

ENANTIOSELECTIVE SYNTHESIS OF ELACESTRANT INTERMEDIATES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to Italian Application No. 102023000027594, filed on December 21, 2023, the contents of which are incorporated herein by reference in their 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.

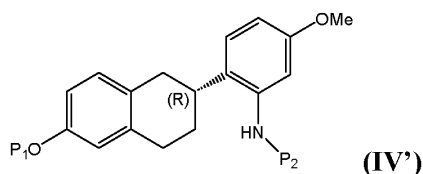
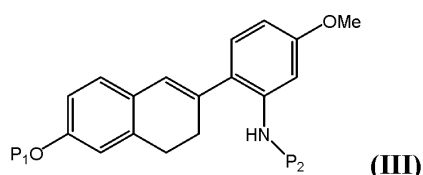
[0003] Elacestrant is an oral nonsteroidal small molecule that acts as a selective estrogen receptor (ER) degrader (SERD). Elacestrant has been approved by the Food and Drug Administration (FDA) for treating postmenopausal women or adult men with ER-positive, HER2-negative, estrogen receptor gene α (ESR1)-mutated 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 method of preparing a compound of **Formula (IV')**, the method comprising:

(a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**

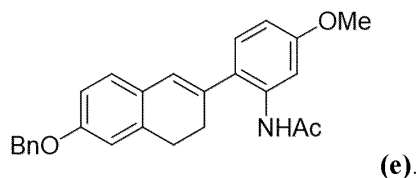


wherein P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and

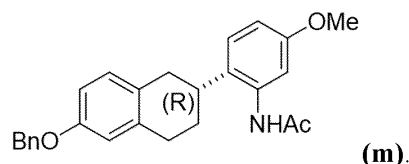
wherein P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O)- wherein n is 2 or 3.

[0006] In some embodiments, P₁ is CH₂-aryl. In some embodiments, P₂ is (C=O)-C₁ alkyl.

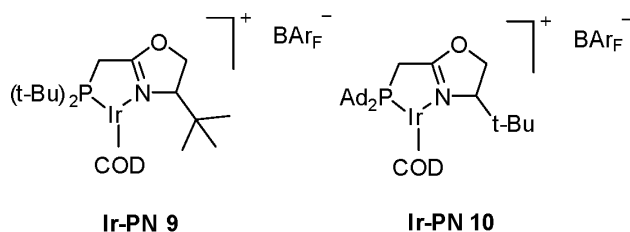
[0007] In some embodiments, the compound of **Formula (III)** is **Compound (e)**:



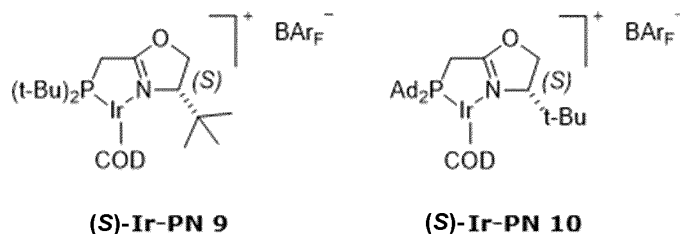
[0008] In some embodiments, the compound of **Formula (IV')** is **Compound (m)**:



[0009] In some embodiments, the enantioselective catalyst comprises a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst. In some embodiments, the enantioselective catalyst comprises an iridium-based catalyst. In some embodiments, the enantioselective catalyst comprises an iridium-PN catalyst. In some embodiments, the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof.



[0010] In some embodiments, the enantioselective catalyst has an (*S*) configuration. In some embodiments, the enantioselective catalyst comprises Ir-PN 9 or Ir-PN 10 in an (*S*) configuration:



[0011] In some embodiments, the catalyst loading is 1.5 mol.% or less, relative to the compound of **Formula (III)**. In some embodiments, the catalyst loading is 1.0 mol.% or less, relative to the compound of **Formula (III)**. In some embodiments, the catalyst loading is 0.5 mol.% to 1.0 mol.%, relative to the compound of **Formula (III)**.

[0012] In some embodiments, the concentration of the compound of **Formula (III)** is greater than 0.07 M. In some embodiments, the concentration of the compound of **Formula (III)** is greater than or equal to 0.1 M. In some embodiments, the concentration of the compound of **Formula (III)** is 0.15 M to 0.5 M. In some embodiments, the concentration of the compound of **Formula (III)** is 0.15 M to 0.22 M.

[0013] In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 7 to 30 bar. In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 14 to 28 bar. In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 25 to 28 bar.

[0014] In some embodiments, the hydrogenation in (a) is performed in trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), or a combination thereof.

[0015] In some embodiments, the hydrogenation in (a) is performed at a temperature of 25 to 90°C. In some embodiments, the hydrogenation in (a) is performed at a temperature of 25 to 40°C.

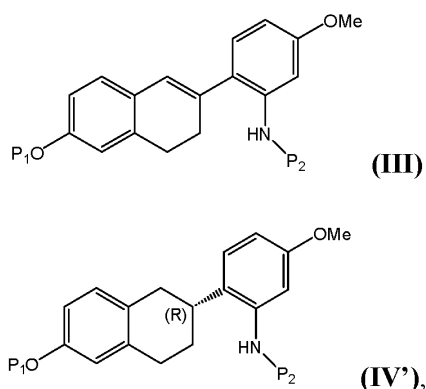
[0016] In some embodiments, the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 90%. In some embodiments, the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 95%.

[0017] In some embodiments, 5% or less of residual compound of **Formula (III)** is present after the hydrogenation in (a).

[0018] In some embodiments, the obtained compound of **Formula (IV')** has a purity of 95% or greater after the hydrogenation in (a).

[0019] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a method of preparing a compound of **Formula (IX)**, the method comprising:

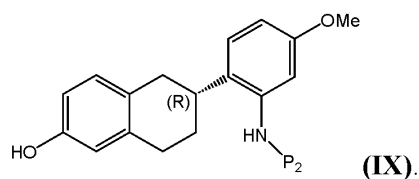
(a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**



wherein 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; and

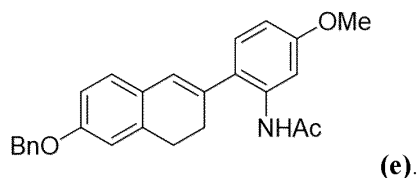
wherein P_2 is H, Et, or an amino protecting group selected from $(C=O)-C_1-C_8$ alkyl, $(C=O)$ -aryl, $(C=O)$ -heteroaryl, $(C=O)-O-C_1-C_8$ alkylaryl, $(C=O)CF_3$, $(C=O)CH_2Cl$, $(C=O)CCl_3$, or $(C=O)-(CH_2)_n-C=O$ - wherein n is 2 or 3; and

(b) deprotecting the compound of **Formula (IV')** in the presence of hydrogen and a second catalyst to obtain a compound of **Formula (IX)**

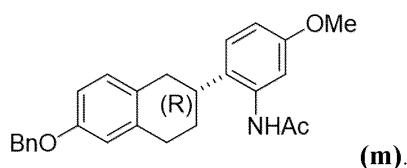


[0020] In some embodiments, P_1 is CH_2 -aryl. In some embodiments, P_2 is $(C=O)-C_1$ alkyl.

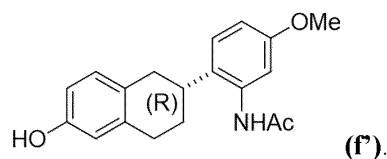
[0021] In some embodiments, the compound of **Formula (III)** is **Compound (e)**:



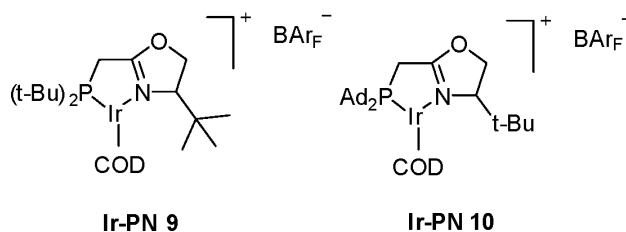
[0022] In some embodiments, the compound of **Formula (IV')** is **Compound (m)**:



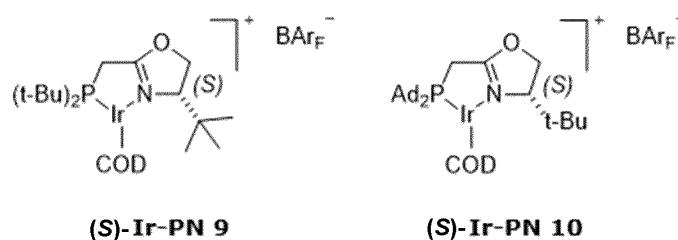
[0023] In some embodiments, the compound of **Formula (IX)** is **Compound (f')**:



[0024] In some embodiments, the enantioselective catalyst comprises a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst. In some embodiments, the enantioselective catalyst comprises an iridium-based catalyst. In some embodiments, the enantioselective catalyst comprises an iridium-PN catalyst. In some embodiments, the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof:



[0025] In some embodiments, the enantioselective catalyst has an (*S*) configuration. In some embodiments, the enantioselective catalyst comprises Ir-PN 9 or Ir-PN 10 in an (*S*) configuration:



[0026] In some embodiments, the catalyst loading is 1.5 mol.% or less, relative to the compound of **Formula (III)**. In some embodiments, the catalyst loading is 1.0 mol.% or less, relative to the compound of **Formula (III)**. In some embodiments, the catalyst loading is 0.5 mol.% to 1.0 mol.%, relative to the compound of **Formula (III)**.

[0027] In some embodiments, the concentration of the compound of **Formula (III)** is greater than 0.07 M. In some embodiments, the concentration of the compound of **Formula (III)** is greater than or equal to 0.1 M. In some embodiments, the concentration of the compound of **Formula (III)** is 0.15 M to 0.5 M. In some embodiments, the concentration of the compound of **Formula (III)** is 0.15 M to 0.22 M.

[0028] In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 7 to 30 bar. In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 14 to 28 bar. In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 25 to 28 bar.

[0029] In some embodiments, the hydrogenation in (a) is performed in trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), or a combination thereof.

[0030] In some embodiments, the hydrogenation in (a) is performed at a temperature of 25 to 90°C. In some embodiments, the hydrogenation in (a) is performed at a temperature of 25 to 40°C.

[0031] In some embodiments, the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 90%. In some embodiments, the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 95%.

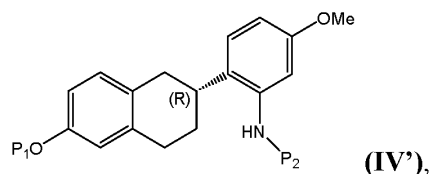
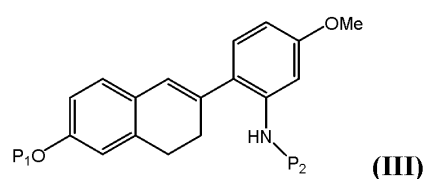
[0032] In some embodiments, 5% or less of the compound of **Formula (III)** is present after the hydrogenation in (a).

[0033] In some embodiments, the obtained compound of **Formula (IV')** has a purity of 95% or greater after the hydrogenation in (a).

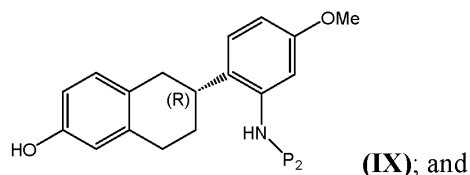
[0034] In some embodiments, the obtained compound of **Formula (IX)** has an enantiomeric excess of 90% or greater. In some embodiments, the obtained compound of **Formula (IX)** has an enantiomeric excess of 95% or greater.

[0035] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a method of preparing **Compound (k)**, the method comprising:

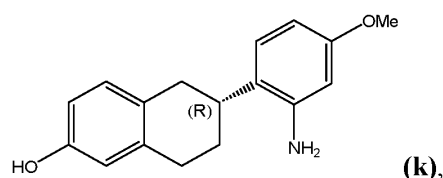
(a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**



(b) deprotecting the compound of **Formula (IV')** in the presence of hydrogen and a second catalyst to obtain the compound of **Formula (IX)**



(c) deprotecting the compound of **Formula (IX)** to obtain the **Compound (k)**

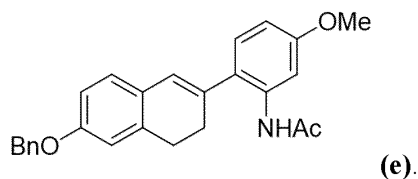


wherein P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and

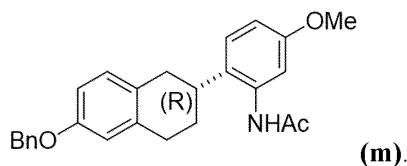
wherein P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O- wherein n is 2 or 3.

[0036] In some embodiments, P₁ is CH₂-aryl. In some embodiments, P₂ is (C=O)-C₁ alkyl.

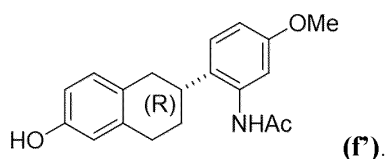
[0037] In some embodiments, the compound of **Formula (III)** is **Compound (e)**:



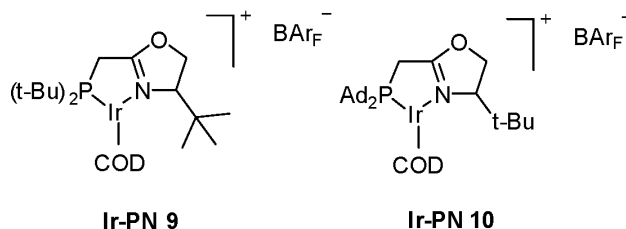
[0038] In some embodiments, the compound of **Formula (IV')** is **Compound (m)**:



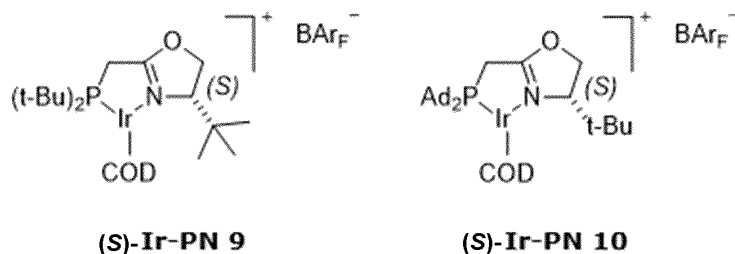
[0039] In some embodiments, the compound of **Formula (IX)** is **Compound (f')**:



[0040] In some embodiments, the enantioselective catalyst comprises a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst. In some embodiments, the enantioselective catalyst comprises an iridium-based catalyst. In some embodiments, the enantioselective catalyst comprises an iridium-PN catalyst. In some embodiments, the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof:



[0041] In some embodiments, the enantioselective catalyst has an (*S*) configuration. In some embodiments, the enantioselective catalyst comprises Ir-PN 9 or Ir-PN 10 in an (*S*) configuration:



[0042] In some embodiments, the catalyst loading is 1.5 mol.% or less, relative to the compound of **Formula (III)**. In some embodiments, the catalyst loading is 1.0 mol.% or less, relative to the compound of **Formula (III)**. In some embodiments, the catalyst loading is 0.5 mol.% to 1.0 mol.%, relative to the compound of **Formula (III)**.

[0043] In some embodiments, the concentration of the compound of **Formula (III)** is greater than 0.07 M. In some embodiments, the concentration of the compound of **Formula (III)** is greater than or equal to 0.1 M. In some embodiments, the concentration of the compound of **Formula (III)** is 0.15 M to 0.5 M. In some embodiments, the concentration of the compound of **Formula (III)** is 0.15 M to 0.22 M.

[0044] In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 7 to 30 bar. In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 14 to 28 bar. In some embodiments, the hydrogenation in (a) is performed at a hydrogen pressure of 25 to 28 bar.

[0045] In some embodiments, the hydrogenation (a) is performed in trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), or a combination thereof.

[0046] In some embodiments, the hydrogenation in (a) is performed at a temperature of 25 to 90°C. In some embodiments, the hydrogenation in (a) is performed at a temperature of 25 to 40°C.

[0047] In some embodiments, the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 90%. In some embodiments, the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 95%.

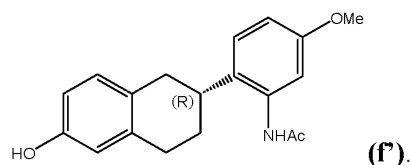
[0048] In some embodiments, 5% or less of the compound of **Formula (III)** is present after the hydrogenation in (a).

[0049] In some embodiments, the obtained compound of **Formula (IV')** has a purity of 95% or greater after the hydrogenation in (a).

[0050] In some embodiments, the **Compound (k)** is obtained in a yield of 70% or greater, relative to the amount of the compound of **Formula (III)**. In some embodiments, the **Compound (k)** is obtained in a yield of 80% or greater, relative to the amount of the compound of **Formula (III)**. In some embodiments, the **Compound (k)** is obtained in a yield of 90% or greater, relative to the amount of the compound of **Formula (III)**.

[0051] In some embodiments, the obtained **Compound (k)** has an optical purity of 90% or greater. In some embodiments, the obtained **Compound (k)** has an optical purity of 95% or greater. In some embodiments, the obtained **Compound (k)** has an optical purity of 97% or greater.

[0052] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to **Compound (f')**, having an optical purity of greater than or equal to about 90%



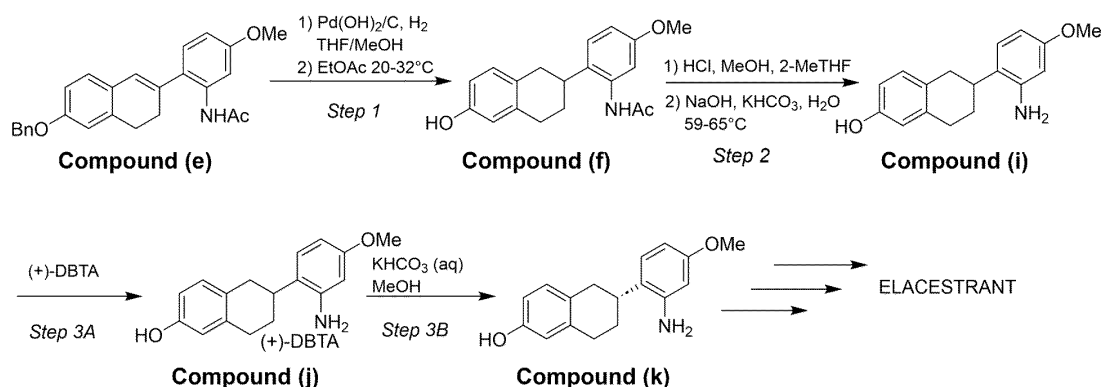
[0053] In some embodiments, the **Compound (f')** has an optical purity of greater than or equal to 95%.

[0054] 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.

DETAILED DESCRIPTION

[0055] A previously reported synthesis of a key chiral intermediate of elacestrant, (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**) is shown in **Scheme 1**. See PCT/US2020/017777.

Scheme 1. Previously reported synthesis of (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**)

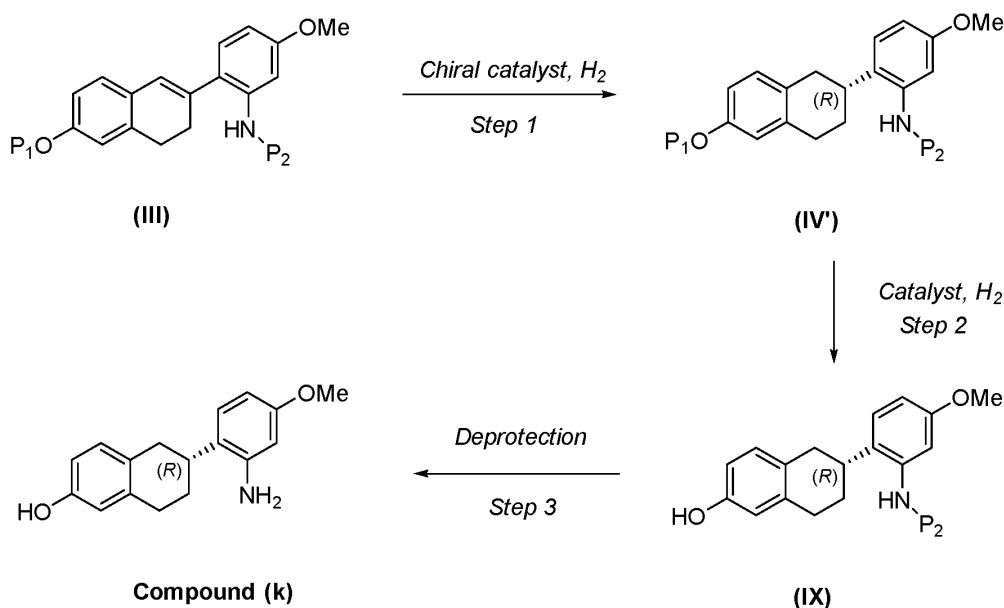


[0056] In particular, the process in PCT/US2020/017777 contemplates a four-step synthesis of **Compound (k)** starting from **Compound (e)**: (1) a Pd-catalyzed hydrogenation; (2) an acid hydrolysis; (3A) resolution by diastereomeric salts crystallization; and (3B) displacement of the chiral auxiliary used to form the diastereomeric salts, to obtain the desired optically pure **Compound (k)**.

[0057] Although the process shown in **Scheme 1** is a viable method for producing elacestrant, the very low overall yield (about 26%) of the process for producing **Compound (k)** from **Compound (e)** is almost exclusively due to the diastereoselective salt resolution step in which the theoretical yield of only 50% is yet further reduced while purging the undesired enantiomer. Indeed, in practice, the yield of this step is much lower than 50% (*e.g.*, 27-32%). Moreover, this key step is also characterized by long cycle times (low productivity), owing to the multiple crystallizations/filtrations necessary to achieve the required optical purity of the diastereomeric salt.

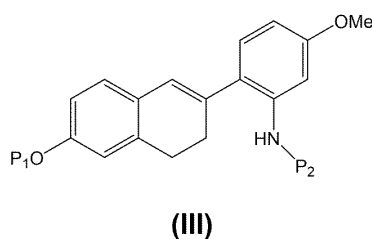
[0058] Therefore, the present inventors endeavored to develop a new process for synthesis of **Compound (k)**, starting from a compound of **Formula (III)**. The method is illustrated in **Scheme 2**.

Scheme 2. Improved synthesis of (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**) according to the present disclosure.



[0059] According to **Scheme 2**, a compound of **Formula (III)** undergoes a three-step transformation to produce the chiral product **Compound (k)**: (1) enantioselective catalytic hydrogenation to form a compound of **Formula (IV')**; (2) deprotection to form a compound of **Formula (IX)**; and (3) deprotection to obtain **Compound (k)** in high yield (greater than 70%) and high optical purity of the (*R*) enantiomer (90% or greater).

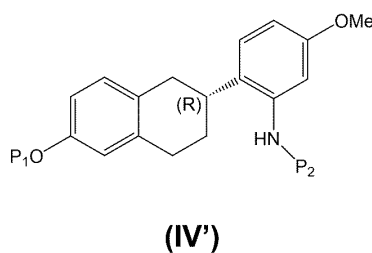
[0060] The compound of **Formula (III)** has the structure shown below:



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

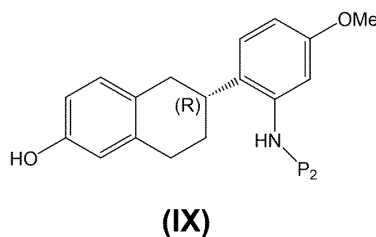
P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O- wherein n is 2 or 3. In some embodiments, P₁ is CH₂-aryl and P₂ is (C=O)-C₁ alkyl.

[0061] The compound of **Formula (IV')** has the structure shown below:



wherein P₁ and P₂ are as defined for **Formula (III)**. The compound of **Formula (IV')** is an enantiomer with high optical purity (*e.g.*, enantiomeric excess > 90%).

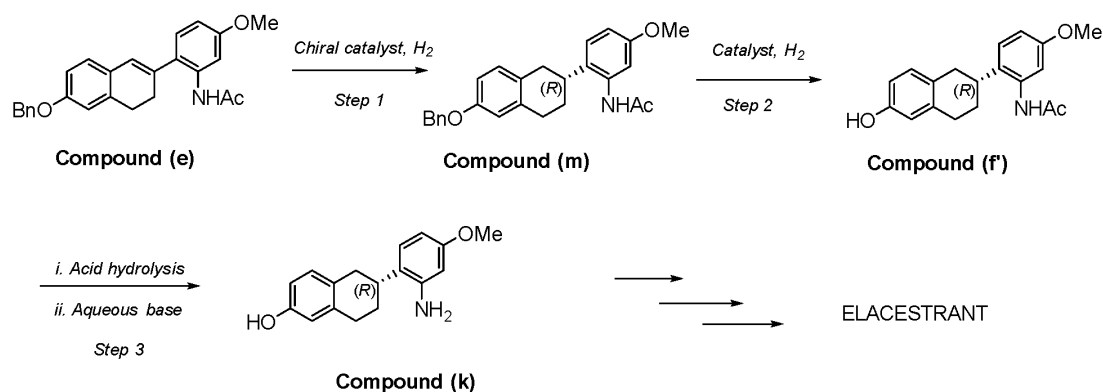
[0062] The compound of **Formula (IX)** has the structure shown below:



wherein P₂ is as defined above for **Formula (III)** and **Formula (IV')**. The compound of **Formula (IX)** is an enantiomer with high optical purity (*e.g.*, enantiomeric excess > 90%).

[0063] In some embodiments, the present disclosure relates to an improved synthesis of **Compound (k)** from starting material **Compound (e)**, with improved safety, reduced cost, and increased yield. By way of non-limiting example, one embodiment of the improved synthesis of (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**) is shown in **Scheme 3**.

Scheme 3. Synthesis of (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**) according to one embodiment of the present disclosure.



[0064] The process of the present disclosure is based on the use of a catalyst (“chiral catalyst”) that unexpectedly promotes formation of a single enantiomer with high yield, upon hydrogenation of an olefinic precursor. This process circumvents the conventional racemate formation, and subsequent enantiomeric resolution, by enantioselectively hydrogenating the olefinic **Compound (e)** to selectively form the *(R)* enantiomer of **Compound (f)**—**Compound (m)**—catalyzed by the enantioselective catalyst. This improved process offers a solution to the aforementioned yield reduction, by introducing the stereocenter with the desired absolute configuration (*R*), without the significant loss of material linked to enantiomeric resolution of the racemate, thus enabling the production of greater amounts of **Compound (k)**—and the eventual API—in a more efficient manner, while decreasing the amount of process waste, including solvents and energy. In fact, the yield achieved by the process according to the present disclosure (**Scheme 3**) is approximately 70% or greater, compared to the yield obtained via the conventional process (**Scheme 1**), which is approximately 26 %.

[0065] Thus, the present inventors have discovered a new route to the key chiral intermediate (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**) that affords high enantioselectivity and enhanced yield.

[0066] As shown in **Scheme 3**, the process proceeds via three steps, compared to the conventional four-step process. In the first step, **Compound (e)** undergoes enantioselective hydrogenation in the presence of an enantioselective catalyst to form the *(R)* enantiomer

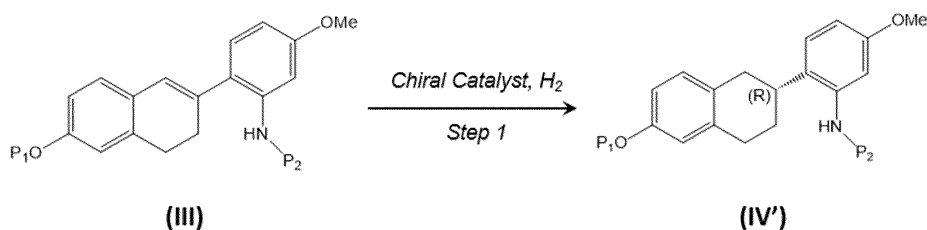
Compound (m). In the second step, the protective benzyl group of the (*R*) enantiomer **Compound (m)** is cleaved in a Pd-catalyzed hydrogenation to produce the (*R*) enantiomer **Compound (f')**. In the third step, **Compound (f')** undergoes deprotection, preferably acid hydrolysis, to produce the key intermediate (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**).

[0067] In addition to the improved yield due to enantioselective hydrogenation, the synthetic process is unexpectedly improved by the use of fluorinated solvents TFE and HFIP, compared to the use of conventionally chlorinated solvents. Fluorinated solvents TFE and HFIP have an improved safety profile compared to the conventionally used DCE, allow lower reaction temperatures, require less catalyst, and require less solvent, all of which contribute to a more efficient process.

Enantioselective Hydrogenation (Step 1)

[0068] In an aspect, the present disclosure relates a method of preparing a compound of **Formula (IV')**, the method comprising hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**, wherein the compound of **Formula (IV')** is an (*R*) enantiomer. See **Scheme 4**.

Scheme 4. Enantioselective Hydrogenation of Compound of **Formula (III)** to Obtain Compound of **Formula (IV')**

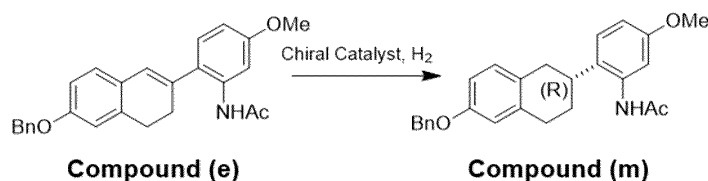


wherein P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and

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, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, 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.

[0069] In some embodiments, compound of **Formula (III)** is **Compound (e)**. In some embodiments, the compound of **Formula (IV')** is **Compound (m)**. Thus, in some embodiments, the present disclosure relates to a method of preparing **Compound (m)**, the method comprising hydrogenating **Compound (e)** in the presence of an enantioselective catalyst to produce **Compound (m)**, wherein **Compound (m)** is an (*R*) enantiomer.

Scheme 5. Enantioselective Hydrogenation of **Compound (e)** to Obtain **Compound (m)**



[0070] In some embodiments, the optical purity of the compound of **Formula (IV')** (*e.g.*, **Compound (m)**) after the enantioselective hydrogenation is greater than or equal to 70%, greater

than or equal to 75%, greater than or equal to 80%, greater than or equal to 85%, greater than or equal to 86%, greater than or equal to 87%, greater than or equal to 88%, greater than or equal to 89%, greater than or equal to 90%, greater than or equal to 91%, greater than or equal to 92%, greater than or equal to 93%, greater than or equal to 94%, greater than or equal to 95%, greater than or equal to 96%, greater than or equal to 97%, greater than or equal to 98%, greater than or equal to 99%, or any range or value therein between.

[0071] In some embodiments, the purity of the compound of **Formula (IV')** (*e.g.*, **Compound (m)**) after the enantioselective hydrogenation is greater than or equal to 70%, greater than or equal to 75%, greater than or equal to 80%, greater than or equal to 85%, greater than or equal to 86%, greater than or equal to 87%, greater than or equal to 88%, greater than or equal to 89%, greater than or equal to 90%, greater than or equal to 91%, greater than or equal to 92%, greater than or equal to 93%, greater than or equal to 94%, greater than or equal to 95%, greater than or equal to 96%, greater than or equal to 97%, greater than or equal to 98%, greater than or equal to 99%, or any range or value therein between.

[0072] In some embodiments, the yield of the compound of **Formula (IV')** (*e.g.*, **Compound (m)**), relative to starting material of **Formula (III)** (*e.g.*, **Compound (e)**), after the enantioselective hydrogenation, is greater than or equal to 70%, greater than or equal to 75%, greater than or equal to 80%, greater than or equal to 85%, greater than or equal to 86%, greater than or equal to 87%, greater than or equal to 88%, greater than or equal to 89%, greater than or equal to 90%, greater than or equal to 91%, greater than or equal to 92%, greater than or equal to 93%, greater than or equal to 94%, greater than or equal to 95%, greater than or equal to 96%, greater than or equal to 97%, greater than or equal to 98%, greater than or equal to 99%, or any range or value therein between.

Enantioselective Catalysts

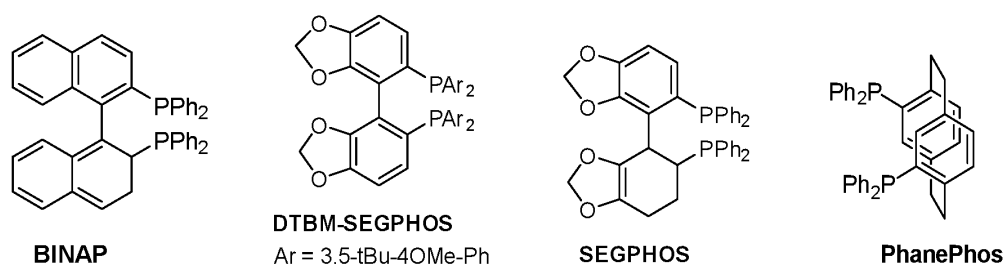
[0073] The enantioselective catalysis step of the present disclosure is based on a stereoselective hydrogenation of the olefinic compound of **Formula (III)** (*e.g.*, **Compound (e)**) (*see, e.g.*,

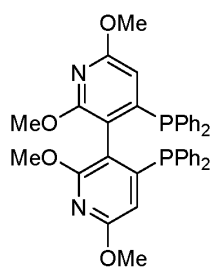
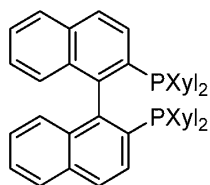
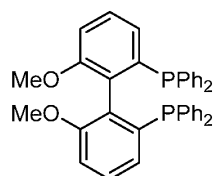
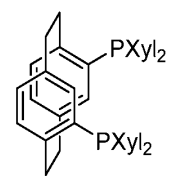
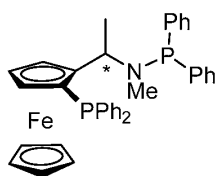
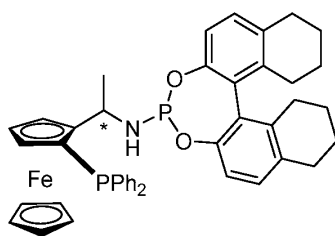
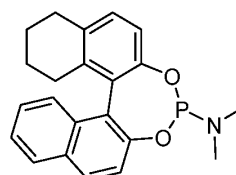
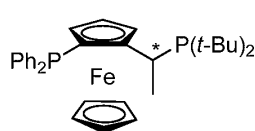
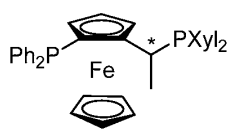
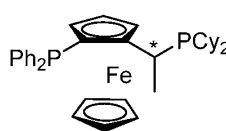
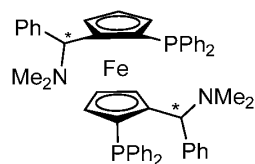
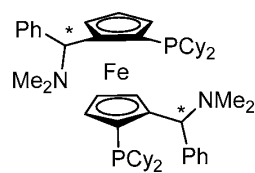
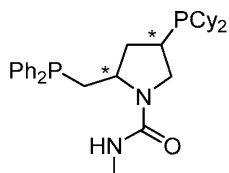
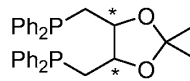
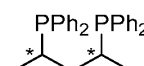
Schemes 3–5). In particular, the desired (*R*)-enantiomer, **Compound (k)**, is obtained in a 3-step synthesis starting from a compound of **Formula III** (such as **Compound (e)**). The process uses a catalyst that permits obtaining the desired enantiomer with high optical purity. For purposes of the present disclosure, the term “enantiomeric excess (e.e.)” or “optical purity” means the percentage excess of the major enantiomer over the minor enantiomer. Unless specified otherwise, with respect to compounds of **Formula (IV’)** (e.g., **Compound (m)**), compounds of **Formula IX** (e.g., **Compound (f’)**), and **Compound (k)**, the enantiomeric excess refers to the relative proportion of the (*R*) enantiomer.

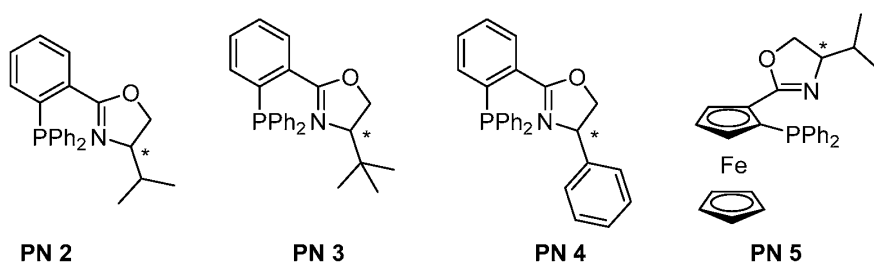
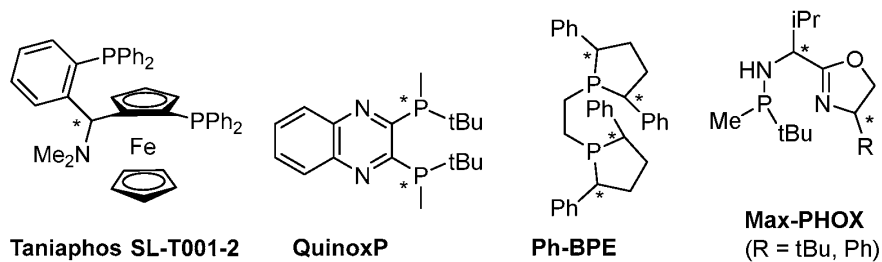
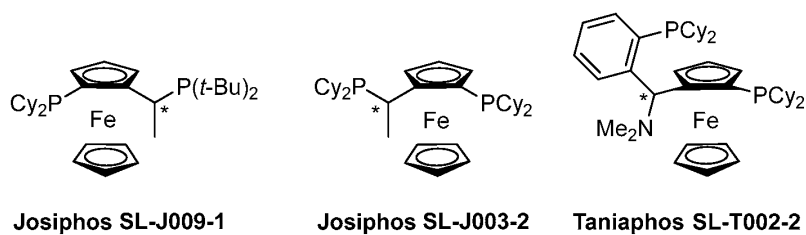
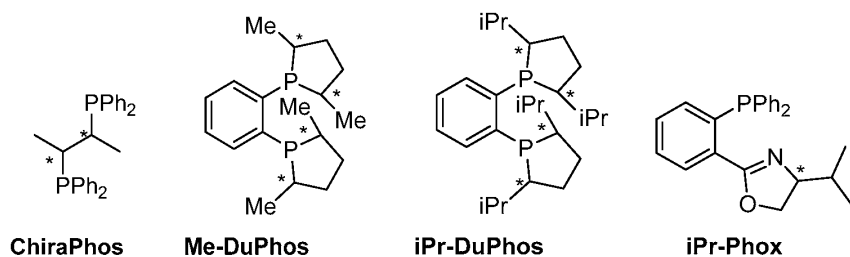
[0074] The enantioselective catalyst (“chiral catalyst”) may be any suitable compound having a transition metal center and a chiral ligand bound to the metal center. In some embodiments, the transition metal center can be Ru, Rh, Ir, Fe, Co, Ni, Pd, Re, Os, or Pt. In some embodiments, the transition metal center is Ir (*i.e.*, the enantioselective catalyst is an iridium-based catalyst). The enantioselective catalyst can be a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst.

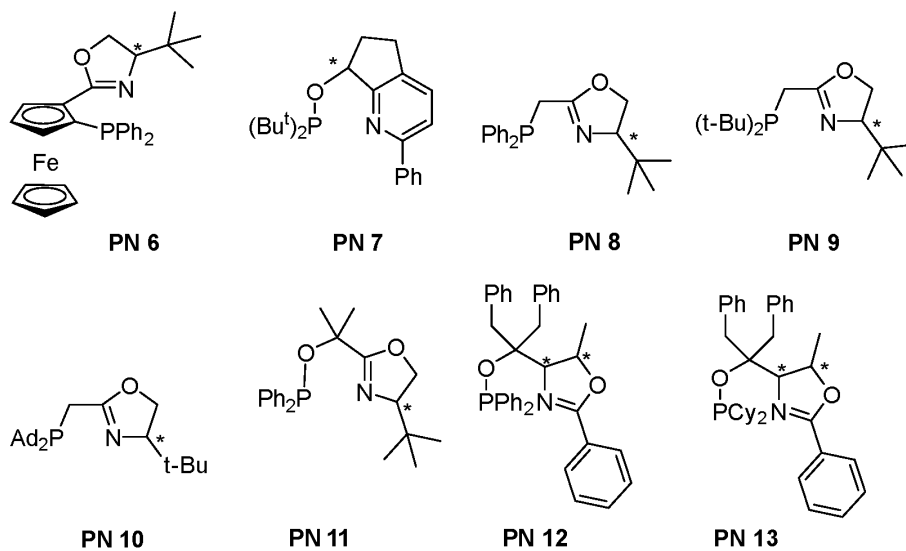
[0075] The chiral ligand may be any suitable ligand for promoting the enantioselective hydrogenation of the compound of **Formula (III)** (e.g., **Compound (e)**) to obtain the compound of **Formula (IV’)** (e.g., **Compound (m)**, an (*R*) enantiomer). Suitable ligands for promoting the enantioselective hydrogenation can be, for example and not limited to, ligands shown in **Scheme 6A**. Ligands listed in **Scheme 6A** can be used with stereochemistry *R* or *S*; *RR*, *SS*, *RS*, or *SR*.

Scheme 6A. Ligands for promoting enantioselective hydrogenation.



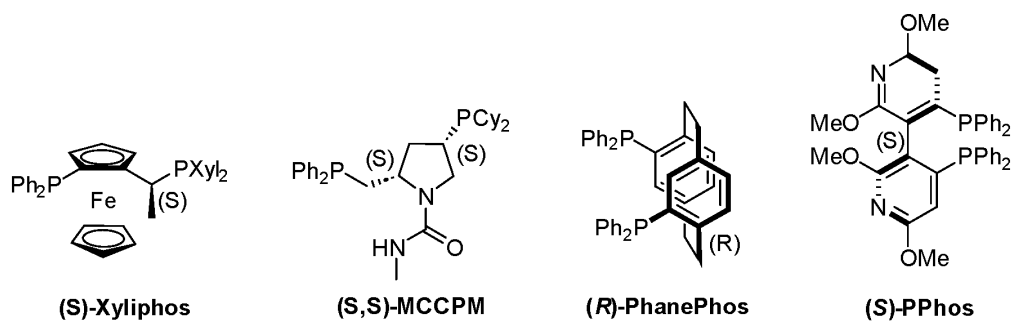
**PPhos****Xyl-BINAP****MeO-BiPhep****Xyl-PhanePhos****Me-BoPhoz****[P-H8-BINOL]-BoPhoz****Monophos****Josiphos SL-J002-1****Xyliphos****Josiphos SL-J001-1****Mandyphos SL-M001-1****Mandyphos SL-M002-1****MCCPM****DIOP****BDPP**

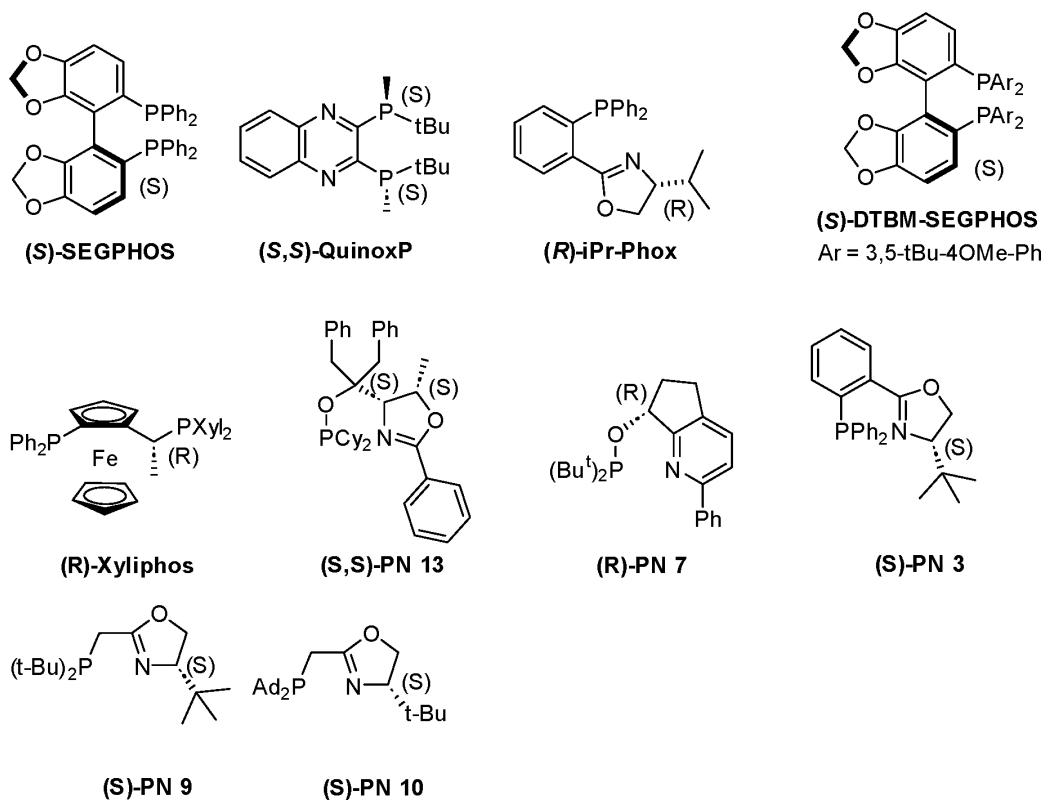




[0076] In some embodiments, the chiral ligand is one or more of the compounds shown in Scheme 6B.

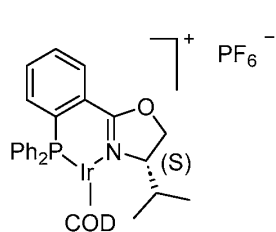
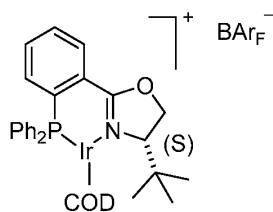
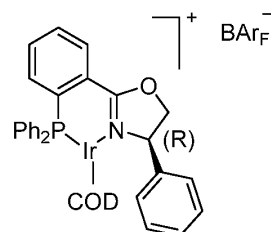
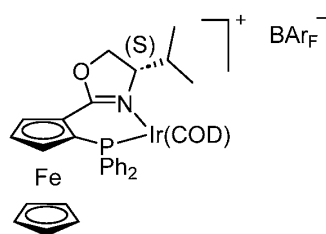
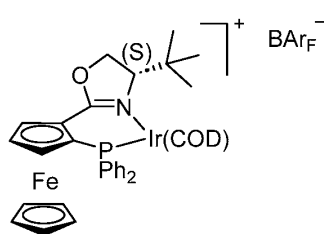
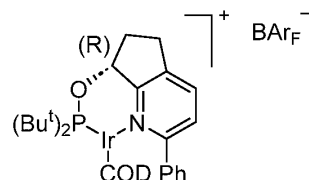
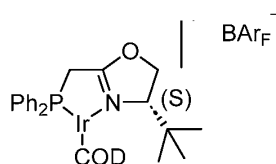
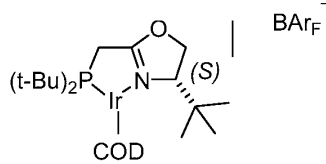
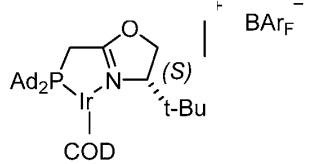
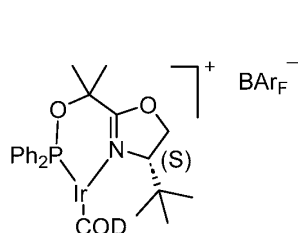
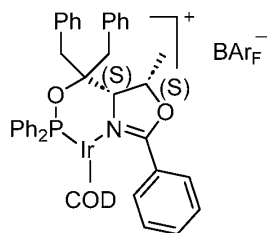
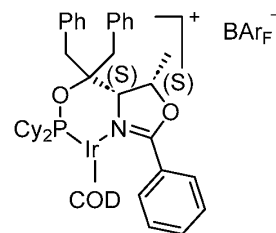
Scheme 6B. Exemplary Chiral Ligands





[0077] In some embodiments, the enantioselective catalyst is an iridium-based catalyst. In some embodiments, the enantioselective catalyst comprises a chiral ligand selected from (*S*)-Xyliphos, (*S,S*)-MCCPM, (*R*)-PhanePhos, (*S*)-PPhos, (*S*)-SEGPHOS, (*S,S*)-QuinoxP, (*R*)-iPr-Phox, (*S*)-DTBM-SEGPHOS, (*R*)-Xyliphos, (*S,S*)-PN 13, (*R*)-PN 7, (*S*)-PN 3, (*S*)-PN 9, and (*S*)-PN 10. In some embodiments, the enantioselective catalyst has an (*S*) configuration. In some embodiments, the Ir-PN catalysts are shown in **Scheme 7**. For sake of clarity in **Scheme 7**, COD stands for 1, 5-cyclooctadiene.

Scheme 7. Exemplary Enantioselective Catalysts

**Ir-PN 2****Ir-PN 3****Ir-PN 4****Ir-PN 5****Ir-PN 6****Ir-PN 7****Ir-PN 8****Ir-PN 9****Ir-PN 10****Ir-PN 11****Ir-PN 12****Ir-PN 13**

[0078] In some embodiments, the enantioselective catalyst is selected from the group consisting of: **Ir-PN 3**; **Ir-PN 7**; **Ir-PN 9**; **Ir-PN 10**; **Ir-PN 13**; and combinations thereof. In some embodiments, the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof. In some embodiments, the enantioselective catalyst comprises **Ir-PN 9**. In some embodiments, the enantioselective catalyst comprises **Ir-PN 10**.

[0079] For the enantioselective hydrogenation, the enantioselective catalyst may be present at a suitable concentration that is high enough to ensure efficient enantioselective conversion of the compound of **Formula (III)** (*e.g.*, **Compound (e)**) to the compound of **Formula (IV')** (*e.g.*, **Compound (m)**) but at a low enough concentration to avoid excess cost associated with the use of transition metal catalysts and purifying the obtained intermediates (and/or the eventual API) to remove residual catalysts or components thereof.

[0080] In some embodiments, the enantioselective catalyst is present at a concentration, relative to the concentration of the compound of **Formula (III)** (*e.g.*, **Compound (e)**), of 2.0 mol.% or less, 1.9 mol.% or less, 1.8 mol.% or less, 1.7 mol.% or less, 1.6 mol.% or less, 1.5 mol.% or less, 1.4 mol.% or less, 1.3 mol.% or less, 1.2 mol.% or less, 1.1 mol.% or less, 0.9 mol.% or less, 0.8 mol.% or less, 0.7 mol.% or less, 0.6 mol.% or less, 0.4 mol.% or less, 0.3 mol.% or less, 0.2 mol.% or less, 0.1 mol.% or less, or any range or value therein between.

[0081] In some embodiments, the enantioselective catalyst is present at a concentration, relative to the concentration of the compound of **Formula (III)** (*e.g.*, **Compound (e)**), of 0.1 mol.% or more, 0.2 mol.% or more, 0.3 mol.% or more, 0.4 mol.% or more, 0.5 mol.% or more, 0.6 mol.% or more, 0.7 mol.% or more, 0.8 mol.% or more, 0.9 mol.% or more, 1.0 mol.% or more, 1.1 mol.% or more, 1.2 mol.% or more, 1.3 mol.% or more, 1.4 mol.% or more, 1.5 mol.% or more, 1.6 mol.% or more, 1.7 mol.% or more, 1.8 mol.% or more, 1.9 mol.% or more, 2.0 mol.% or more or any range or value therein between.

[0082] In some embodiments, the enantioselective catalyst is present at a concentration, relative to the concentration of the compound of **Formula (III)** (*e.g.*, **Compound (e)**), of about 0.1

mol.%, about 0.2 mol.%, about 0.3 mol.%, about 0.4 mol.%, about 0.5 mol.%, about 0.6 mol.%, about 0.7 mol.%, about 0.8 mol.%, about 0.9 mol.%, about 1.0 mol.%, about 1.1 mol.%, about 1.2 mol.%, about 1.3 mol.%, about 1.4 mol.%, about 1.5 mol.%, about 1.6 mol.%, about 1.7 mol.%, about 1.8 mol.%, about 1.9 mol.%, about 2.0 mol.%, or any range or value therein between.

[0083] In some embodiments, the enantioselective catalyst is present at a concentration, relative to the concentration of the compound of **Formula (III)** (*e.g.*, **Compound (e)**), of 0.1 mol.% to 2.0 mol.%, 0.1 mol.% to 1.5 mol.%, 0.1 mol.% to 1.0 mol.%, 0.1 mol.% to 0.5 mol.%, 0.5 mol.% to 2.0 mol.%, 0.5 mol.% to 1.5 mol.%, 0.5 mol.% to 1.0 mol.%, 1.0 mol.% to 2.0 mol.%, 1.0 mol.% to 1.5 mol.%, or any range or value therein. In some embodiments, the enantioselective catalyst is present at a concentration, relative to the concentration of the compound of **Formula (III)** (*e.g.*, **Compound (e)**), of 0.5 mol.% to 1.0 mol.%.

[0084] The compound of **Formula III** (*e.g.*, **Compound (e)**) may be present at any suitable concentration high enough to ensure adequate yield of intermediate compound of **Formula (IV')** (*e.g.*, **Compound (m)**) but low enough to ensure uniform dissolution in the reaction solvent.

[0085] In some embodiments, the compound of **Formula (III)** (*e.g.*, **Compound (e)**) is present at a concentration of 0.07 M or more, 0.08 M or more, 0.09 M or more, 0.10 M or more, 0.15 M or more, 0.20 M or more, 0.22 M or more, 0.25 M or more, 0.30 M or more, 0.35 M or more, 0.40 M or more, 0.45 M or more, 0.50 M or more, 0.55 M or more, 0.60 M or more, 0.65 M or more, 0.70 M or more, 0.75 M or more, 0.80 M or more, 0.85 M or more, 0.90 M or more, 0.95 M or more, 1.0 M or more, or any range or value therein between.

[0086] In some embodiments, the compound of **Formula (III)** (*e.g.*, **Compound (e)**) is present at a concentration of 1.0 M or less, 0.95 M or less, 0.90 M or less, 0.85 M or less, 0.80 M or less, 0.75 M or less, 0.70 M or less, 0.65 M or less, 0.60 M or less, 0.55 M or less, 0.50 M or less, 0.45 M or less, 0.40 M or less, 0.35 M or less, 0.30 M or less, 0.25 M or less, 0.22 M or less,

0.20 M or less, 0.15 M or less, 0.10 M or less, 0.09 M or less, 0.08 M or less, or any range or value therein between.

[0087] In some embodiments, the compound of **Formula (III)** (*e.g.*, **Compound (e)**) is present at a concentration of 0.1 M to 5 M, 0.1 M to 4.5 M, 0.1 M to 4.0 M, 0.1 M to 3.5 M, 0.1 M to 3.0 M, 0.1 M to 2.5 M, 0.1 M to 2.0 M, 0.1 M to 1.5 M, 0.1 M to 1.0 M, 0.1 M to 0.9 M, 0.1 M to 0.8 M, 0.1 M to 0.7 M, 0.1 M to 0.6 M, 0.1 M to 0.5 M, 0.1 M to 0.4 M, 0.1 M to 0.3 M, 0.1 M to 0.25 M, 0.1 M to 0.22 M, 0.1 M to 0.2 M, 0.1 M to 0.15 M, 0.15 M to 5 M, 0.15 M to 4.5 M, 0.15 M to 4.0 M, 0.15 M to 3.5 M, 0.15 M to 3.0 M, 0.15 M to 2.5 M, 0.15 M to 2.0 M, 0.15 M to 1.5 M, 0.15 M to 1.0 M, 0.15 M to 0.9 M, 0.15 M to 0.8 M, 0.15 M to 0.7 M, 0.15 M to 0.6 M, 0.15 M to 0.5 M, 0.15 M to 0.4 M, 0.15 M to 0.3 M, 0.15 M to 0.25 M, 0.15 M to 0.22 M, 0.15 M to 0.2 M, or any range or value therein.

[0088] During enantioselective hydrogenation, the hydrogen pressure may be any suitable pressure to ensure high yield of the compound of **Formula (IV')** (*e.g.*, **Compound (m)**) without presenting a safety hazard. In some embodiments, the hydrogen pressure is 1 bar or more, 2 bar or more, 3 bar or more, 4 bar or more, 5 bar or more, 6 bar or more, 7 bar or more, 8 bar or more, 9 bar or more, 10 bar or more, 11 bar or more, 12 bar or more, 13 bar or more, 14 bar or more, 15 bar or more, 16 bar or more, 17 bar or more, 18 bar or more, 19 bar or more, 20 bar or more, 21 bar or more, 22 bar or more, 23 bar or more, 24 bar or more, 25 bar or more, 26 bar or more, 27 bar or more, 28 bar or more, 29 or more, 30 bar or more, 35 bar or more, 40 bar or more, or any range or value therein between.

[0089] In some embodiments, the hydrogen pressure is 40 bar or less, 35 bar or less, 30 bar or less, 29 bar or less, 28 bar or less, 27 bar or less, 26 bar or less, 25 bar or less, 24 bar or less, 23 bar or less, 22 bar or less, 21 bar or less, 20 bar or less, 19 bar or less, 18 bar or less, 17 bar or less, 16 bar or less, 15 bar or less, 14 bar or less, 13 bar or less, 12 bar or less, 11 bar or less, 10 bar or less, 9 bar or less, 8 bar or less, 7 bar or less, 6 bar or less, 5 bar or less, 4 bar or less, 3 bar or less, 2 bar or less, 1 bar or less, or any range or value therein between.

[0090] In some embodiments, the hydrogen pressure is 5 bar to 30 bar, 5 bar to 28 bar, 5 bar to 25 bar, 5 bar to 22 bar, 5 bar to 20 bar, 5 bar to 18 bar, 5 bar to 15 bar, 5 bar to 12 bar, 5 bar to 10 bar, 5 bar to 7 bar, 7 bar to 30 bar, 7 bar to 28 bar, 7 bar to 25 bar, 7 bar to 22 bar, 7 bar to 20 bar, 7 bar to 18 bar, 7 bar to 15 bar, 7 bar to 12 bar, 7 bar to 10 bar, 10 bar to 30 bar, 10 bar to 25 bar, 10 bar to 22 bar, 10 bar to 20 bar, 10 bar to 18 bar, 10 bar to 15 bar, 7 bar to 28 bar, 10 bar to 28 bar, 12 bar to 28 bar, 14 bar to 28 bar, 15 bar to 28 bar, 20 bar to 28 bar, 22 bar to 28 bar, 22 bar to 25 bar, 25 to 28 bar, or any range or value therein between.

[0091] In some embodiments, the enantioselective hydrogenation is performed at a temperature of 10°C or more, 15°C or more, 20°C or more, 25°C or more, 30°C or more, 35°C or more, 40°C or more, 45°C or more, 50°C or more, 55°C or more, 60°C or more, 65°C or more, 70°C or more, or any range or value therein between.

[0092] In some embodiments, the enantioselective hydrogenation is performed at a temperature of 90°C or less, 85°C or less, 80°C or less, 75°C or less, 70°C or less, 65°C or less, 60°C or less, 55°C or less, 50°C or less, 45°C or less, 40°C or less, 35°C or less, 30°C or less, 25°C or less, 20°C or less, or any range or value therein between.

[0093] In some embodiments, the enantioselective hydrogenation is performed at a temperature of 10°C to 90°C, 15°C to 90°C, 20°C to 90°C, 25°C to 90°C, 30°C to 90°C, 35°C to 90°C, 40°C to 90°C, 45°C to 90°C, 50°C to 90°C, 55°C to 90°C, 60°C to 90°C, 65°C to 90°C, 70°C to 90°C, 10°C to 80°C, 15°C to 80°C, 20°C to 80°C, 25°C to 80°C, 30°C to 80°C, 35°C to 80°C, 40°C to 80°C, 45°C to 80°C, 50°C to 80°C, 55°C to 80°C, 60°C to 80°C, 10°C to 70°C, 15°C to 70°C, 20°C to 70°C, 25°C to 70°C, 30°C to 70°C, 35°C to 70°C, 40°C to 70°C, 45°C to 70°C, 50°C to 70°C, 10°C to 60°C, 15°C to 60°C, 20°C to 60°C, 25°C to 60°C, 30°C to 60°C, 35°C to 60°C, 40°C to 60°C, 45°C to 60°C, 50°C to 60°C, 10°C to 50°C, 15°C to 50°C, 20°C to 50°C, 25°C to 50°C, 30°C to 50°C, 35°C to 50°C, 40°C to 50°C, 10°C to 40°C, 15°C to 40°C, 20°C to 40°C, 25°C to 40°C, 30°C to 40°C, or any range or value therein.

[0094] Additionally, the reaction solvent plays a role in achieving the desired conversion of the precursor compound of **Formula (III)** (*e.g.*, **Compound (e)**), depressing the formation of unwanted impurities and promoting a high optical purity of the intermediate compound of **Formula (IV')** (*e.g.*, **Compound (m)**). In some embodiments, the solvent comprises trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), dichloromethane (DCM), tetrahydrofuran (THF), 1,2-dichloroethane (DCE), ethyl acetate (EtOAc), 1,4-dioxane, ethanol (EtOH), isopropanol (IPA), trichloroethylene, tetrachloroethylene, chloromethane, 1,1,1-trichloroethane, 1,1,2,2-tetrachloroethane, chlorobenzene, 1,2-dichlorobenzene, 1,1-dichloroethene, dichlorodifluoromethane, 1,2-dichloropropane, 1,3-dichloropropene, chloroform, 1,2,3-trichloropropane, carbon tetrachloride, trichlorofluoromethane, hexafluorobenzene, tetradecafluorohexane, octafluorotoluene, octadecafluorooctane, octafluorocyclopentene, or any combination thereof. In some embodiments, the solvent comprises a fluorinated solvent. In some embodiments, the solvent comprises TFE, HFIP, or a combination thereof. In some embodiments, the solvent comprises TFE. In some embodiments, the solvent comprises HFIP.

[0095] In some embodiments, the enantioselective hydrogenation is performed using an additive. In some embodiments, the additive comprises $\text{BF}_3 \cdot \text{OEt}_2$, AcOH, NaBPh₄, 2-(N-morpholin)ethane sulfonic acid, benzanilide, Zn, Na₂SO₄, KOTf, MgO, Zn₃(BO₄)₂.

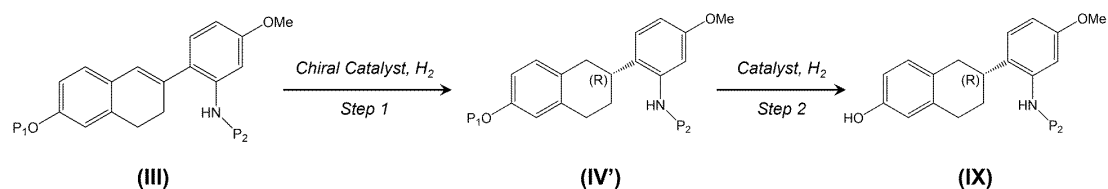
[0096] In some embodiments, the additive is present in the hydrogenation reaction solution at a concentration, relative to the of **Formula (III)** (*e.g.*, **Compound (e)**), of 0.1 mol% or more, 0.2 mol.% or more, 0.3 mol% or more, 0.4 mol% or more, 0.5 mol% or more, 0.6 mol% or more, 0.7 mol% or more, 0.8 mol% or more, 0.9 mol% or more, 1.0 mol% or more, 1.5 mol% or more, 2.0 mol% or more, 2.5 mol% or more, 3.0 mol% or more, 3.5 mol% or more, 4.0 mol% or more, 4.5 mol% or more, 5.0 mol% or more, 5.5 mol% or more, 6.0 mol% or more, 6.5 mol% or more, 7.0 mol% or more, 7.5 mol% or more, 8.0 mol% or more, 8.5 mol% or more, 9.0 mol% or more, 10.0 mol% or more, 11 mol% or more, 12 mol% or more, 13 mol% or more, 14 mol% or more, 15 mol% or more, or any range or value therein between.

[0097] In some embodiments, the additive is present in the hydrogenation reaction solution at a concentration, relative to the of **Formula (III)** (*e.g.*, **Compound (e)**), of 15 mol.% or less, 14 mol.% or less, 13 mol.% or less, 12 mol.% or less, 11 mol.% or less, 10.0 mol.% or less, 9.5 mol.% or less, 9.0 mol.% or less, 8.5 mol.% or less, 8.0 mol.% or less, 7.5 mol.% or less, 7.0 mol.% or less, 6.5 mol.% or less, 6.0 mol.% or less, 5.5 mol.% or less, 5.0 mol.% or less, 4.5 mol.% or less, 4.0 mol.% or less, 3.5 mol.% or less, 3.0 mol.% or less, 2.5 mol.% or less, 2.0 mol.% or less, 1.5 mol.% or less, 1.0 mol.% or less, 0.9 mol.% or less, 0.8 mol.% or less, 0.7 mol.% or less, 0.6 mol.% or less, 0.5 mol.% or less, 0.4 mol.% or less, 0.3 mol.% or less, 0.2 mol.% or less, 0.1 mol.% or less, or any range or value therein between.

[0098] In some embodiments, the enantioselective hydrogenation is carried out using continuous-, semi-continuous- or batch-mode. In some embodiments, the enantioselective hydrogenation is carried out using continuous-flow mode. In some embodiments, the enantioselective hydrogenation in continuous-flow mode is performed using a bubbling bed or a trickle-bed configuration. In some embodiments, the enantioselective hydrogenation in continuous-flow mode is performed using a bubbling bed configuration.

Deprotection (*e.g.*, Catalyzed Hydrogenation) (Step 2)

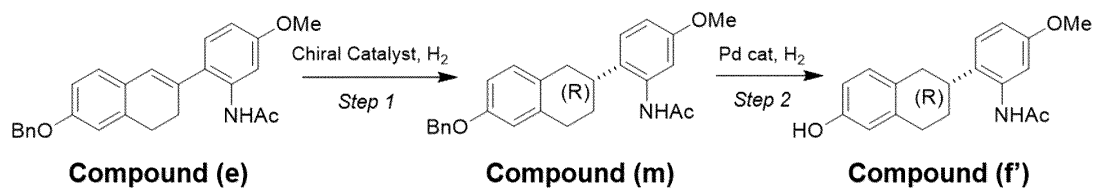
[0099] In another aspect, which may be combined with any other aspect or embodiment, the present disclosure relates to a method of preparing a compound of **Formula (IX)**, the method comprising: (a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce a compound of **Formula (IV')**; and (b) deprotecting the compound of **Formula (IV')** in the presence of hydrogen and a second catalyst to obtain the compound of **Formula (IX)**. *See Scheme 8.*

Scheme 8. Method of Preparing a Compound of **Formula (IX)**

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, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, 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.

[0100] In some embodiments, the compound of **Formula (III)** is **Compound (e)**. In some embodiments, the compound of **Formula (IV')** is **Compound (m)**. In some embodiments, the compound of **Formula (IX)** is **Compound (f')**. Thus, in some embodiments the present disclosure relates to a method of preparing **Compound (f')**, the method comprising: (a) hydrogenating **Compound (e)** in the presence of an enantioselective catalyst to produce **Compound (m)**; and (b) deprotecting the **Compound (m)** in the presence of hydrogen and a second catalyst to obtain **Compound (f')**. See **Scheme 9**.

Scheme 9. Method for Preparing **Compound (f')** from **Compound (e)**

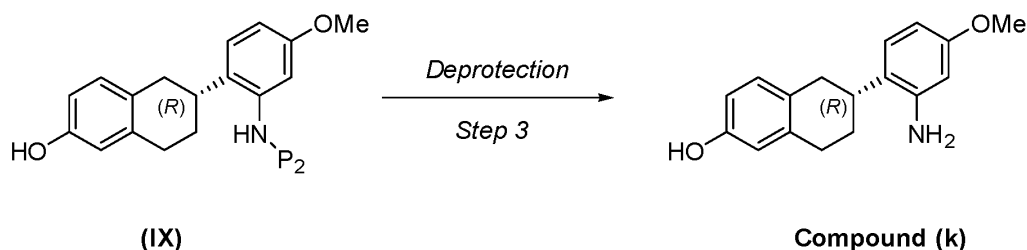
[0101] The catalyzed hydrogenation of the compound of **Formula (IV')** (e.g., **Compound (m)**) is performed using one or more transition metal catalysts. In some embodiments, the transition

metal catalyst comprises a metal selected from Pd, Pt, Rh, Ru, Ni, Co, Fe, and combinations thereof. In some embodiments, the metal catalyst is supported on a material selected from: carbon, Al₂O₃, Al₂CO₃, CaCO₃, BaSO₄, SiO₂, TiO₂, zeolites, CeO₂, organic polymers (such as polystyrene and copolymers), cyclodextrins, or any combination 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 transition metal catalyst comprises or consists of FeCl₃. In some embodiments, the transition metal catalyst comprises or consists of FeCl₃ in a chlorinated solvent.

[0102] In some embodiments, the catalyzed hydrogenation is carried out using continuous-, semi-continuous- or batch-mode. In some embodiments, the catalyzed hydrogenation is carried out using continuous-flow mode. In some embodiments, the catalyzed hydrogenation in continuous-flow mode is performed using a bubbling bed or a trickle-bed configuration. In some embodiments, the catalyzed hydrogenation in continuous-flow mode is performed using a bubbling bed configuration.

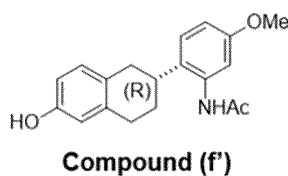
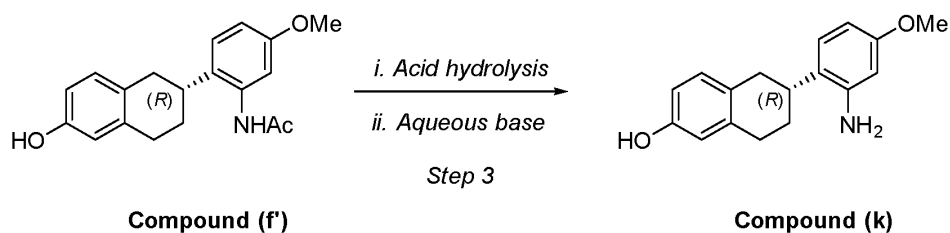
[0103] Deprotection (Step 3)

[0104] In the third step, the compound of **Formula (IX)** (*e.g.*, **Compound (f')**) undergoes a deprotection reaction, preferably acid hydrolysis, to produce the key intermediate (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**), as shown in **Scheme 10** below.

Scheme 10. Deprotection of Compound of **Formula (IX)** to Obtain **Compound (k)**

wherein 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, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O)- wherein n is 2 or 3. In some embodiments, P₂ is (C=O)-C₁ alkyl.

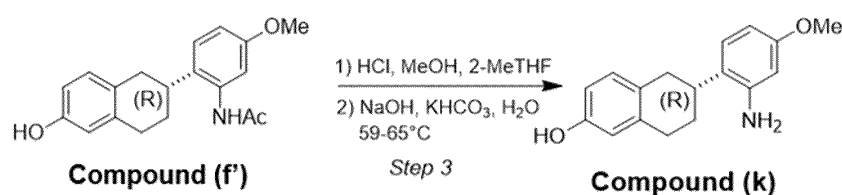
[0105] In some embodiments, the compound of **Formula (IX)** is **Compound (f')**.

**Scheme 11.** Deprotection of **Compound (f')** to Obtain **Compound (k)**

[0106] The deprotection step may be carried out under any suitable conditions, which will be known to those in the art. Thus, conversion of the N-acetyl moiety of **Compound (f')** to the amine moiety of **Compound (k)** may be carried out by a number of mechanisms. In some embodiments, the deprotection is an acid hydrolysis, preferably carried out in a two-step process

using HCl in methanol, followed by treatment with an alkali hydroxide (*e.g.*, NaOH) in water, as shown in **Scheme 12**. This embodiment is not intended to be limiting, and other methods will be persons having ordinary skill in the art.

Scheme 12. Exemplary Deprotection of Compound (f') to Obtain Compound (k)



Overall Process Yield and Optical Purity of Compound (k)

[0107] Methods according to the present disclosure improve the overall yield of **Compound (k)** when compared to the conventional four-step synthesis shown in **Scheme 1**, which has an overall yield of approximately 26%, relative to starting material **Compound (e)**. In some embodiments, the overall yield of **Compound (k)**, with reference to starting material compound of **Formula (III)** (*e.g.*, **Compound (e)**), is greater than or equal to 70%, greater than or equal to 71%, greater than or equal to 72%, greater than or equal to 73%, greater than or equal to 74%, greater than or equal to 75%, greater than or equal to 76%, greater than or equal to 77%, greater than or equal to 78%, greater than or equal to 79%, greater than or equal to 80%, greater than or equal to 81%, greater than or equal to 82%, greater than or equal to 83%, greater than or equal to 84%, greater than or equal to 85%, greater than or equal to 86%, greater than or equal to 87%, greater than or equal to 88%, greater than or equal to 89%, greater than or equal to 90%, greater than or equal to 91%, greater than or equal to 92%, greater than or equal to 93%, greater than or equal to 94%, greater than or equal to 95%, greater than or equal to 96%, greater than or equal to 97%, greater than or equal to 98%, or any range or value therein between.

[0108] Thus, in some embodiments, the concentration of residual compound of **Formula (III)** (*e.g.*, **Compound (e)**) and other impurities (side products, residual reactants, etc.) in **Compound**

(**k**), is less than or equal to 20%, less than or equal to 19%, less than or equal to 18%, less than or equal to 17%, less than or equal to 16%, less than or equal to 15%, less than or equal to 14%, less than or equal to 13%, less than or equal to 12%, less than or equal to 11%, less than or equal to 10%, less than or equal to 9%, less than or equal to 8%, less than or equal to 7%, less than or equal to 6%, less than or equal to 5%, less than or equal to 4%, less than or equal to 3%, less than or equal to 2%, less than or equal to 1%, or any range or value therein between.

[0109] In some embodiments, the product **Compound (k)** has an e.e. greater than or equal to 70%, greater than or equal to 75%, greater than or equal to 80%, greater than or equal to 85%, greater than or equal to 86%, greater than or equal to 87%, greater than or equal to 88%, greater than or equal to 89%, greater than or equal to 90%, greater than or equal to 91%, greater than or equal to 92%, greater than or equal to 93%, greater than or equal to 94%, greater than or equal to 95%, greater than or equal to 96%, greater than or equal to 97%, greater than or equal to 98%, greater than or equal to 99%, or any range or value therein between.

EXAMPLES

Chemical Abbreviations

[0110] In the Examples, the following abbreviations are used throughout: COD: 1,5-cyclooctadiene; DCM: dichloromethane; EtOAc: ethyl acetate; HFIP: hexafluoroisopropanol; IPA: isopropyl alcohol; TFA: trifluoroacetic acid; TFE: trifluoroethanol; EtOH: ethanol; MeOH: methanol; THF: tetrahydrofuran.

Ligands and Enantioselective Catalysts

[0111] Throughout the Examples, reference is made to ligands, the structures of which are shown in **Scheme 6**. Reference is also made to preformed Ir catalysts, the structures of which are shown in **Scheme 7**. Persons having ordinary skill in the art will recognize that the counterions shown in **Scheme 7** are not intended to be limiting and that other counterions known in the art may be substituted for those shown in **Scheme 7**.

Example 1. Screening of Catalysts Formed *In Situ* by Reaction Between Ru(COD)TFA₂ and Various Ligands

[0112] To test the feasibility of obtaining the (*R*) enantiomer **Compound (m)** in enantiomeric excess (preferably 90% or greater) from catalytic hydrogenation of **Compound (e)**, catalytic hydrogenation was performed using catalysts formed *in situ* by combining the metal precursor Ru(COD)TFA₂ with different ligands shown in **Scheme 6**. The ligands used are listed in **Table 1** and **Table 2**.

[0113] A solution of ligand (1 μmol, 10 mol. %) was added to a glass reaction vial, followed by a solution of metal precursor (1 μmol, 10 mol.% in DCM, 50 μL), followed by a solution of **Compound (e)** (3.99 mg, 10 μmol) in DCM-TFE (3:1, 0.27 mL). The vial was transferred to a Cat24 reactor, purged with N₂, then pressurized with H₂ (20 bar), and heated at 70°C (external temperature) for 16 hours with stirring rate of 750 rpm. The reaction solutions were cooled, vented, diluted with IPA (1 mL), and analyzed by supercritical fluid chromatography (SFC) to assess yield of **Compound (m)** and optical purity.

[0114] Results of the ligand screening with Ru(COD)TFA₂ at 70°C are summarized in **Table 1**. Enantiomeric excess (e.e.) values indicate the percentage excess of the major enantiomer over the minor enantiomer.

Table 1. Ligand Screening With Ru(COD)TFA₂ at 70°C

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-BINAP	40	57	3	n.c.
(<i>R</i>)-Xyl-BINAP	35	60	4	n.c.
(<i>S</i>)-Segphos	38	59	4	n.c.
(<i>S</i>)-DTBM-Segphos	41	53	6	n.c.
(<i>R</i>)-Phanephos	43	54	3	n.c.
(<i>S</i>)-Xyl-Phanephos	41	55	4	n.c.
(<i>R</i>)-MeBoPhoz	25	73	2	n.c.
(<i>S</i>)-H8Binol-BoPhoz	34	62	4	n.c.
(<i>R</i>)-Josiphos SL-J002-1 (Ph/tBu)	31	66	2	n.c.
(<i>R</i>)-Josiphos SL-J009-1 Cy/tBu	36	58	5	n.c.
(<i>R</i>)-Josiphos SL-J001-1 Ph/Cy	34	62	4	n.c.
(<i>S</i>)-Josiphos SL-J003-2 Cy/Cy	29	67	5	n.c.
(<i>S</i>)-Taniaphos SL-T001-2 Ph	26	69	6	n.c.
(<i>S</i>)-Taniaphos SL-T002-2 Cy	19	75	6	n.c.
(<i>R</i>)-Mandyphos SL-M002-1 Cy	33	60	7	n.c.
(<i>R,R</i>)-QuinoxP*	38	60	2	n.c.
(<i>S,S</i>)-MCCPM	36	61	3	n.c.
(<i>S</i>)-Xyliphos SL-J005-1	41	40	19	57.2
(<i>R,R</i>)-BDPP	49	48	3	n.c.
(<i>S,S</i>)-Ph-BPE	45	47	8	35.8
(<i>S,S</i>)-Me-DuPhos	39	56	5	n.c.
(<i>S</i>)-PPhos	39	59	2	n.c.
(<i>R</i>)-iPr-PHOX	33	63	4	n.c.

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
none	41	52	7	n.c.

n.c. = not calculated

[0115] The ligand screening experiments summarized in **Table 1** were repeated at lower temperature (50°C). A solution of ligand (1 µmol, 10 mol.%) was added to a glass reaction vial, followed by a solution of metal precursor (1 µmol, 10 mol.% in DCM 50 µL), followed by a solution of **Compound (e)** (3.99 mg, 10 µmol) in DCM-TFE (3:1 0.27 mL). The vial was transferred to a Cat24 reactor, purged with N₂, then pressurized with H₂ (20 bar) and heated at 50°C (external temperature) for 16 hours with stirring rate set to 750 rpm. The reaction solutions were cooled, vented, diluted with IPA (1 mL), and analyzed by SFC. The results are summarized in **Table 2**.

Table 2. Ligand Screening With Ru(COD)TFA₂ at 50°C

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-BINAP	16	82	3	42.5
(<i>R</i>)-Xyl-BINAP	8	89	3	18.1
(<i>S</i>)-Segphos	16	81	3	26.0
(<i>S</i>)-DTBM-Segphos	7	79	14	0.9
(<i>R</i>)-Phanephos	21	77	2	66.2
(<i>S</i>)-Xyl-Phanephos	16	80	5	30.3
(<i>R</i>)-MeBoPhoz	5	94	1	35.6
(<i>R</i>)-Josiphos SL-J002-1 Ph/tBu	9	88	3	43.5
(<i>R</i>)-Josiphos SL-J009-1 Cy/tBu	6	88	6	18.9
(<i>R</i>)-Josiphos SL-J001-1 Ph/Cy	7	88	5	46.2
(<i>S</i>)-Josiphos SL-J003-2 Cy/Cy	3	90	7	15.8

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-Taniaphos SL-T001-2 Ph	3	90	7	14.8
(<i>S</i>)-Taniaphos SL-T002-2 Cy	1	93	7	14.1
(<i>R</i>)-Mandyphos SL-M002-1 Cy	0	94	5	14.5
(<i>R,R</i>)-QuinoxP*	15	83	2	48.5
(<i>S,S</i>)-MCCPM	10	89	2	58.7
(<i>S</i>)-Xyliphos SL-J005-1	10	70	20	43.1
(<i>R,R</i>)-BDPP	19	78	3	38.3
(<i>S,S</i>)-Ph-BPE	16	75	8	25.4
(<i>S,S</i>)-Me-DuPhos	11	83	6	20.4
(<i>S</i>)-PPhos	20	77	2	58.2
(<i>R</i>)-iPr-PHOX	10	87	3	25.5
none	17	68	16	6.1

[0116] As shown in **Table 1** and **Table 2**, an enantiomeric excess of greater than 50% was obtained with some of the ligands, particularly (*R*)-Xyliphos in **Table 1**, as well as (*R*)-Phanephos, (*S,S*)-MCCPM, and (*S*)-PPhos in **Table 2**. However, conversion of the precursor **Compound (e)** was very low in all trials that is, the amount of **Compound (e)** remaining was greater than 40% (*e.g.*, between 52% and 94%). Impurities were also prevalent, with amounts of impurities as high as 49%.

Example 2. Screening of Catalysts Formed *In Situ* by Reaction Between [Rh(COD)₂]OTf and Various Ligands

[0117] To test the feasibility of obtaining the (*R*) enantiomer **Compound (m)** in enantiomeric excess (preferably 90% or greater) from catalytic hydrogenation of **Compound (e)** using different transition metal catalysts, catalytic hydrogenation was performed using catalysts formed *in situ* by combining the metal precursor Rh(COD)OTf with different ligands shown in **Scheme 6**. The ligands used are listed in **Table 3**.

[0118] For each trial, a solution of ligand (1 μmol, 10 mol.%) was added to a glass reaction vial, followed by a solution of metal precursor (1 μmol, 10 mol.% in THF, 50 μL), followed by a solution of **Compound (e)** (3.99 mg, 10 μmol) in THF (0.15 mL). The vial was transferred to a Cat24 reactor, purged with N₂, then pressurized with H₂ (20 bar) and heated at 50°C (external temperature) for 16 hours with stirring rate set to 750 rpm. The reaction solutions were cooled, vented, diluted with IPA (1 mL), to assess yield of **Compound (m)** and optical purity.

[0119] Results of the ligand screening with [Rh(COD)₂]OTf at 50°C are shown in **Table 3**. Enantiomeric excess (e.e.) values indicate the percentage excess of the major enantiomer over the minor enantiomer.

Table 3. Ligand Screening With [Rh(COD)₂]OTf at 50°C

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>R</i>)-BINAP	14	81	5	5.4
(<i>R</i>)-Xyl-BINAP	66	0	34	4.1
(<i>S</i>)-Segphos	6	72	22	73.6
(<i>S</i>)-DTBM-Segphos	3	89	7	47.0
(<i>S</i>)-Phanephos	16	0	84	14.5
(<i>R</i>)-Xyl-Phanephos	99	0	1	24.6
(<i>R</i>)-MeBoPhoz	26	21	53	6.5

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-H8Binol-BoPhoz	3	38	59	22.9
(<i>R</i>)-Josiphos SL-J002-1 Ph/tBu	44	0	56	4.3
(<i>R</i>)-Josiphos SL-J009-1 Cy/tBu	9	16	75	2.9
(<i>S</i>)-Josiphos SL-J001-1 Ph/Cy	3	0	97	9.8
(<i>S</i>)-Josiphos SL-J003-2 Cy/Cy	82	0	18	24.1
(<i>R</i>)-Taniaphos SL-T001-2 Ph	3	56	42	3.4
(<i>R</i>)-Taniaphos SL-T002-2 Cy	81	7	12	3.9
(<i>R</i>)-Mandyphos SL-M002-1 Cy	0	95	5	2.3
(<i>S,S</i>)-QuinoxP*	1	29	71	69.5
(<i>S,S</i>)-MCCPM	100	0	0	0
(<i>S</i>)-Xyliphos SL-J005-1	5	31	63	21.5
(<i>S,S</i>)-BDPP	1	17	82	44.1
(<i>S,S</i>)-Ph-BPE	99	0	1	n.c.
(<i>S,S</i>)-Me-DuPhos	2	38	61	18.6
(<i>S</i>)-PPhos	5	83	13	53.3
(<i>R</i>)-iPr-PHOX	3	34	63	58.4
none	98	0	2	5.4

n.c. = not calculated

[0120] As shown in **Table 3**, catalytic hydrogenation using the following chiral ligands all resulted in an e.e. of greater than 50%: (*S*)-Segphos; (*R,R*)-QuinoxP*; (*S*)-PPhos; and (*R*)-iPr-PHOX. Of those, only (*R,R*)-QuinoxP* and (*R*)-iPr-PHOX achieved a **Compound (e)** conversion higher than 60% with a low amount of impurities (*e.g.*, 5% or less).

Example 3. Screening of Catalysts Formed *In Situ* by Reaction Between Iridium Precursor Complex [Ir(COD)Cl]₂ and Various Chiral Ligands

[0121] To test the feasibility of obtaining the (*R*) enantiomer **Compound (m)** in enantiomeric excess (preferably 90% or greater) from catalytic hydrogenation of **Compound (e)** using Ir-based transition metal catalysts, catalytic hydrogenation was performed using catalysts formed *in situ* by combining the metal precursor [Ir(COD)Cl]₂ with different chiral ligands shown in **Scheme 6**. The ligands used are listed in **Table 4**.

[0122] For each trial, a solution of ligand (1 μmol, 10 mol.%) as added to a glass reaction vial, followed by a solution of metal precursor (1 μmol, 10 mol.% in THF, 50 μL), followed by a solution of **Compound (e)** (3.99 mg, 10 μmol) in THF (0.15 mL). The vial was transferred to a Cat24 reactor, purged with N₂, then pressurized with H₂ (20 bar) and heated at 50°C (external temperature) for 16 hours with stirring rate set to 750 rpm. The reactions were cooled, vented, diluted with IPA (1 mL), and analyzed by SFC to assess the yield of **Compound (m)** and optical purity.

[0123] Results of the ligand screening with [Ir(COD)Cl]₂ in THF at 50°C are shown in **Table 4**. Enantiomeric excess (e.e.) values indicate the percentage excess of the major enantiomer over the minor enantiomer.

Table 4. Ligand Screening with [Ir(COD)Cl]₂ at 50°C With THF as Solvent

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-BINAP	1	91	8	8.4
(<i>R</i>)-Xyl-BINAP	2	83	14	2.1
(<i>S</i>)-Segphos	0	96	4	3.5
(<i>S</i>)-DTBM-Segphos	1	46	52	76.5
(<i>S</i>)-Phanephos	2	92	6	8.1
(<i>S</i>)-Xyl-Phanephos	8	67	25	27.2

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>R</i>)-MeBoPhoz	0	88	12	20.8
(<i>R</i>)-H8Binol-BoPhoz	1	93	6	1.7
(<i>R</i>)-Josiphos SL-J002-1 Ph/tBu	0	96	4	24.2
(<i>R</i>)-Josiphos SL-J009-1 Cy/tBu	0	93	7	29.6
(<i>R</i>)-Josiphos SL-J001-1 Ph/Cy	1	96	3	29.5
(<i>R</i>)-Josiphos SL-J003-2 Cy/Cy	0	78	21	16.8
(<i>S</i>)-Taniaphos SL-T001-2 Ph	1	98	1	44.7
(<i>S</i>)-Taniaphos SL-T002-2 Cy	1	97	2	27.5
(<i>R</i>)-Mandyphos SL-M002-1 Cy	0	97	3	26.1
(<i>R,R</i>)-QuinoxP*	0	97	3	12.9
(<i>S,S</i>)-MCCPM	1	95	4	16.7
(<i>R</i>)-Xyliphos SL-J005-1	1	95	3	56.6
(<i>R,R</i>)-BDPP	-2	97	6	16.0
(<i>R,R</i>)-Ph-BPE	11	71	18	2.7
(<i>S,S</i>)-Me-DuPhos	0	97	3	8.6
(<i>R</i>)-PPhos	4	89	7	3.7
(<i>R</i>)-iPr-PHOX	1	88	12	44.4
none	7	39	54	0.6

[0124] The effect of changing the solvent was tested by replacing THF with TFE-THF. For each trial, a solution of ligand (1 μ mol, 10 mol.%) was added to a glass reaction vial, followed by a solution of metal precursor (1 μ mol, 10 mol.% in THF, 50 μ L), followed by a solution of **Compound (e)** (3.99 mg, 10 μ mol) in TFE-THF (3:1 mixture, 0.2 mL). The vial was transferred to a Cat24 reactor, purged with N₂, then pressurized with H₂ (20 bar) and heated at 50°C

(external temperature) for 16 hours with stirring rate set to 750 rpm. The reactions were cooled, vented, diluted with IPA (1 mL), and analyzed by SFC to assess yield of **Compound (m)** and optical purity.

[0125] Results of the ligand screening with $[\text{Ir}(\text{COD})\text{Cl}]_2$ in TFE-THF at 50°C are shown in **Table 5**.

Table 5. Ligand Screening with $[\text{Ir}(\text{COD})\text{Cl}]_2$ at 50°C With TFE-THF as Solvent

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-BINAP	0	92	8	20.8
(<i>R</i>)-Xyl-BINAP	0	66	33	13.4
(<i>R</i>)-Segphos	0	88	12	5.6
(<i>R</i>)-DTBM-Segphos	2	39	59	31.1
(<i>R</i>)-Phanephos	2	88	10	8.3
(<i>S</i>)-Xyl-Phanephos	17	33	50	32.0
(<i>R</i>)-MeBoPhoz	0	92	8	0.6
(<i>R</i>)-H8Binol-BoPhoz	6	67	27	12.3
(<i>R</i>)-Josiphos SL-J002-1 Ph/tBu	0	96	4	9.9
(<i>R</i>)-Josiphos SL-J009-1 Cy/tBu	1	96	3	22.9
(<i>S</i>)-Josiphos SL-J001-1 Ph/Cy	3	72	25	2.1
(<i>R</i>)-Josiphos SL-J003-2 Cy/Cy	4	81	15	4.5
(<i>R</i>)-Taniaphos SL-T001-2 Ph	0	97	3	3.0
(<i>S</i>)-Taniaphos SL-T002-2 Cy	0	97	3	5.0
(<i>R</i>)-Mandyphos SL-M002-1 Cy	1	96	4	34.3
(<i>R,R</i>)-QuinoxP*	1	95	4	10.6
(<i>R,R</i>)-MCCPM	0	92	7	2.3

Ligand	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
(<i>S</i>)-Xyliphos SL-J005-1	6	56	38	5.1
(<i>R,R</i>)-BDPP	1	70	28	0.5
(<i>S,S</i>)-Ph-BPE	43	5	51	7.8
(<i>S,S</i>)-Me-DuPhos	1	88	11	6.9
(<i>S</i>)-PPhos	2	72	26	0.9
(<i>S</i>)-iPr-PHOX	15	29	57	1.3
none	100	0	0	0

[0126] As shown in **Table 4**, only two trials using Ir-based catalysts achieved e.e. greater than 50% (**Table 4**): (*S*)-DTBM-Segphos; and (*R*)-Xyliphos. Of those, only (*S*)-DTBM-Segphos had a **Compound (e)** conversion to **Compound (m)** of greater than 50%. As shown in **Table 5**, the use of a mixture of THF and TFE (versus the use of THF alone, as in **Table 4**) reduces the enantioselectivity.

Example 4. Screening of Preformed Iridium Catalysts Using DCM as Solvent With and Without Additive BF₃.OEt₂

[0127] Although some of the above-described trials using catalysts formed *in situ* achieved enantiomeric excesses greater than or equal to 50%, and some achieved yields of **Compound (m)** greater than 50%, none of the trials using catalysts formed *in situ* achieved an enantiomeric excess of greater than 90%, a yield of **Compound (m)** of 95% or greater, and an impurity level of 5% or less. Thus, the present inventors performed analogous trials to those described in **Examples 1–3**, using preformed catalysts instead of catalysts formed *in situ*.

[0128] To test the feasibility of obtaining the (*R*) enantiomer **Compound (m)** in enantiomeric excess (preferably 90% or greater) from catalytic hydrogenation of **Compound (e)** using

preformed Ir-based transition metal catalysts, catalytic hydrogenation was performed using the catalysts shown in **Scheme 7**.

[0129] For each trial, a solution of the catalyst (**Scheme 7**, 0.5 μmol , 5 mol.%) was added to a glass reaction vial, followed by a solution of **Compound (e)** (3.99 mg, 10 μmol) in DCM (0.2 mL) and boron trifluoride etherate ($\text{BF}_3 \cdot \text{OEt}_2$, 10 mol.%), where applicable. The vial was transferred to a Cat24 reactor, purged with N_2 , then pressurized with H_2 (20 bar) and heated at 30°C (external temperature) for 16 hours with stirring rate set to 750 rpm. The reaction solutions were cooled, vented, diluted with IPA (1 mL), and analyzed by SFC to assess yield of **Compound (m)** and optical purity.

[0130] Results of the preformed catalyst screening with $[\text{Ir}(\text{COD})\text{Cl}]_2$ in DCM at 30°C are shown in **Table 6**.

Table 6. Catalyst Screening with Ir-P^N Complexes Using Dichloromethane as Solvent

Catalyst	$\text{BF}_3 \cdot \text{OEt}_2$ (mol.%)	Impurities (%)	Compound(e) (%)	Compound (m) (%)	e.e. (%)
Ir-PN 2	-	0	100	0	-
Ir-PN 3	-	9	89	3	n.c.
Ir-PN 4	-	4	95	0	-
Ir-PN 5	-	7	93	0	-
Ir-PN 6	-	19	81	1	n.c.
Ir-PN 7	-	22	70	8	79.3
Ir-PN 8	-	21	78	1	n.c.
Ir-PN 9	-	12	83	5	n.c.
Ir-PN 10	-	23	77	0	-
Ir-PN 11	-	12	88	0	-
No catalyst	-	0	100	0	-
Ir-PN 13	-	7	93	0	-
Ir-PN 2	10	17	83	0	-

Catalyst	BF ₃ ·OEt ₂ (mol.%)	Impurities (%)	Compound(e) (%)	Compound (m) (%)	e.e. (%)
Ir-PN 3	10	24	76	0	-
Ir-PN 4	10	47	53	0	-
Ir-PN 5	10	21	78	0	-
Ir-PN 6	10	19	81	0	-
Ir-PN 7	10	22	78	0	-
Ir-PN 8	10	13	87	0	-
Ir-PN 9	10	23	77	0	-
Ir-PN 10	10	20	75	5	n.c.
Ir-PN 11	10	20	79	1	n.c.
No catalyst	10	12	88	0	-
Ir-PN 13	10	16	80	4	n.c.

n.c. = not calculated

[0131] As shown in **Table 6**, with dichloromethane as solvent, only the catalyst **Ir-PN7** (without BF₃.OEt₂) achieved an enantioselectivity higher than 50%, but this trial achieved a very low conversion (8%) and had a high amount of impurities (22%).

Example 5. Screening of Preformed Iridium Catalysts Using DCM-TFE as Solvent With and Without Additive BF₃.OEt₂

[0132] Based on the results in **Example 4**, the present inventors screened preformed Ir catalysts using a different reaction solvent (DCM-TFE). A solution of catalyst (**Scheme 7**, 0.5 μmol, 5 mol.%) was added to a glass reaction vial, followed by a solution of **Compound (e)** (3.99 mg, 10 μmol) and BF₃.OEt₂ (where applicable, 10 mol.%) in DCM-TFE (3:1, 0.27 mL). The vial was transferred to a Cat24 reactor, purged with N₂, then pressurized with H₂ (20 bar) and heated at 30°C (external temperature) for 16 hours, with stirring rate set to 750 rpm. The reaction solutions

were cooled, vented, diluted with IPA (1 mL), and analyzed by SFC to assess yield of **Compound (m)** and optical purity.

[0133] Results of the preformed catalyst screening in DCM:TFE (3:1) at 30°C are shown in **Table 7**.

Table 7. Catalyst Screening With Ir-P^N Complexes Using DCM-TFE as Solvent

Catalyst	BF ₃ ·OEt ₂ (mol.%)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
Ir-PN 2	-	17	77	6	26.8
Ir-PN 3	-	72	19	10	51.6
Ir-PN 4	-	30	69	2	34.8
Ir-PN 5	-	22	77	1	3.6
Ir-PN 6	-	62	35	3	42.7
Ir-PN 7	-	55	8	37	97.7
Ir-PN 8	-	13	87	0	-
Ir-PN 9	-	6	1	93	98.1
Ir-PN 10	-	2	0	97	99.5
Ir-PN 11	-	82	14	3	n.c.
No catalyst	-	1	99	0	-
Ir-PN 13	-	45	24	32	86.8
Ir-PN 2	10	85	12	3	n.c.
Ir-PN 3	10	82	12	7	78.2
Ir-PN 4	10	86	12	2	n.c.
Ir-PN 5	10	87	12	1	n.c.
Ir-PN 6	10	86	12	2	n.c.
Ir-PN 7	10	52	7	41	97.0
Ir-PN 8	10	86	12	1	n.c.
Ir-PN 9	10	15	2	83	97.4

Catalyst	BF ₃ ·OEt ₂ (mol.%)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
Ir-PN 10	10	12	0	88	99.3
Ir-PN 11	10	86	12	2	n.c.
No catalyst	10	85	13	1	n.c.
Ir-PN 13	10	74	11	15	87.6

n.c. = not calculated

[0134] As shown in **Table 7**, using a mixture of DCM and TFE as solvent, whether in the presence or absence of additive (BF₃·OEt₂), three catalysts achieved e.e. greater than 90%: **Ir-PN 7**, **Ir-PN 9**, and **Ir-PN 10**. Further, **Ir-PN 9** and **Ir-PN 10** had fewer impurities than **Ir-PN 7** (**Table 7**). Thus, catalysts **Ir-PN 9** and **Ir-PN 10** were suitable to achieve the enantioselective hydrogenation of **Compound (e)** with target **Compound (e)** conversion, along with target chemical purity and optical purity (e.e.) for **Compound (m)**.

Example 6. Solvent Screening with Ir-PN 9 and Ir-PN 10

[0135] To assess the effect of solvent type on the catalytic hydrogenation of **Compound (e)**, the two catalysts identified in **Example 5** were used to perform enantioselective catalytic hydrogenation.

[0136] For each trial, a solution of catalyst (**Ir-PN 10**, **Table 8** or **Ir-PN 9**, **Table 9**) was added to an ENDEAVOR® vial, followed by a solution of **Compound (e)** (0.1 mmol, solvent as indicated), with a total solvent volume of 2 mL. The vials were transferred to an ENDEAVOR® reactor, sealed, purged with N₂ three times, and then pressurized with H₂ (28 bar). The reactions were heated to 30°C and pressure-regulated at 28 bar for 16 hours while stirring at 600 rpm. The reaction solutions were then cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess yield of **Compound (m)** and optical purity.

[0137] Results for **Ir-PN 9** and **Ir-PN 10** at 30°C are shown in **Table 8** and **Table 9**, respectively.

Table 8. Solvent Screening Using Catalyst Ir-PN 9

Catalyst Loading (mol.%)	Solvent	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
4	TFE	19	21.5	59.2	97.4
2	TFE	9	43.7	47.2	96.2
4	HFIP	2	0.4	97.2	97.8
2	HFIP	3	0.3	96.6	98.1
4	DCE	2	90.8	7.5	82.7
2	DCE	1	96.4	2.6	70.7
4	EtOAc	0	52.8	47.2	98.3
2	EtOAc	0	69.4	30.6	96.9
4	1,4-Dioxane	0	51.9	48.1	97.3
2	1,4-Dioxane	0	84.2	15.8	92.3
4	THF	0	71.3	28.7	95.1
2	THF	0	83.0	17.0	92.8

Table 9. Solvent Screening Using Catalyst Ir-PN 10

Catalyst Loading (mol.%)	Solvent	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
4	TFE	1	0.0	99.3	99.5
2	TFE	0	0.0	99.7	99.3
4	HFIP	4	0.0	96.4	99.1
2	HFIP	6	0.0	93.8	99.1
4	DCE	2	90.6	7.8	100.0

Catalyst Loading (mol.%)	Solvent	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
2	DCE	1	96.7	2.6	n.c.
4	EtOAc	0	46.5	53.5	100.0
2	EtOAc	0	64.7	35.4	99.5
4	1,4-Dioxane	0	87.2	12.4	100.0
2	1,4-Dioxane	0	94.3	5.8	100.0
4	IPA	0	99.7	0.3	n.c.
2	IPA	0	99.5	0.5	n.c.

n.c. = not calculated

[0138] As shown in **Table 8**, in almost all the investigated solvents (except DCE), the catalyst **Ir-PN 9** achieved e.e. > 90%, but only reactions in HFIP (**Table 8**) achieved high precursor conversion (**Compound (e)** < 5% in final solution) and a low amount of impurities.

[0139] As shown in **Table 9**, in almost all the investigated solvents (except IPA and DCE), the catalyst **Ir-PN 10** achieved e.e. > 90%. However, only reactions performed in fluorinated solvents TFE and HFIP achieved high precursor conversion (**Compound (e)** < 5% in final solution).

[0140] Next, additional experimentation was performed using ethyl acetate as a solvent and either TFE or HFIP as co-solvent. For each trial, **Compound (e)** (0.1 mmol) and catalyst (**Ir-PN 9** or **Ir-PN 10**) were added to ENDEAVOR® vials as solutions. Co-solvent or additional solvent was added so that the total solvent volume was 2 mL. The vials were transferred to an ENDEAVOR® reactor, sealed, purged with N₂ three times, and then pressurized with H₂ (28bar). The reactions were heated to the desired temperature and pressure-regulated at 28 bar for 16 hours, while stirring at 600 rpm. The reaction solutions were then cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess yield of **Compound (m)** and optical purity.

[0141] Results for **Ir-PN 9** and **Ir-PN 10** are shown in **Table 10**.

Table 10. Solvent Screening Using Ir-PN 9 and Ir-PN 10 With Ethyl Acetate as Solvent With Optional Co-solvent

Temp. (°C)	Co-solvent (10 vol.%, 0.2 mL)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
2 mol.% Ir-PN 10 catalyst					
30	none	0	61.5	38.5	100
50	none	0	52.5	47.5	98.8
30	TFE	0	54.4	45.7	99.3
50	TFE	0	44.4	55.6	98.8
2 mol.% Ir-PN 9 catalyst					
30	none	0	59.5	40.5	98.3
50	none	0	46.5	53.3	97.4
30	HFIP	0	41.4	58.6	98.7
50	HFIP	1	31.3	68.0	97.2

[0142] As shown in **Table 10**, ethyl acetate as both a single solvent and in mixture with 10 vol.% of HFIP with catalyst **Ir-PN 9** and ethyl acetate as both a single solvent and in mixture with 10 vol.% TFE with catalyst **Ir-PN 10**, achieved e.e. > 95% with low amounts of impurities (0–1%). Further, the **Compound (e)** conversion was between 35% and 70% in the trials shown in **Table 10**.

Example 7. Reactions of Longer Duration With Catalyst Ir-PN 10 in Ethyl Acetate

[0143] Solutions of **Compound (e)** (0.2 mmol) and catalyst **Ir-PN 10** were added to ENDEAVOR® vials, with a total solvent (EtOAc) volume of 2 mL. The vials were transferred to

an ENDEAVOR® reactor, sealed, purged with N₂ three times, and then pressurized with H₂ (28 bar). The reactions were heated to the desired temperature and were pressure-regulated at 28 bar for 48 hours, while stirring at 600 rpm. The reactions were then cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess yield of **Compound (m)** and optical purity. Results are shown in **Table 11**.

Table 11. 48-hour Catalytic Hydrogenation Using IR-PN 10 as Catalyst and Ethyl Acetate as Solvent at Varied Catalyst Loadings and Temperatures.

Ir-PN 10 Loading (mol.%)	Temp. (°C)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
2	30	0	54.6	45.4	99.0
1	30	0	67.3	32.7	99.3
2	50	0	44.0	56.0	99.4
1	50	0	56.9	43.1	97.4
2	70	2	31.8	66.6	97.5
1	70	0	58.2	41.6	97.8

[0144] As shown in **Table 11**, with **Ir-PN 10** as a catalyst, in a 48-hour reaction the solvent ethyl acetate provided high enantioselectivity (e.e. > 97%) and low amounts of impurities at all catalyst loadings and temperatures tested. However, the **Compound (e)** conversion was not higher than 70% in any trial.

Example 8. Effect of Catalyst Loading

[0145] **Ir-PN10**: The effects of substrate (**Compound (e)**) and catalyst form and quantity on **Compound (m)** yield and optical purity were investigated for catalyst **Ir-PN 10**. In **Table 12** entries 1-4, **Compound (e)** (0.1 mmol) and catalyst **Ir-PN 10** were added to ENDEAVOR® vials as solutions, with a total solvent (TFE) volume of 2 mL. In **Table 12** entries 5-8, **Compound (e)** (0.1 mmol) and catalyst **Ir-PN 10** were added to ENDEAVOR® vials, followed

by solvent (2 mL). The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm, purged with N₂ three times, and then pressurized with H₂ (28 bar). The reaction solutions were heated to 30°C and pressure-regulated at 28 bar for 16 hours. The reaction solutions were then cooled, vented, and a sample was removed and diluted with IPA for SFC analysis. The results are shown in **Table 12**.

Table 12. Effect of Catalyst Form and Loading with Catalyst Ir-PN 10 in TFE

Catalyst Loading (mol.%)	Catalyst Molarity	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
2	0.001	0	0.0	99.6	99.5
1	0.0005	1	0.0	99.5	99.1
0.5	0.00025	0	28.0	72.0	96.9
0.25	0.000125	0	91.0	9.0	40.7
2	0.001	1	0.0	98.7	99.1
1	0.0005	2	0.0	98.3	98.8
0.5	0.00025	0	11.5	88.3	98.4
0.25	0.000125	0	86.6	13.4	50.9

[0146] As shown in **Table 12**, when dispensed in solution or as a solid, a catalyst loading of 0.5 mol.% or higher for **Ir-PN 10** provided e.e. > 96%, with low amounts of impurities and **Compound (e)** conversion of >70%. Further, a catalyst loading of 1 mol.% to 2 mol.% resulted in > 98% conversion of **Compound (e)** to **Compound (m)**.

[0147] Ir-PN 9: The effect of catalyst loading on **Compound (m)** yield and optical purity were investigated for catalyst **Ir-PN 9** in HFIP. For each trial, **Compound (e)** (0.1 mmol) and catalyst **Ir-PN 9** were added to ENDEAVOR® vials as solutions with a total solvent (HFIP) volume of 2 mL. The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm, then were purged with N₂ three times and were pressurized with H₂ (28 bar). The reactions were heated to 30°C and pressure-regulated at 28 bar for 16 hours. The reaction

solutions then were cooled, vented, and a sample was removed and diluted with IPA for SFC analysis to assess **Compound (m)** yield and optical purity. The results are shown in **Table 13**.

Table 13. Effect of Catalyst Loading for Catalyst Ir-PN 9

Catalyst loading (mol.%)	Catalyst molarity	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
2	0.001	1	0.0	98.7	98.8
1	0.0005	2	0.3	97.9	98.1
0.5	0.00025	0	28.1	71.9	97.9
0.25	0.000125	0	56.0	44.0	98.0

[0148] As shown in **Table 13**, all tested catalyst loadings for **Ir-PN 9** in HFIP achieved e.e. > 97%, with little to no impurities (0–2%). Further, catalyst loadings of 1 mol.% to 2 mol.% achieved **Compound (e)** conversion to **Compound (m)** of > 97%.

Example 9. Effect of Catalyst Loading with Additive Boron Trifluoride Etherate

[0149] **Ir-PN 10; Compound (e)** (0.1 mmol or 0.2 mmol) and catalyst **Ir-PN 10** were added to ENDEAVOR® vials, followed by solvent (TFE) (2 mL). $\text{BF}_3 \cdot \text{OEt}_2$ (1 mol.%) was added as a solution in TFE (0.1 mL or 0.2 mL of a 0.01 M solution). The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm, then were purged with N_2 three times and pressurized with H_2 (28 bar). The reactions were heated to 30°C and pressure-regulated at 28 bar for 16 hours. The reaction solutions then were cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess **Compound (m)** yield and optical purity. The results are shown in **Table 14**.

Table 14. Effect of Increasing Compound (e) Concentration and $\text{BF}_3 \cdot \text{OEt}_2$ Additive Using Ir-PN 10 as Catalyst and TFE as solvent

Catalyst Loading (mol.%)	Additive	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
0.1 mmol substrate, [Compound (e)] = 0.05 M					
2	none	3	8.5	88.9	98.2
1	none	1	12.7	86.4	97.3
2	BF ₃ ·OEt ₂	19	4.7	76.5	99.0
1	BF ₃ ·OEt ₂	28	6.4	65.5	99.1
0.2 mmol substrate, [Compound (e)] = 0.1 M					
1	none	1	17.5	81.1	97.9
0.5	none	1	40.3	59.1	94.7
1	BF ₃ ·OEt ₂	25	5.8	69.6	98.4
0.5	BF ₃ ·OEt ₂	39	8.8	52.7	98.1

[0150] As shown in **Table 14**, all tested combinations of catalyst loading, additive presence, and substrate quantity provided e.e. > 94%. However, reactions using additive BF₃·OEt₂ had higher levels of impurities. With 0.1 mmol substrate, **Compound (e)** conversion was > 80% at both tested catalyst loadings, without additive BF₃·OEt₂. With 0.2mmol substrate, **Compound (e)** conversion to **Compound (m)** was > 80% only at a catalyst loading of 1 mol.% (without additive BF₃·OEt₂).

Ir-PN 9: Compound (e) (0.1 mmol or 0.2 mmol) and catalyst **Ir-PN 9** were added to ENDEAVOR® vials, followed by solvent (HFIP) (2 mL). BF₃·OEt₂ (1 mol.%) was added as a solution in TFE (0.1 mL or 0.2 mL of a 0.01 M solution). The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm, then were purged with N₂ three times and pressurized with H₂ (28 bar). The reaction solutions were heated to 30°C and were pressure-regulated at 28 bar for 16 hours. The reaction solutions then were cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess **Compound (m)** yield and optical purity. The results are shown in **Table 15**.

Table 15. Effect of increasing Compound (e) Concentration and BF₃·OEt₂ Additive Using Ir-PN 9 as Catalyst and TFE as solvent

Catalyst Loading (mol.%)	Additive	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
0.1 mmol substrate, [Compound (e)] = 0.05 M					
2	none	3	0.6	96.5	98.0
1	none	8	2.4	89.7	97.7
2	BF ₃ ·OEt ₂	38	2.5	59.9	95.5
1	BF ₃ ·OEt ₂	51	4.1	45.0	94.3
0.2 mmol substrate, [Compound (e)] = 0.1 M					
1	none	1	2.5	96.4	97.2
0.5	none	1	13.5	85.4	97.3
1	BF ₃ ·OEt ₂	42	3.5	54.4	94.7
0.5	BF ₃ ·OEt ₂	52	4.1	44.1	93.4

[0151] As shown in **Table 15**, all tested combinations of catalyst loading, presence of additive, and substrate quantity achieved e.e. > 94%. However, reactions using BF₃·OEt₂ additive had higher levels of impurities. With 0.1 and 0.2 mmol substrate, and without additive BF₃·OEt₂, **Compound (e)** conversion to **Compound (m)** was > 80% at both tested **Ir-PN 9** loadings, and in some reactions the conversion was > 95%.

Example 9. Effect of Reaction Temperature on Substrate Conversion

[0152] **Ir-PN 10**: Substrate **Compound (e)** (0.1 mmol) and catalyst **Ir-PN 10** were added to ENDEAVOR® vials as solutions with a total solvent (TFE) volume of 2 mL. The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm, then were purged with N₂ three times and were pressurized with H₂ (28 bar). The reaction solutions were heated to the desired temperature and were pressure-regulated at 28 bar for 16 hours. The reaction solutions were then cooled, vented, and a sample was removed and diluted with IPA for

SFC analysis, to assess **Compound (m)** yield and optical purity. The results are shown in **Table 16**.

Table 16. Ir-PN 10 as Catalyst at Varied Loadings and Reaction Temperatures in TFE as solvent

Catalyst Loading (mol.%)	Temp. (°C)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
1	30	0	0.0	100.0	99.4
0.5	30	0	16.8	83.2	98.7
1	40	0	0.0	99.7	99.1
0.5	40	0	19.3	80.4	97.6
1	50	1	0.0	99.1	99.2
0.5	50	0	21.5	78.5	94.8
1	60	1	0.0	99.4	98.5
0.5	60	1	14.9	84.2	90.1

[0153] As shown, in **Table 16**, with **Ir-PN 10** as catalyst and TFE as solvent, all temperatures and loadings tested achieved e.e. > 90%. A catalyst loading 1 mol.%, at 30°C and 40°C, achieved 100% and 99.7% conversion of **Compound (e)**, respectively, with no observed impurities. At 50°C and 60°C, a catalyst loading of 1 mol.% achieved > 98% conversion of **Compound (e)** to **Compound (m)** but had measurable impurities on the order of about 1%.

[0154] Ir-PN 9: Solutions of substrate **Compound (e)** (0.1 mmol) and catalyst **Ir-PN 9** were added to ENDEAVOR® vials with a solvent (HFIP) volume of 2 mL. The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm, then were purged with N₂ three times and were pressurized with H₂ (28 bar). The reaction solutions were heated to the desired temperature and were pressure regulated at 28 bar for 16 hours. The reaction solutions then were cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess **Compound (m)** yield and optical purity. The results are shown in **Table 17**.

Table 17. Ir-PN 9 as Catalyst at Varied Loadings and Reaction Temperatures in HFIP as solvent

Catalyst Loading (mol.%)	Temp. (°C)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
1	30	2	0.8	97.0	98.1
0.5	30	1	1.0	97.6	98.4
1	40	2	0.6	97.4	98.2
0.5	40	2	4.8	93.1	97.7
1	50	3	0.6	96.6	98.0
0.5	50	3	4.0	93.3	97.9
1	60	2	0.7	97.0	98.2
0.5	60	5	1.4	93.4	98.2

[0155] With **Ir-PN 9** as catalyst and HFIP as solvent, all tested temperatures and loadings achieved e.e. > 97%. A catalyst loading of 0.5 mol.% achieved 97.6% conversion of **Compound (e)** to **Compound (m)**, with 1% impurity. All other reactions produced higher levels of impurities (*e.g.*, 2–5%).

Example 10. Effect of Hydrogen Pressure on Substrate Conversion

[0156] Substrate **Compound (e)** (0.2 mmol) and catalyst **Ir-PN 10** were added to ENDEAVOR® vials as solutions, with a total solvent (TFE) volume of 2 mL. The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 rpm or 900 rpm, were purged with N₂ three times and then were pressurized with H₂. The reaction solutions then were heated to 30°C and pressure-regulated at the desired pressure for 16 hours. The reaction solutions then were cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess **Compound (m)** yield and optical purity. The results are shown in **Table 18**.

Table 18. Effect of Varying Hydrogen Pressure on Substrate Conversion

Ir-PN 10 Loading (mol.%)	H ₂ Pressure (bar)	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
600 rpm Stirring Rate					
0.5	28	0	28.4	71.6	97.6
1	14	0	11.0	89.1	99.3
0.5	14	0	30.6	69.4	99.1
1	5	0	21.7	78.3	99.4
0.5	5	0	41.8	58.2	99.3
900 rpm Stirring Rate					
0.5	28	0	29.9	70.1	98.1
0.5	14	0	29.8	70.2	98.5
0.5	5	0	49.9	50.1	99.2

[0157] As shown in **Table 18**, for **Ir-PN 10** in TFE, all tested H₂ pressures and catalyst loadings achieved e.e. > 97% with no observed impurities. Although multiple reactions had **Compound (e)** conversion > 70%, only **Ir-PN 10** loading at 1 mol.% and H₂ pressure of 14 bar achieved **Compound (e)** conversion > 80%.

Example 11. Effect of Increasing Substrate Concentration on Substrate Conversion

[0158] For **Table 19** entries 1-5: substrate **Compound (e)** (0.8–1.4 mmol) and catalyst were added to ENDEAVOR® vials as solutions, with a total solvent volume (TFE or HFIP) of 7 mL. For **Table 19** entries 6-7: substrate **Compound (e)** (0.4 or 0.8 mmol) and catalyst were added to ENDEAVOR® vials as solutions, with a total solvent (TFE) volume of 2 mL. The vials were transferred to an ENDEAVOR® reactor, were sealed, and were set to stir at 600 or 900 rpm, then were purged with N₂ three times and were pressurized to 28 bar with H₂. The reaction solutions were heated to 25°C and were pressure-regulated at 28 bar for 16 hours. The reaction solutions then were cooled, vented, and a sample was removed and diluted with IPA for SFC analysis, to assess **Compound (m)** yield and optical purity. The results are shown in **Table 19**.

Table 19. Variable Substrate Concentration Tested With Catalysts Ir-PN 9 and Ir-PN 10

[Compound (e)] [M]	Solvent Volumes	Impurities (%)	Compound (e) (%)	Compound (m) (%)	e.e. (%)
Ir-PN 9 catalyst, HFIP solvent					
0.11	22	0	0.4	99.2	98.3
0.17	14.6	1	0.1	98.8	97.7
0.2	12.5	1	0.1	99.3	97.2
Ir-PN 10 catalyst, TFE solvent					
0.11	22	0	25.7	74.3	98.1
0.17	14.6	0	18.3	81.7	97.8
0.2	12.5	0	34.8	65.3	94.2
0.4	6.3	0	29.7	70.3	95.1

[0159] As shown in Table 19, for all substrate concentration tested, both catalysts achieved e.e. > 94%. Substrate concentration 0.2 M, with catalyst **Ir-PN 9** in HFIP, had the highest **Compound (e)** to **Compound (m)** conversion at 99.3%. However, the other reactions with **Ir-PN 9** also had substrate conversion of > 98%. Substrate conversion was not as high with **Ir-PN 10** as catalyst at the tested molarities.

Example 12. Preparation of Intermediate Compound (k) from Substrate Compound (e)

[0160] The conversion of **Compound (e)** to **Compound (k)** according to Scheme 2 was carried out using a hydrogenation reaction using Ir-PF-9 as a catalyst, followed by a Pd/C-catalyzed hydrogenation reaction and a hydrolysis reaction using concentration hydrochloric acid.

(R)-N-(2-(6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (m)), Crystallization from DCM/EtOH

[0161] Catalyst Ir-PN9 (0.457 g, 0.5 mol%) was stirred in 80 mL HFIP (3.2 vol) under N₂. A solution of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide

(**Compound (e)**, 25.17 g, 0.063 mol) in 95 mL of HFIP (3.8 vol) was prepared under N₂. The catalyst and the substrate solution were added in an autoclave. The autoclave was purged with N₂ five times without stirring and three times with stirring, and then purged with H₂ at 7 bar and vented. The autoclave was pressurized with H₂ at 7 bar under stirring. After 20 h the autoclave was vented. The mixture was concentrated under vacuum to remove HFIP. 10 mL of DCM was added to obtain a brown solution. 30 mL of EtOH was added and the solution was cooled at -20 °C overnight. The precipitated was collected by filtration. (R)-N-(2-(6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (**Compound (m)**) was obtained (23.18 g, 92% yield, 99.4 % purity, e.e. > 99%).

(R)-N-(2-(6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (m)), Crystallization from MeOH

[0162] Catalyst Ir-PN9 (0.381 g, 0.5 mol%) was stirred in 67 mL HFIP (3.2 vol) under N₂. A solution of N-(2-(6-(benzyloxy)-3,4-dihydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (**Compound (e)**, 21.0 g, 0.053 mol) in 80 mL of HFIP (3.8 vol) was prepared under N₂. The catalyst and the substrate solution were added to an autoclave. The autoclave was purged with N₂ five times without stirring and three times with stirring, and then purged with H₂ at 7 bar and vented. The autoclave was pressurized with H₂ at 7 bar under stirring. After 20 h the autoclave was vented. The mixture was filtered, then concentrated under vacuum to 2 volumes (about 40 ml), 147 mL of MeOH (7 v/w) was added, and the solution was concentrated to 2-3 v/w; this was repeated 2 times. 105 mL of MeOH (5 v/w) was added, and the suspension was stirred for about 1-2 h at about -10 to -5°C. The precipitate was collected by filtration and washed with 40 mL (~ 2v/w) of MeOH. (R)-N-(2-(6-(benzyloxy)-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (**Compound (m)**) was obtained (19.36 g, 91% corrected yield, 99.1% purity, e.e. 99.7%).

Preparation of (R)-N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (Compound (f'))

[0163] (*R*)-N-(2-(6-benzyloxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide ((**Compound (m)**), 22.36 g, 0.056 mol), 5% Pd/C catalyst (1.343 g; 0.5 mol %), and 300 mL of MeOH/THF 1:1 were added to an autoclave. The autoclave was purged with N₂ five times without stirring and three times with stirring, and then purged with H₂ at 2 bar and vented. The autoclave was pressurized at 2 bar with H₂ under agitation and heated to 30 °C for 20 h, then was cooled to RT and vented. The mixture was heated to 40 °C, then filtered, and the filter cake was rinsed with 67 mL (3 vol) of THF/MeOH 1:1 preheated at 40 °C. The organic layers were combined and, after a solvent switch, a suspension with 130 mL (5.7-6 vol) of EtOAc (THF and MeOH ≤ 2% w/w) was formed. The precipitate was collected by filtration and rinsed with 34 mL of EtOAc (1.5 vol). (*R*)-N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (**Compound (f')**) was obtained (15.1 g, 87 % yield, 99.9 % purity; e.e. >99%).

Preparation of (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (Compound (k)**)**

[0164] MeOH (90 ml, 9.0 v/w) and (*R*)-N-(2-(6-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methoxyphenyl) acetamide (**Compound (f')**), 10 g, 0.037 mol, 1 equiv) were added to a flask under N₂, and the resulting suspension was stirred at 20°C. HCl 37 % (12.5 ml, 4.7 equiv) was added, and the suspension was stirred and heated to a target temperature of 63°C. After 24 hrs, the mixture was cooled, and after a solvent switch (MeOH residual < 20% w/w), a suspension in 160 mL Me-THF was obtained. The suspension was added to 32 g of a 12 % w/w NaOH solution and 18.7 g of a 20% w/w KHCO₃ solution to obtain a biphasic mixture (pH 8-10). After separation of the phases, the organic layer was collected and wash twice with a solution of NaCl 4.8 % (2 x 10.5 g, 2.1 w/w). The organic layers were collected and concentrated at T≤51°C, under reduced pressure, to 2.5~3.5 v/w (60 ml). The mixture was cooled to 20°C, and n-heptane (70 ml, 7 v/w) was slowly added to the residue and stirred overnight. The suspension was filtered and the wet cake rinsed with n-Heptane (20 ml, 2.02 v/w). (*R*)-6-(2-amino-4-methoxyphenyl)-5,6,7,8-tetrahydronaphthalen-2-ol (**Compound (k)**) was obtained (8.2 g, 93% corrected yield; 99.8% purity, e.e. > 99.9%).

Definitions

[0165] The following terms are used throughout as defined below.

[0166] As used herein and in the appended claims, singular articles such as “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.

[0167] 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 – for example, “about 10 wt. %” would be understood to mean “9 wt. % to 11 wt. %.” It is to be understood that when “about” precedes a term, the term is to be construed as disclosing “about” the term as well as the term without modification by “about” – for example, “about 10 wt. %” discloses “9 wt. % to 11 wt. %” as well as disclosing “10 wt. %.”

[0168] The phrase “and/or” as used in the present disclosure will be understood to mean any one of the recited members individually or a combination of any two or more thereof – for example,

“A, B, and/or C” would mean “A, B, C, A and B, A and C, B and C, or the combination of A, B, and C.”

[0169] Generally, reference to a certain element such as hydrogen or H is meant to include all isotopes of that element. For example, if an R group is defined to include hydrogen or H, it also includes deuterium and tritium. Compounds comprising radioisotopes such as tritium, C¹⁴, P³² and S³⁵ are thus within the scope of the present technology. Procedures for inserting such labels into the compounds of the present technology will be readily apparent to those skilled in the art based on the disclosure herein.

[0170] In general, “substituted” refers to an organic group as defined below (e.g., an alkyl group) in which one or more bonds to a hydrogen atom contained therein are replaced by a bond to non-hydrogen or non-carbon atoms. Substituted groups also include groups in which one or more bonds to a carbon(s) or hydrogen(s) atom are replaced by one or more bonds, including double or triple bonds, to a heteroatom. Thus, a substituted group is substituted with one or more substituents, unless otherwise specified. In some embodiments, a substituted group is substituted with 1, 2, 3, 4, 5, or 6 substituents. Examples of substituent groups include: halogens (*i.e.*, F, Cl, Br, and I); hydroxyls; alkoxy, alkenoxy, aryloxy, aralkyloxy, heterocyclyl, heterocyclylalkyl, heterocycloxy, and heterocyclylalkoxy groups; carbonyls (oxo); carboxylates; esters; urethanes; oximes; hydroxylamines; alkoxyamines; aralkoxyamines; thiols; sulfides; sulfoxides; sulfones; sulfonyls; pentafluorosulfanyl (*i.e.*, SF₅), sulfonamides; amines; N-oxides; hydrazines; hydrazides; hydrazones; azides; amides; ureas; amidines; guanidines; enamines; imides; isocyanates; isothiocyanates; cyanates; thiocyanates; imines; nitro groups; and nitriles (*i.e.*, CN).

[0171] Substituted ring groups such as substituted cycloalkyl, aryl, heterocyclyl, and heteroaryl groups also include rings and ring systems in which a bond to a hydrogen atom is replaced with a bond to a carbon atom. Therefore, substituted cycloalkyl, aryl, heterocyclyl and heteroaryl groups may also be substituted with substituted or unsubstituted alkyl, alkenyl, and alkynyl groups as defined below.

[0172] Alkyl groups include straight chain and branched chain alkyl groups having from 1 to 12 carbon atoms, and typically from 1 to 10 carbons or, in some embodiments, from 1 to 8, 1 to 6, or 1 to 4 carbon atoms. Alkyl groups may be substituted or unsubstituted. Examples of straight chain alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, tert-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. Representative substituted alkyl groups may be substituted one or more times with substituents such as those listed above, and include without limitation haloalkyl (e.g., trifluoromethyl), hydroxyalkyl, thioalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxyalkyl, carboxyalkyl, and the like.

[0173] Cycloalkyl groups include mono-, bi- or tricyclic alkyl groups having from 3 to 12 carbon atoms in the ring(s), or, in some embodiments, 3 to 10, 3 to 8, or 3 to 4, 5, or 6 carbon atoms. Cycloalkyl groups may be substituted or unsubstituted. Exemplary monocyclic cycloalkyl groups include, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group has 3 to 8 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 5, 3 to 6, or 3 to 7. Bi- and tricyclic ring systems include both bridged cycloalkyl groups and fused rings, such as, but not limited to, bicyclo[2.1.1]hexane, adamantyl, decalanyl, and the like. Substituted cycloalkyl groups may be substituted one or more times with, non-hydrogen and non-carbon groups as defined above. However, substituted cycloalkyl groups also include rings that are substituted with straight or branched chain alkyl groups as defined above. Representative substituted cycloalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, 2,2-, 2,3-, 2,4-, 2,5- or 2,6-disubstituted cyclohexyl groups, which may be substituted with substituents such as those listed above.

[0174] Cycloalkylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a cycloalkyl group as defined above. Cycloalkylalkyl groups may be substituted or unsubstituted. In some embodiments, cycloalkylalkyl groups have from 4 to 16 carbon atoms, 4 to 12 carbon atoms, and typically 4 to

10 carbon atoms. Substituted cycloalkylalkyl groups may be substituted at the alkyl, the cycloalkyl or both the alkyl and cycloalkyl portions of the group. Representative substituted cycloalkylalkyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[0175] Alkenyl groups include straight and branched chain alkyl groups as defined above, except that at least one double bond exists between two carbon atoms. Alkenyl groups may be substituted or unsubstituted. Alkenyl groups have from 2 to 12 carbon atoms, and typically from 2 to 10 carbons or, in some embodiments, from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. In some embodiments, the alkenyl group has one, two, or three carbon-carbon double bonds. Examples include, but are not limited to vinyl, allyl, $-\text{CH}=\text{CH}(\text{CH}_3)$, $-\text{CH}=\text{C}(\text{CH}_3)_2$, $-\text{C}(\text{CH}_3)=\text{CH}_2$, $-\text{C}(\text{CH}_3)=\text{CH}(\text{CH}_3)$, $-\text{C}(\text{CH}_2\text{CH}_3)=\text{CH}_2$, among others. Representative substituted alkenyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[0176] Cycloalkenyl groups include cycloalkyl groups as defined above, having at least one double bond between two carbon atoms. Cycloalkenyl groups may be substituted or unsubstituted. In some embodiments the cycloalkenyl group may have one, two or three double bonds but does not include aromatic compounds. Cycloalkenyl groups have from 4 to 14 carbon atoms, or, in some embodiments, 5 to 14 carbon atoms, 5 to 10 carbon atoms, or even 5, 6, 7, or 8 carbon atoms. Examples of cycloalkenyl groups include cyclohexenyl, cyclopentenyl, cyclohexadienyl, cyclobutadienyl, and cyclopentadienyl.

[0177] Cycloalkenylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of the alkyl group is replaced with a bond to a cycloalkenyl group as defined above. Cycloalkenylalkyl groups may be substituted or unsubstituted. Substituted cycloalkenylalkyl groups may be substituted at the alkyl, the cycloalkenyl or both the alkyl and cycloalkenyl portions of the group. Representative substituted cycloalkenylalkyl groups may be substituted one or more times with substituents such as those listed above.

[0178] Alkynyl groups include straight and branched chain alkyl groups as defined above, except that at least one triple bond exists between two carbon atoms. Alkynyl groups may be substituted or unsubstituted. Alkynyl groups have from 2 to 12 carbon atoms, and typically from 2 to 10 carbons or, in some embodiments, from 2 to 8, 2 to 6, or 2 to 4 carbon atoms. In some embodiments, the alkynyl group has one, two, or three carbon-carbon triple bonds. Examples include, but are not limited to $-\text{C}\equiv\text{CH}$, $-\text{C}\equiv\text{CCH}_3$, $-\text{CH}_2\text{C}\equiv\text{CCH}_3$, and $-\text{C}\equiv\text{CCH}_2\text{CH}(\text{CH}_2\text{CH}_3)_2$, among others. Representative substituted alkynyl groups may be mono-substituted or substituted more than once, such as, but not limited to, mono-, di- or tri-substituted with substituents such as those listed above.

[0179] Aryl groups are cyclic aromatic hydrocarbons that do not contain heteroatoms. Aryl groups herein include monocyclic, bicyclic and tricyclic ring systems. Aryl groups may be substituted or unsubstituted. Thus, aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, fluorenyl, phenanthrenyl, anthracenyl, indenyl, indanyl, pentalenyl, and naphthyl groups. In some embodiments, aryl groups contain 6-14 carbons, and in others from 6 to 12 or even 6-10 carbon atoms in the ring portions of the groups. In some embodiments, the aryl groups are phenyl or naphthyl. The phrase “aryl groups” includes groups containing fused rings, such as fused aromatic-aliphatic ring systems (e.g., indanyl, tetrahydronaphthyl, and the like). Representative substituted aryl groups may be mono-substituted (e.g., tolyl) or substituted more than once. For example, monosubstituted aryl groups include, but are not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or naphthyl groups, which may be substituted with substituents such as those listed above.

[0180] Aralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined above. Aralkyl groups may be substituted or unsubstituted. In some embodiments, aralkyl groups contain 7 to 16 carbon atoms, 7 to 14 carbon atoms, or 7 to 10 carbon atoms. Substituted aralkyl groups may be substituted at the alkyl, the aryl or both the alkyl and aryl portions of the group. Representative aralkyl groups include but are not limited to benzyl and phenethyl groups and fused (cycloalkylaryl)alkyl

groups such as 4-indanylethyl. Representative substituted aralkyl groups may be substituted one or more times with substituents such as those listed above.

[0181] Heterocyclyl groups include aromatic (also referred to as heteroaryl) and non-aromatic ring compounds containing 3 or more ring members, of which one or more is a heteroatom such as, but not limited to, N, O, and S. Heterocyclyl groups may be substituted or unsubstituted. In some embodiments, the heterocyclyl group contains 1, 2, 3 or 4 heteroatoms. In some embodiments, heterocyclyl groups include mono-, bi- and tricyclic rings having 3 to 16 ring members, whereas other such groups have 3 to 6, 3 to 10, 3 to 12, or 3 to 14 ring members. Heterocyclyl groups encompass aromatic, partially unsaturated and saturated ring systems, such as, for example, imidazolyl, imidazoliny and imidazolidiny groups. The phrase “heterocyclyl group” includes fused ring species including those comprising fused aromatic and non-aromatic groups, such as, for example, benzotriazolyl, 2,3-dihydrobenzo[1,4]dioxiny, and benzo[1,3]dioxolyl. The phrase also includes bridged polycyclic ring systems containing a heteroatom such as, but not limited to, quinuclidyl. The phrase includes heterocyclyl groups that have other groups, such as alkyl, oxo or halo groups, bonded to one of the ring members, referred to as “substituted heterocyclyl groups”. Heterocyclyl groups include, but are not limited to, aziridiny, azetidiny, pyrrolidiny, imidazolidiny, pyrazolidiny, thiazolidiny, tetrahydrothiophenyl, tetrahydrofuranyl, dioxolyl, furanyl, thiophenyl, pyrrolyl, pyrroliny, imidazolyl, imidazoliny, pyrazolyl, pyrazoliny, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, thiazoliny, isothiazolyl, thiadiazolyl, oxadiazolyl, piperidyl, piperaziny, morpholiny, thiomorpholiny, tetrahydropyranyl, tetrahydrothiopyranyl, oxathiane, dioxyl, dithianyl, pyranyl, pyridyl, pyrimidiny, pyridaziny, pyraziny, triaziny, dihydropyridyl, dihydrodithiiny, dihydrodithionyl, homopiperaziny, quinuclidyl, indolyl, indoliny, isoindolyl, azaindolyl (pyrrolopyridyl), indazolyl, indoliziny, benzotriazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzthiazolyl, benzoxadiazolyl, benzoxaziny, benzodithiiny, benzoxathiiny, benzothiaziny, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[1,3]dioxolyl, pyrazolopyridyl, imidazopyridyl (azabenzimidazolyl), triazolopyridyl, isoxazolopyridyl, puriny, xanthiny, adeniny, guaniny, quinoliny, isoquinoliny, quinoliziny, quinoxaliny, quinazoliny,

cinnolinyl, phthalazinyl, naphthyridinyl, pteridinyl, thianaphthyl, dihydrobenzothiazinyl, dihydrobenzofuranyl, dihydroindolyl, dihydrobenzodioxinyl, tetrahydroindolyl, tetrahydroindazolyl, tetrahydrobenzimidazolyl, tetrahydrobenzotriazolyl, tetrahydropyrrolopyridyl, tetrahydropyrazolopyridyl, tetrahydroimidazopyridyl, tetrahydrotriazolopyridyl, and tetrahydroquinolinyl groups. Representative substituted heterocyclyl groups may be mono-substituted or substituted more than once, such as, but not limited to, pyridyl or morpholinyl groups, which are 2-, 3-, 4-, 5-, or 6-substituted, or disubstituted with various substituents such as those listed above.

[0182] Heteroaryl groups are aromatic ring compounds containing 5 or more ring members, of which, one or more is a heteroatom such as, but not limited to, N, O, and S. Heteroaryl groups may be substituted or unsubstituted. Heteroaryl groups include, but are not limited to, groups such as pyrrolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, thiophenyl, benzothiophenyl, furanyl, benzofuranyl, indolyl, azaindolyl (pyrrolopyridinyl), indazolyl, benzimidazolyl, imidazopyridinyl (azabenzimidazolyl), pyrazolopyridinyl, triazolopyridinyl, benzotriazolyl, benzoxazolyl, benzothiazolyl, benzothiadiazolyl, imidazopyridinyl, isoxazolopyridinyl, thianaphthyl, purinyl, xanthinyl, adeninyl, guaninyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, quinoxalinyl, and quinazolinyl groups. Heteroaryl groups include fused ring compounds in which all rings are aromatic such as indolyl groups and include fused ring compounds in which only one of the rings is aromatic, such as 2,3-dihydro indolyl groups. Representative substituted heteroaryl groups may be substituted one or more times with various substituents such as those listed above.

[0183] Heterocyclylalkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heterocyclyl group as defined above. Heterocyclylalkyl groups may be substituted or unsubstituted. Substituted heterocyclylalkyl groups may be substituted at the alkyl, the heterocyclyl or both the alkyl and heterocyclyl portions of the group. Representative heterocyclyl alkyl groups include, but are not limited to, morpholin-4-yl-ethyl, furan-2-yl-methyl, imidazol-4-yl-methyl, pyridin-3-yl-methyl,

tetrahydrofuran-2-yl-ethyl, and indol-2-yl-propyl. Representative substituted heterocyclalkyl groups may be substituted one or more times with substituents such as those listed above.

[0184] Heteroaralkyl groups are alkyl groups as defined above in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined above. Heteroaralkyl groups may be substituted or unsubstituted. Substituted heteroaralkyl groups may be substituted at the alkyl, the heteroaryl or both the alkyl and heteroaryl portions of the group. Representative substituted heteroaralkyl groups may be substituted one or more times with substituents such as those listed above.

[0185] Groups described herein having two or more points of attachment (i.e., divalent, trivalent, or polyvalent) within the compound of the present technology are designated by use of the suffix, “ene.” For example, divalent alkyl groups are alkylene groups, divalent aryl groups are arylene groups, divalent heteroaryl groups are divalent heteroarylene groups, and so forth. Substituted groups having a single point of attachment to the compound of the present technology are not referred to using the “ene” designation. Thus, e.g., chloroethyl is not referred to herein as chloroethylene.

[0186] Alkoxy groups are hydroxyl groups (-OH) in which the bond to the hydrogen atom is replaced by a bond to a carbon atom of a substituted or unsubstituted alkyl group as defined above. Alkoxy groups may be substituted or unsubstituted. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy, and the like. Examples of branched alkoxy groups include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy, and the like. Examples of cycloalkoxy groups include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. Representative substituted alkoxy groups may be substituted one or more times with substituents such as those listed above.

[0187] The term “amide” (or “amido”) includes C- and N-amide groups, i.e., -C(O)NR⁷¹R⁷², and -NR⁷¹C(O)R⁷² groups, respectively. R⁷¹ and R⁷² are independently hydrogen, or a substituted or

unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclalkyl or heterocycl group as defined herein. Amido groups therefore include but are not limited to carbamoyl groups ($-\text{C}(\text{O})\text{NH}_2$) and formamide groups ($-\text{NHC}(\text{O})\text{H}$). In some embodiments, the amide is $-\text{NR}^{71}\text{C}(\text{O})-(\text{C}_{1-5} \text{ alkyl})$ and the group is termed "carbonylamino," and in others the amide is $-\text{NHC}(\text{O})\text{-alkyl}$ and the group is termed "alkanoylamino."

[0188] The term "amine" (or "amino") as used herein refers to $-\text{NR}^{75}\text{R}^{76}$ groups, wherein R^{75} and R^{76} are independently hydrogen, or a substituted or unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, heterocyclalkyl or heterocycl group as defined herein. In some embodiments, the amine is alkylamino, dialkylamino, arylamino, or alkylarylamino. In other embodiments, the amine is NH_2 , methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino, phenylamino, or benzylamino.

[0189] The term "hydroxyl" as used herein can refer to $-\text{OH}$ or its ionized form, $-\text{O}^-$. A "hydroxyalkyl" group is a hydroxyl-substituted alkyl group, such as $\text{HO-CH}_2\text{-}$.

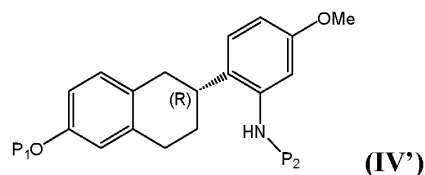
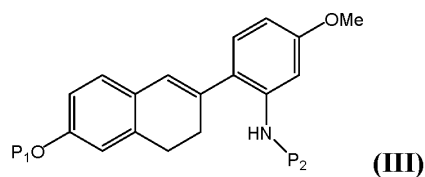
[0190] As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently 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 includes each individual member. Thus, for example, a group having 1-3 atoms refers to groups having 1, 2, or 3 atoms. Similarly, a group having 1-5 atoms refers to groups having 1, 2, 3, 4, or 5 atoms, and so forth.

[0191] The present disclosure is not limited to the particular embodiments set forth herein, and 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. 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.

WHAT IS CLAIMED IS:

1. A method of preparing a compound of **Formula (IV')**, the method comprising:

(a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**



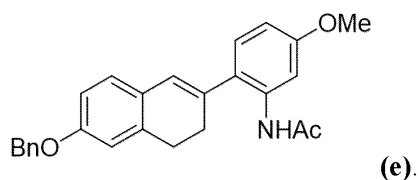
wherein P₁ is H or a phenol protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C₁-C₅ alkyl)₃, Si(aryl)₂(C₁-C₅ alkyl) and CH₂-aryl; and

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, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O- wherein n is 2 or 3.

2. The method of claim 1, wherein P₁ is CH₂-aryl.

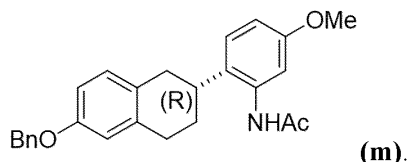
3. The method of claim 1 or claim 2, wherein P₂ is (C=O)-C₁ alkyl.

4. The method of any one of claims 1 to 3, wherein the compound of **Formula (III)** is **Compound (e)**:



5. The method of any one of claims 1 to 4, wherein the compound of **Formula (IV')** is

Compound (m):

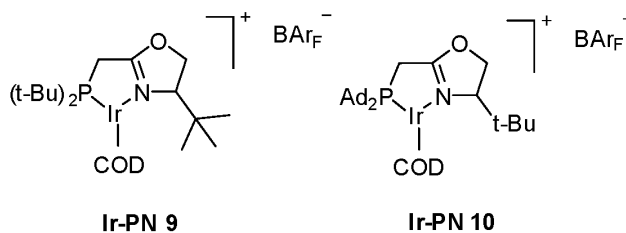


6. The method of any one of claims 1 to 5, wherein the enantioselective catalyst comprises a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst.

7. The method of any one of claims 1 to 6, wherein the enantioselective catalyst comprises an iridium-based catalyst.

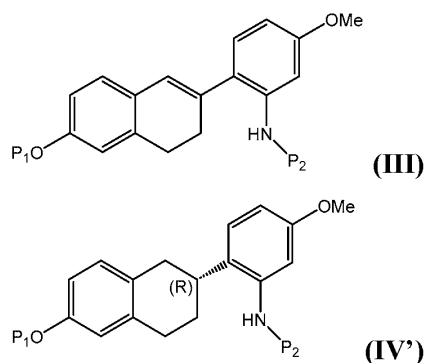
8. The method of any one of claims 1 to 7, wherein the enantioselective catalyst comprises an iridium-PN catalyst.

9. The method of any one of claims 1 to 8, wherein the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof:



10. The method of any one of claims 1 to 9, wherein the enantioselective catalyst has an (*S*) configuration.
11. The method of any one of claims 1 to 10, wherein the catalyst loading is 1.5 mol.% or less, relative to the compound of **Formula (III)**.
12. The method of any one of claims 1 to 11, wherein the catalyst loading is 1.0 mol.% or less, relative to the compound of **Formula (III)**.
13. The method of any one of claims 1 to 12, wherein the catalyst loading is 0.5 mol.% to 1.0 mol.%, relative to the compound of **Formula (III)**.
14. The method of any one of claims 1 to 13, wherein the concentration of the compound of **Formula (III)** is greater than 0.07 M.
15. The method of any one of claims 1 to 14, wherein the concentration of the compound of **Formula (III)** is greater than or equal to 0.1 M.
16. The method of any one of claims 1 to 15, wherein the concentration of the compound of **Formula (III)** is 0.15 M to 0.5 M.
17. The method of any one of claims 1 to 16, wherein the concentration of the compound of **Formula (III)** is 0.15 M to 0.22 M.
18. The method of any one of claims 1 to 17, wherein the hydrogenating (a) is performed at a hydrogen pressure of 7 to 30 bar.
19. The method of any one of claims 1 to 18, wherein the hydrogenating (a) is performed at a hydrogen pressure of 14 to 28 bar.
20. The method of any one of claims 1 to 19, wherein the hydrogenating (a) is performed at a hydrogen pressure of 25 to 28 bar.

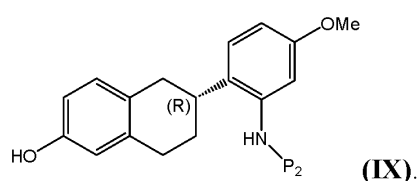
21. The method of any one of claims 1 to 20, wherein the hydrogenating (a) is performed in trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), or a combination thereof.
22. The method of any one of claims 1 to 21, wherein the hydrogenating (a) is performed at a temperature of 25 to 90°C.
23. The method of any one of claims 1 to 22, wherein the hydrogenating (a) is performed at a temperature of 25 to 40°C.
24. The method of any one of claims 1 to 23, wherein the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 90%.
25. The method of any one of claims 1 to 24, wherein the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 95%.
26. The method of any one of claims 1 to 25, wherein 5% or less of residual compound of **Formula (III)** is present after the hydrogenating (a).
27. The method of any one of claims 1 to 26, wherein the obtained compound of **Formula (IV')** has a purity of 95% or greater after the hydrogenating (a).
28. A method of preparing a compound of **Formula (IX)**, the method comprising:
(a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**



wherein P_1 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

P_2 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, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O)- wherein n is 2 or 3; and

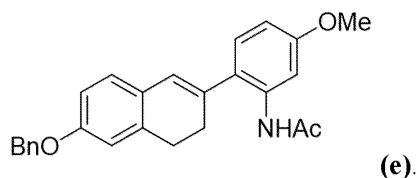
(b) deprotecting the compound of **Formula (IV')** in the presence of hydrogen and a second catalyst to obtain a compound of **Formula (IX)**



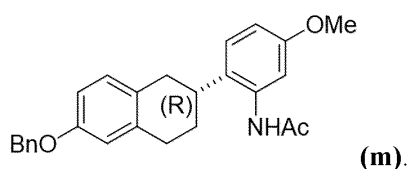
29. The method of claim 28, wherein P_1 is CH₂-aryl.

30. The method of claim 28 or claim 29, wherein P_2 is (C=O)-C₁ alkyl.

31. The method of any one of claims 28 to 30, wherein the compound of **Formula (III)** is **Compound (e)**:

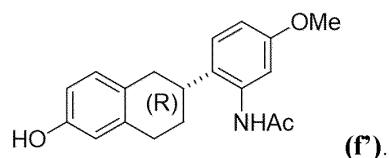


32. The method of any one of claims 28 to 31, wherein the compound of **Formula (IV')** is **Compound (m)**:



33. The method of any one of claims 28 to 32, wherein the compound of **Formula (IX)** is

Compound (f'):

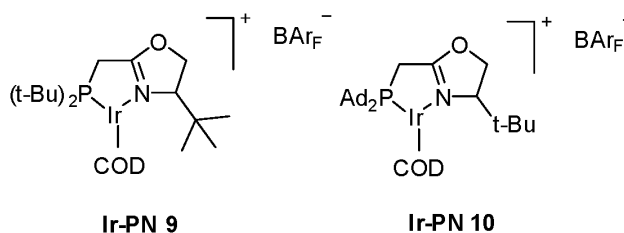


34. The method of any one of claims 28 to 33, wherein the enantioselective catalyst comprises a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst.

35. The method of any one of claims 28 to 34, wherein the enantioselective catalyst comprises an iridium-based catalyst.

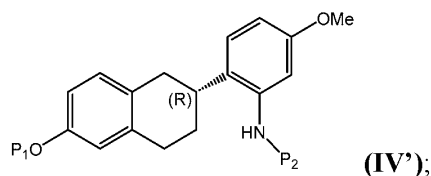
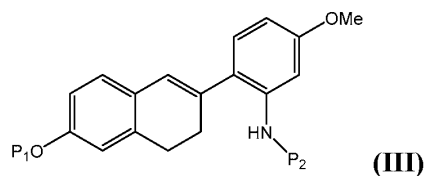
36. The method of any one of claims 28 to 35, wherein the enantioselective catalyst comprises an iridium-PN catalyst.

37. The method of any one of claims 28 to 36, wherein the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof:

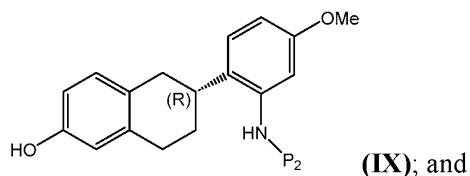


38. The method of any one of claims 28 to 37, wherein the enantioselective catalyst has an (*S*) configuration.
39. The method of any one of claims 28 to 38, wherein the catalyst loading is 1.5 mol.% or less, relative to the compound of **Formula (III)**.
40. The method of any one of claims 28 to 39, wherein the catalyst loading is 1.0 mol.% or less, relative to the compound of **Formula (III)**.
41. The method of any one of claims 28 to 40, wherein the catalyst loading is 0.5 mol.% to 1.0 mol.%, relative to the compound of **Formula (III)**.
42. The method of any one of claims 28 to 41, wherein the concentration of the compound of **Formula (III)** is greater than 0.07 M.
43. The method of any one of claims 28 to 42, wherein the concentration of the compound of **Formula (III)** is greater than or equal to 0.1 M.
44. The method of any one of claims 28 to 43, wherein the concentration of the compound of **Formula (III)** is 0.15 M to 0.5 M.
45. The method of any one of claims 28 to 44, wherein the concentration of the compound of **Formula (III)** is 0.15 M to 0.22 M.
46. The method of any one of claims 28 to 45, wherein the hydrogenating (a) is performed at a hydrogen pressure of 7 to 30 bar.
47. The method of any one of claims 28 to 46, wherein the hydrogenating (a) is performed at a hydrogen pressure of 14 to 28 bar.
48. The method of any one of claims 28 to 47, wherein the hydrogenating (a) is performed at a hydrogen pressure of 25 to 28 bar.

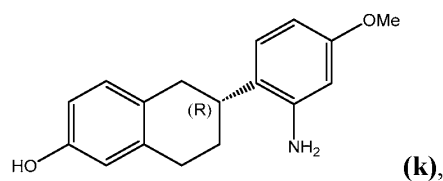
49. The method of any one of claims 28 to 48, wherein the hydrogenating (a) is performed in trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), or a combination thereof.
50. The method of any one of claims 28 to 49, wherein the hydrogenating (a) is performed at a temperature of 25 to 90°C.
51. The method of any one of claims 28 to 50, wherein the hydrogenating (a) is performed at a temperature of 25 to 40°C.
52. The method of any one of claims 28 to 51, wherein the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 90%.
53. The method of any one of claims 28 to 52, wherein the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 95%.
54. The method of any one of claims 28 to 53, wherein 5% or less of the compound of **Formula (III)** is present after the hydrogenating (a).
55. The method of any one of claims 28 to 54, wherein the obtained compound of **Formula (IV')** has a purity of 95% or greater after the hydrogenating (a).
56. The method of any one of claims 28 to 55, wherein the obtained compound of **Formula (IX)** has an enantiomeric excess of 90% or greater.
57. The method of any one of claims 28 to 56, wherein the obtained compound of **Formula (IX)** has an enantiomeric excess of 95% or greater.
58. A method of preparing **Compound (k)**, the method comprising:
(a) hydrogenating a compound of **Formula (III)** in the presence of an enantioselective catalyst to produce the compound of **Formula (IV')**



(b) deprotecting the compound of **Formula (IV')** in the presence of hydrogen and a second catalyst to obtain the compound of **Formula (IX)**



(c) deprotecting the compound of **Formula (IX)** to obtain the **Compound (k)**



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

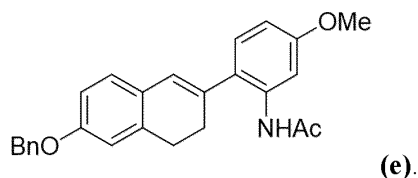
wherein P₂ is H, Et, or an amino protecting group selected from (C=O)-C₁-C₈ alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C₁-C₈ alkylaryl, (C=O)CF₃, (C=O)CH₂Cl, (C=O)CCl₃, or (C=O)-(CH₂)_n-C=O)- wherein n is 2 or 3.

59. The method of claim 58, wherein P₁ is CH₂-aryl.

60. The method of claim 58 or claim 59, wherein P₂ is (C=O)-C₁ alkyl.

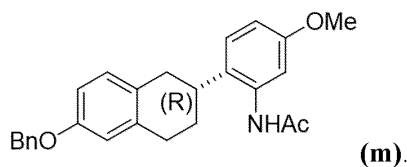
61. The method of any one of claims 58 to 60, wherein the compound of **Formula (III)** is

Compound (e):



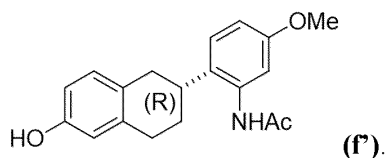
62. The method of any one of claims 58 to 61, wherein the compound of **Formula (IV')** is

Compound (m):



63. The method of any one of claims 58 to 62, wherein the compound of **Formula (IX)** is

Compound (f'):

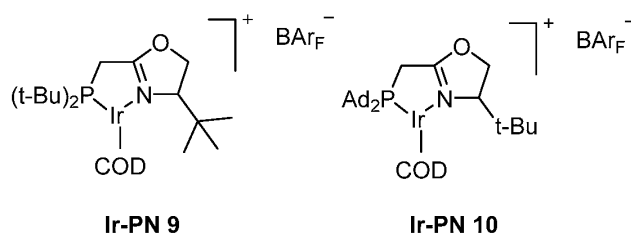


64. The method of any one of claims 58 to 63, wherein the enantioselective catalyst comprises a ruthenium (Ru)-based, rhodium (Rh)-based, iridium (Ir)-based, iron (Fe)-based, cobalt (Co)-based, nickel (Ni)-based, palladium (Pd)-based, rhenium (Re)-based, osmium (Os)-based, or platinum (Pt)-based catalyst.

65. The method of any one of claims 58 to 64, wherein the enantioselective catalyst comprises an iridium-based catalyst.

66. The method of any one of claims 58 to 65, wherein the enantioselective catalyst comprises an iridium-PN catalyst.

67. The method of any one of claims 58 to 66, wherein the enantioselective catalyst comprises **Ir-PN 9**, **Ir-PN 10**, or a combination thereof:



68. The method of any one of claims 58 to 67, wherein the enantioselective catalyst has an (*S*) configuration.

69. The method of any one of claims 58 to 68, wherein the catalyst loading is 1.5 mol.% or less, relative to the compound of **Formula (III)**.

70. The method of any one of claims 58 to 69, wherein the catalyst loading is 1.0 mol.% or less, relative to the compound of **Formula (III)**.

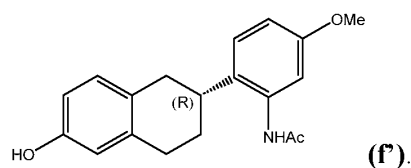
71. The method of any one of claims 58 to 70, wherein the catalyst loading is 0.5 mol.% to 1.0 mol.%, relative to the compound of **Formula (III)**.

72. The method of any one of claims 58 to 71, wherein the concentration of the compound of **Formula (III)** is greater than 0.07 M.

73. The method of any one of claims 58 to 72, wherein the concentration of the compound of **Formula (III)** is greater than or equal to 0.1 M.

74. The method of any one of claims 58 to 73, wherein the concentration of the compound of **Formula (III)** is 0.15 M to 0.5 M.
75. The method of any one of claims 58 to 74, wherein the concentration of the compound of **Formula (III)** is 0.15 M to 0.22 M.
76. The method of any one of claims 58 to 75, wherein the hydrogenating (a) is performed at a hydrogen pressure of 7 to 30 bar.
77. The method of any one of claims 58 to 76, wherein the hydrogenating (a) is performed at a hydrogen pressure of 14 to 28 bar.
78. The method of any one of claims 58 to 77, wherein the hydrogenating (a) is performed at a hydrogen pressure of 25 to 28 bar.
79. The method of any one of claims 58 to 78, wherein the hydrogenating (a) is performed in trifluoroethanol (TFE), hexafluoroisopropanol (HFIP), or a combination thereof.
80. The method of any one of claims 58 to 79, wherein the hydrogenating (a) is performed at a temperature of 25 to 90°C.
81. The method of any one of claims 58 to 80, wherein the hydrogenating (a) is performed at a temperature of 25 to 40°C.
82. The method of any one of claims 58 to 81, wherein the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 90%.
83. The method of any one of claims 58 to 82, wherein the obtained compound of **Formula (IV')** has an enantiomeric excess of greater than or equal to 95%.
84. The method of any one of claims 58 to 83, wherein 5% or less of the compound of **Formula (III)** is present after the hydrogenating (a).

85. The method of any one of claims 58 to 84, wherein the obtained compound of **Formula (IV')** has a purity of 95% or greater after the hydrogenating (a).
86. The method of any one of claims 58 to 85, wherein the **Compound (k)** is obtained in a yield of 70% or greater, relative to the amount of the compound of **Formula (III)**.
87. The method of any one of claims 58 to 86, wherein the **Compound (k)** is obtained in a yield of 80% or greater, relative to the amount of the compound of **Formula (III)**.
88. The method of any one of claims 58 to 87, wherein the **Compound (k)** is obtained in a yield of 90% or greater, relative to the amount of the compound of **Formula (III)**.
89. The method of any one of claims 58 to 88, wherein the obtained **Compound (k)** has an optical purity of 90% or greater.
90. The method of any one of claims 58 to 89, wherein the obtained **Compound (k)** has an optical purity of 95% or greater.
91. The method of any one of claims 58 to 90, wherein the obtained **Compound (k)** has an optical purity of 97% or greater.
92. A **Compound (f')**, having an optical purity of greater than or equal to about 90%



93. The compound of claim 92, having an optical purity of greater than or equal to about 95%.