 28.6 mL) and 90 mL of THF to obtain solution C. Solution A and solution B were pumped through pre-cooling loop (316L, length = 1.6 m, diameter = 3 mm) and reacted in a first plug-flow reactor (PFR1, 316L, length = 3.2 m, diameter = 3 mm) at about -60°C to about -50°C for 20 s (pumping rate of solution A: 26 mL/min; pumping rate solution B: 4.0 mL/min). The system was then reacted with solution C (pumping rate of solution C: 9.6 mL/min) in a second plug-flow reactor (PFR2, 316L, length = 7.7 m, diameter = 3 mm) at about -60°C to about -50°C for 35 s. The mixture was flowed into a continuous stirred tank reactor (CSTR) and quenched by 15% H₂SO₄ solution and 20% brine to adjust the mixture to pH ~7-8. The mixture was separated, and the organic phase was washed with 20% brine solution. The organic phase was concentrated to ~7 vol. (THF as solvent), and 90 mL of H₂O was charged into the vessel. TEA (3.0 equiv., 0.286 mol, 28.9 g, 39.8 mL) and *N*-(2-bromo-5-methoxyphenyl)acetamide (1.02 equiv., 0.097 mol, 23.7 g) were charged into the mixture at ~15°C to ~30°C. The internal gas in the vessel was exchanged with N₂ at 25°C. This operation was repeated until oxygen content was NMT 1000 ppm. Pd/C 5% (0.1 g/g, wet basis, 3.0 g) was added as catalyst into the reactor. The gas in the vessel was exchanged with N₂. The mixture was heated to 65°C until consumption of **Compound (a)**. The mixture was cooled to 20°C, filtered, and rinsed with 90 mL of THF (3 vol.). A solvent switch was performed to obtain a suspension in 180 mL of EtOH (6 vol.). The mixture was cooled to ~10-20°C, filtered and rinsed with 60 mL EtOH. The resulting cake was dried at T ≤ 45°C. *N*-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (**Compound (e)**) (29.06 g solid) was obtained, with 98.73% purity and 99.27% assay (Q-NMR) in 76% corrected yield.

[00107] The embodiments, illustratively described herein may suitably be practiced in the absence of any element or elements, limitation or limitations, not specifically disclosed herein. Thus, for example, the terms “comprising,” “including,” “containing,” etc. shall be read expansively and without limitation. Additionally, the terms and expressions employed herein have been used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the claimed technology. Additionally, the phrase “consisting essentially of” will be understood to include those elements specifically recited and those additional

elements that do not materially affect the basic and novel characteristics of the claimed technology. The phrase “consisting of” excludes any element not specified.

[00108] The present disclosure is not to be limited in terms of the particular embodiments described in this application. Many modifications and variations can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and compositions within the scope of the disclosure, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the appended claims. The present disclosure is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. It is to be understood that this disclosure is not limited to particular methods, reagents, compounds, or compositions, which can of course vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

[00109] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[00110] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as “up to,” “at least,” “greater than,” “less than,” and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range comprises each individual member.

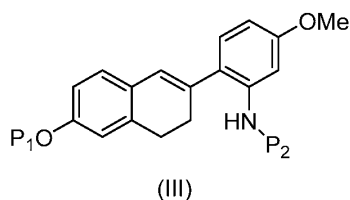
[00111] All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and individually

indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

[00112] Other embodiments are set forth in the following claims.

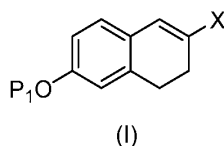
WHAT IS CLAIMED IS

1. A process of preparing a compound of Formula (III),

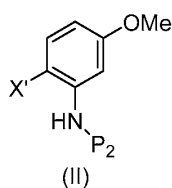


the process comprising:

reacting a compound of Formula (I):



with a compound of Formula (II):



in the presence of a transition metal catalyst, a base, and a solvent, wherein:

P₁ is H or a phenol protecting group;

P₂ is H, Et, or an amino protecting group;

X is B(OH)₂;

X' is a halogen; and

X and X' are suitable for cross-coupling of Formula (I) with Formula (II).

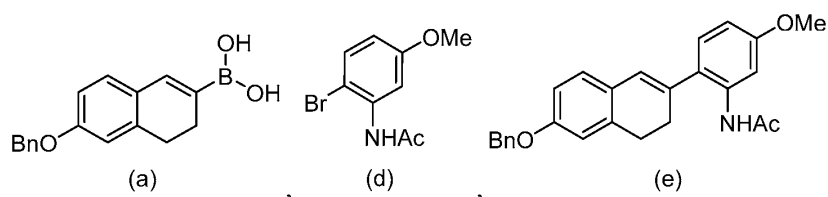
2. The process of claim 1, wherein:

P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl;

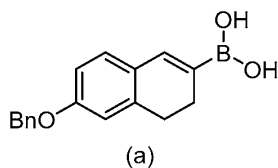
P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, or (C=O)-(CH₂)_n-C(=O)-; and

X' is Cl, Br, or I.

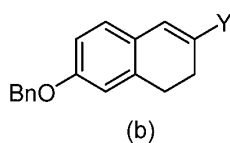
3. The process of claim 1 or claim 2, wherein:
- P₁ is CH₂-aryl;
- P₂ is (C=O)-C₁ alkyl; and
- X' is Cl, Br, or I.
4. The process of any one of claims 1-3, wherein the transition metal catalyst is a palladium-containing catalyst.
5. The process of any one of claims 1-4, wherein the transition metal catalyst comprises Pd(0).
6. The process of any one of claims 1-5, wherein the transition metal catalyst comprises Pd/C.
7. The process of any one of claims 1-6, wherein the base is an inorganic base, an organic base, or a combination thereof.
8. The process of any one of claims 1-7, wherein the base is selected from the group consisting of: K₂CO₃, KO^tBu, Cs₂CO₃, Na₃PO₄, K₃PO₄, KOH, NaOH, CsOH, LiOH, NEt₃, and combinations thereof.
9. The process of any one of claims 1-8, wherein the base is Na₃PO₄.
10. The process of any one of claims 1-9, wherein the compounds of Formulas (I), (II), and (III) are (a), (d) and (e):



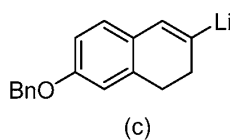
11. The process of any one of claims 1-10, wherein the compound of Formula (I) is a compound of Formula (a):



wherein the compound of Formula (a) is prepared by a process comprising:
reacting a compound of Formula (b):

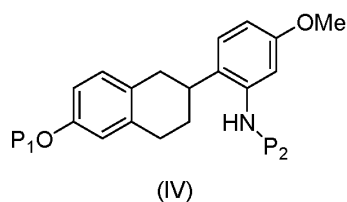


with a lithiation reagent to form a compound of Formula (c):

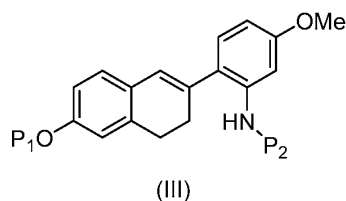


wherein the compound of Formula (c) is reacted with a borate ester and is hydrolyzed to form the compound of Formula (a), wherein Y is Br, Cl, or I.

12. The process of claim 11, wherein the lithiation reagent is *n*-butyl lithium.
13. The process of claim 11 or claim 12, wherein the borate ester is triisopropyl borate.
14. The process of any one of claims 11-13, wherein the process of preparing the compound of Formula (a) is carried out in continuous-flow mode or in batch mode.
15. The process of any one of claims 11-14, wherein the process of preparing the compound of Formula (a) is carried out in continuous-flow mode.
16. A process of preparing a compound of Formula (IV),



the process comprising reduction of a compound of Formula (III):



in the presence of a transition metal catalyst comprising Pd(0),
wherein:

P₁ is H or a phenol protecting group; and

P₂ is H, Et, or an amino protecting group.

17. The process of claim 16, wherein:

P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and

P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, or (C=O)-(CH₂)_n-C(=O)-.

18. The process of claim 16 or 17, wherein P₁ is CH₂-aryl and P₂ is (C=O)-C₁ alkyl.

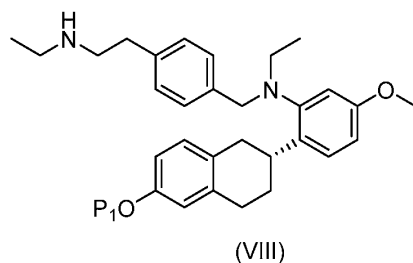
19. The process of any one of claims 16-18, wherein the transition metal catalyst comprises Pd/C.

20. The process of any one of claims 16-19, wherein the reduction is conducted in the presence of H₂.

21. The process of any one of claims 16-20, wherein the process is carried out using continuous-flow mode or batch mode.

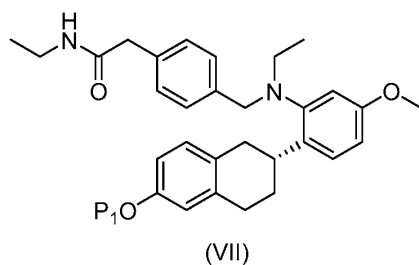
22. The process of any one of claims 16-21, wherein the process is carried out using continuous-flow mode.

23. A process of preparing a compound of Formula (VIII),

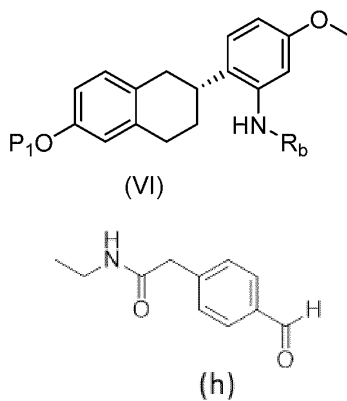


the process comprising:

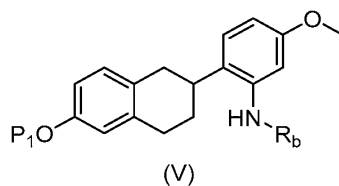
reducing a compound of Formula (VII):



wherein the compound of Formula (VII) is prepared by reductive amination of a compound of Formula (VI) in the presence of a compound of Formula (h):

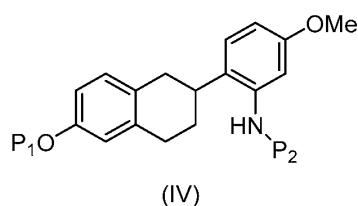


wherein the compound of Formula (VI) is prepared by reacting a compound of Formula (V)

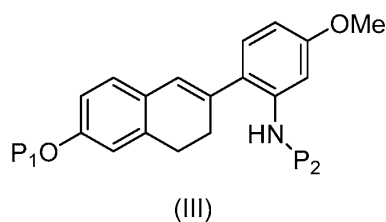


with a chiral acid to form an enantiomerically enriched salt, crystallizing the enantiomerically enriched salt, and freeing the compound of Formula (VI),

wherein the compound of Formula (V) is prepared by treating a compound of Formula (IV) with a deprotecting agent:

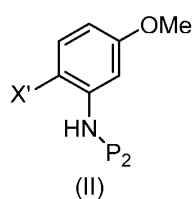
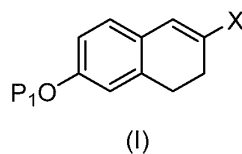


wherein the compound of Formula (IV) is prepared by reduction of a compound of Formula (III):



wherein reduction of the compound of Formula (III) is carried out using a Pd(0) catalyst;

wherein the compound of Formula (III) is prepared by coupling a compound of Formula (I) with a compound of Formula (II):



and wherein P_1 is H or a phenol protecting group; R_b is H or Et; P_2 is (C=O)- C_1 alkyl; X is a boronic acid; X' is a halogen; and

wherein X and X' are suitable for cross-coupling the compound of Formula (I) with the compound of Formula (II).

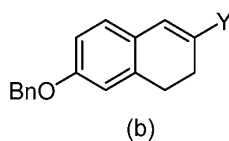
24. The process of claim 23, wherein reduction of the compound of Formula (III) is carried out using batch mode or continuous-flow mode.

25. The process of claim 23 or 24, wherein reduction of the compound of Formula (III) is carried out using continuous-flow mode.

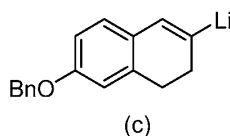
26. The process of any one of claims 23-25, wherein the compound of Formula (I) is the compound of Formula (a).

27. The process of claim 26 wherein the compound of Formula (a) is prepared by a process comprising:

reacting a compound of Formula (b):



with a lithiation reagent to form a compound of Formula (c):



wherein the compound of Formula (c) is reacted with a borate ester and is hydrolyzed to form the compound of Formula (a), wherein Y is Br, Cl, or I.

28. The process of claim 27, wherein the lithiation reagent is *n*-butyl lithium.

29. The process of claim 27 or claim 28, wherein the borate ester is triisopropyl borate.

30. The process of any one of claims 27-29, wherein the process of preparing the compound of Formula (a) is carried out in continuous-flow mode or in batch mode.

31. The process of any one of claims 27-30, wherein the process of preparing the compound of Formula (a) is carried out in continuous-flow mode.