Innovation, Sciences et Développement économique Canada
Office de la Propriété Intellectuelle du Canada

Innovation, Science and Economic Development Canada
Canadian Intellectual Property Office

CA 2970933 C 2023/10/10

(11)(21) 2 970 933

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2015/12/17
(87) Date publication PCT/PCT Publication Date: 2016/06/23
(45) Date de délivrance/Issue Date: 2023/10/10
(85) Entrée phase nationale/National Entry: 2017/06/14
(86) N° demande PCT/PCT Application No.: US 2015/066345
(87) N° publication PCT/PCT Publication No.: 2016/100645
(30) Priorité/Priority: 2014/12/19 (US62/094,425)

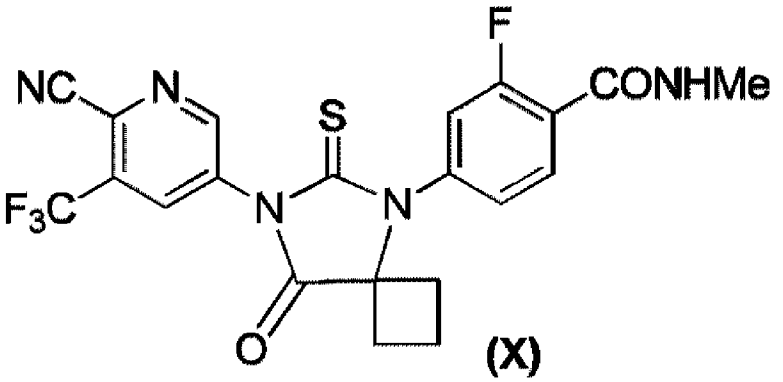
(51) Cl.Int./Int.Cl. *C07D 401/04* (2006.01)

(72) Inventeurs/Inventors:
HAIM, CYRIL BEN, BE;
HORVATH, ANDRAS, BE;
WEERTS, JOHAN ERWIN EDMOND, BE;
ALBANEZE-WALKER, JENNIFER, BE

(73) Propriétaire/Owner:
ARAGON PHARMACEUTICALS, INC., US

(74) Agent: NORTON ROSE FULBRIGHT CANADA LLP/S.E.N.C.R.L., S.R.L.

(54) Titre : PROCEDES POUR LA PREPARATION D'UN COMPOSE DIARYL-THIOHYDANTOINE
(54) Title: PROCESSES FOR THE PREPARATION OF A DIARYLTHIOHYDANTOIN COMPOUND




(X)

(57) Abrégé/Abstract:
Disclosed are processes and intermediates for the preparation of compound (X), which is currently being investigated for the treatment of prostate cancer.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 June 2016 (23.06.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/100645 A1

(51) International Patent Classification:
*C07D 401/04* (2006.01)

(21) International Application Number:
PCT/US2015/066345

(22) International Filing Date:
17 December 2015 (17.12.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/094,425 19 December 2014 (19.12.2014) US

(71) Applicant: **ARAGON PHARMACEUTICALS, INC.** [US/US]; 12780 El Camino Real, Suite 301, San Diego, California 92130 (US).

(72) Inventors: **HAIM, Cyril Ben**; Krommenhof 54, 2340 Beerse (BE). **HORVATH, Andras**; Smalvoortstraat 46 bus 2, B2300 Turnhout (BE). **WEERTS, Johan Erwin Edmond**; Statiestraat 7, 2340 Beerse (BE). **ALBANEZE-WALKER, Jennifer**; Frankfurtlaan 1, 2400 Mol (BE).

(74) Agents: **PLANTZ, Bernard F.** et al.; JOHNSON & JOHNSON, One Johnson & Johnson Plaza, New Brunswick, New Jersey 08933 (US).

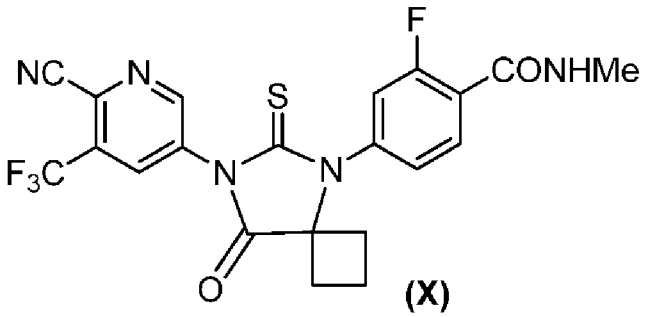
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP,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

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

**Published**:

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

(54) Title: PROCESSES FOR THE PREPARATION OF A DIARYLTHIOHYDANTOIN COMPOUND




(X)

(57) Abstract: Disclosed are processes and intermediates for the preparation of compound (X), which is currently being investigated for the treatment of prostate cancer.

WO 2016/100645 A1

# PROCESSES FOR THE PREPARATION OF A DIARYLTHIOHYDANTOIN COMPOUND

## FIELD OF THE INVENTION

The present invention is directed to the preparation of compound (X) and intermediates in its synthesis. More specifically, the present invention is directed to processes for the preparation of compound (X), disclosed in United States Patent No. 8,445,507, issued on May 21, 2013.

## BACKGROUND OF THE INVENTION

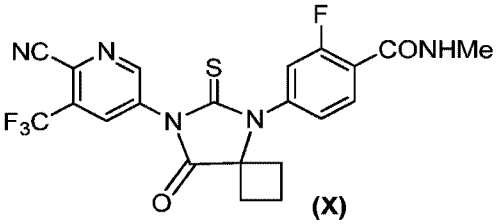
Compound (X) of the present invention is currently being investigated for use in the treatment of prostate cancer. The present invention describes processes and intermediates for the preparation of such compound.

## SUMMARY OF THE INVENTION

The present invention is directed to a process for the preparation of compound (X)

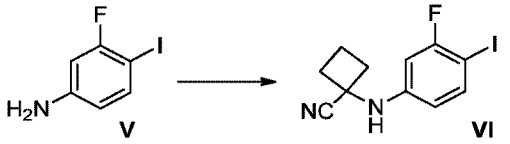


Date Reçue/Date Received 2022-06-16



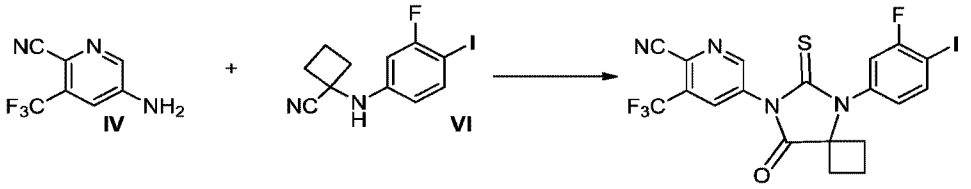

(X)

Comprising, consisting of, and/or consisting essentially of



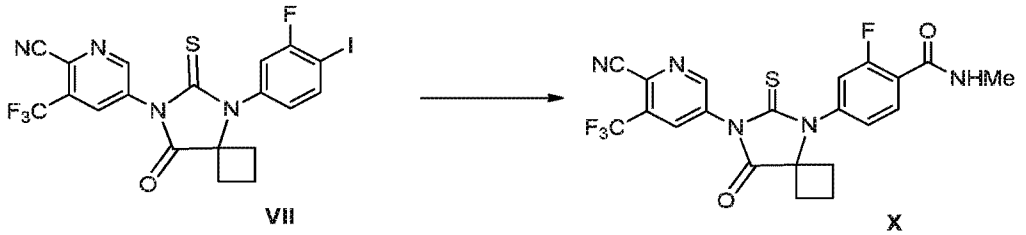

V VI (1a)

reacting compound (V) with cyclobutanone in the presence of sodium cyanide; in a solvent such as acetic acid, or a solvent system comprised, consisting, or consisting essentially of an alcoholic solvent and a protic acid; at a temperature of about 0 °C to about 20 °C; to yield the corresponding compound (VI);




IV VI VII (1b)

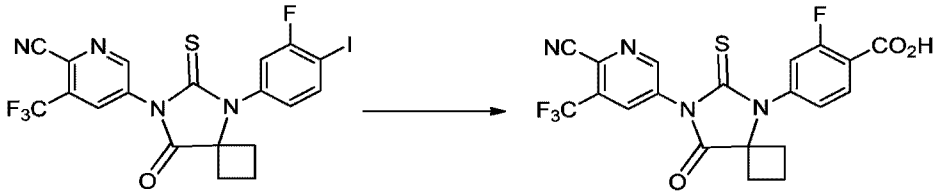
reacting compound (IV) and compound (VI) in the presence of a thiocarbonylating agent; in an organic solvent; at a temperature of about 0 °C to about 100 °C; to yield the corresponding compound (VII);




VII X (1x)

converting compound (VII) to compound (X), discussed in further detail below.

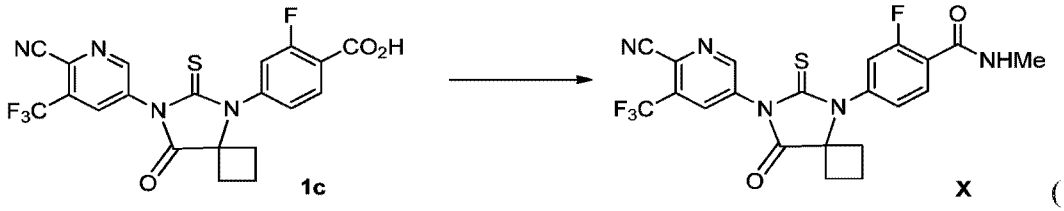
In one embodiment, compound (VII) is converted to compound (X) via its corresponding carboxylic acid (1c), as shown in scheme (1c), by




VII 1c (1c)

(i) reacting compound (VII) with an organomagnesium halide; in the presence or absence of a lithium halide; followed by the addition of carbon dioxide gas; in an aprotic organic solvent; at a temperature of about 0 °C; to yield the corresponding carboxylic acid compound (1c); or,

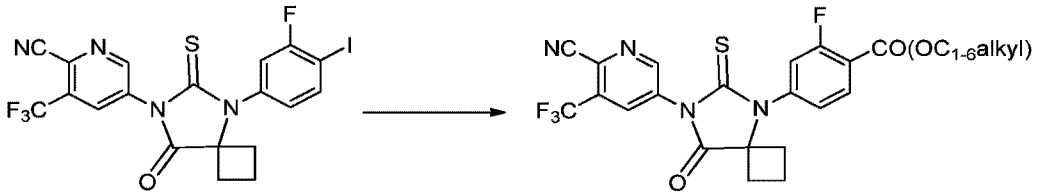
(ii) reacting compound (VII) under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; in the presence of an organic base; in a the presence of water; in an organic solvent; at a temperature of about 0 °C to about 100 °C; to yield the corresponding compound (1c); then,




1c X (1d)

reacting compound (1c) with a coupling agent; in an aprotic or protic solvent; at about room temperature; followed by the addition of methylamine; to yield the corresponding compound (X).

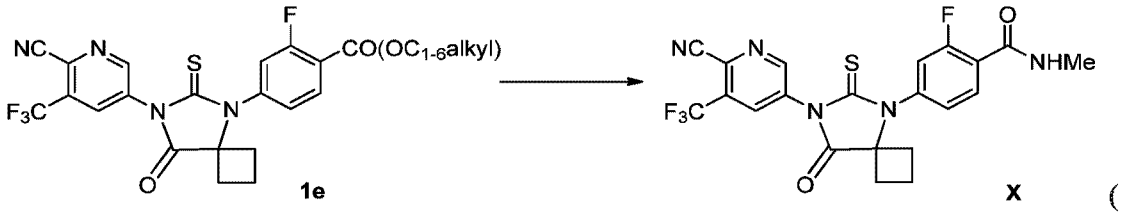
In another embodiment, compound (VII) is converted to compound (X) via its corresponding $C_{1-6}$alkyl ester (1e), as shown in scheme (1e), by




VII 1e (1e)

(i) reacting compound (VII) with an organomagnesium halide; in the presence or absence of a lithium halide; in an aprotic organic solvent; at a temperature of about -50 °C to about room temperature; followed by the addition of an $C_{1-6}$alkyl chloroformate or $C_{1-6}$alkyl cyanoformate; to yield the corresponding ester of formula (1e); or

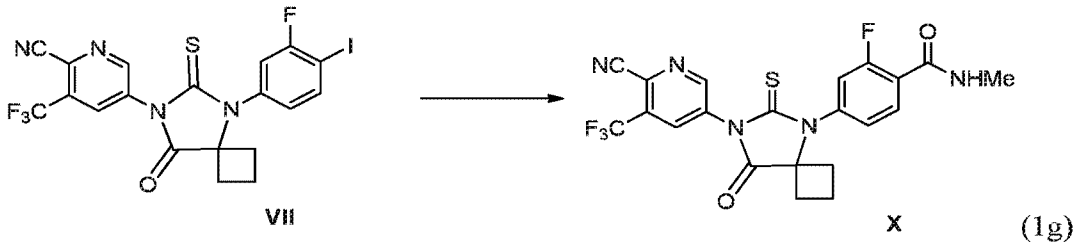
(ii) reacting compound (VII) under suitable alkoxycarbonylation conditions; under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; in the presence of a base; in a $C_{1-6}$alcoholic solvent; at a temperature of about room temperature to about 100 °C; to yield the corresponding compound of formula (1e); then




(1f)

treating a compound of formula (1e) with methylamine; in a protic or aprotic solvent; at a temperature of about 0 °C to about 60 °C; to yield the corresponding compound (X).

In another embodiment, compound (VII) is converted directly to compound (X), as shown in scheme (1g), by




(1g)

(i) reacting compound (VII) in the presence of molybdenum hexacarbonyl; optionally in the presence of one or more reagents such as norbornadiene, tetrabutylammonium bromide, or a base selected from triethylamine or DABCO; in an

organic solvent; followed by the addition of methylamine; at a temperature of about 60 °C to about 140 °C; to yield the corresponding compound (X); or,

(ii) reacting compound (VII) under suitable aminocarbonylation conditions; under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; in the presence of a base; in the presence of methylamine; in an organic solvent; at a temperature of about room temperature to about 100 °C; to yield the corresponding compound (X).

## DETAILED DESCRIPTION OF THE INVENTION

The term "alkyl" whether used alone or as part of a substituent group, refers to straight and branched carbon chains having 1 to 8 carbon atoms. Therefore, designated numbers of carbon atoms (e.g., $C_{1-8}$) refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger alkyl-containing substituent. In substituent groups with multiple alkyl groups such as, $(C_{1-6}alkyl)_2amino$-, the $C_{1-6}alkyl$ groups of the dialkylamino may be the same or different.

The term "alkoxy" refers to an -O-alkyl group, wherein the term "alkyl" is as defined above.

The term "cycloalkyl" refers to a saturated or partially saturated, monocyclic hydrocarbon ring of 3 to 8 carbon atoms. Examples of such rings include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

The term "aryl" refers to an unsaturated, aromatic monocyclic or bicyclic ring of 6 to 10 carbon members. Examples of aryl rings include phenyl and naphthalenyl.

The term "halogen", "halide", or "halo" refers to fluorine, chlorine, bromine and iodine atoms.

The term "carboxy" refers to the group –C(=O)OH.

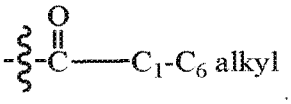
The term "formyl" refers to the group –C(=O)H.

The term "oxo" or "oxido" refers to the group (=O).

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., arylalkyl, alkylamino) the name is to be interpreted as including

those limitations given above for "alkyl" and "aryl." Designated numbers of carbon atoms (e.g., $C_1$-$C_6$) refer independently to the number of carbon atoms in an alkyl moiety, an aryl moiety, or in the alkyl portion of a larger substituent in which alkyl appears as its prefix root. For alkyl and alkoxy substituents, the designated number of carbon atoms includes all of the independent members included within a given range specified. For example $C_{1-6}$ alkyl would include methyl, ethyl, propyl, butyl, pentyl and hexyl individually as well as sub-combinations thereof (e.g., $C_{1-2}$, $C_{1-3}$, $C_{1-4}$, $C_{1-5}$, $C_{2-6}$, $C_{3-6}$, $C_{4-6}$, $C_{5-6}$, $C_{2-5}$, etc.).

In general, under standard nomenclature rules used throughout this disclosure, the terminal portion of the designated side chain is described first followed by the adjacent functionality toward the point of attachment. Thus, for example, a "$C_1$-$C_6$ alkylcarbonyl" substituent refers to a group of the formula:



The term "room temperature" or "ambient temperature", as used herein refers to a temperature in the range of from about 18 °C to about 22 °C.

Abbreviations used in the instant specification, particularly the schemes and examples, are as follows:

Abbreviations

| | |
|---|---|
| aq | aqueous |
| BA | [1,1'-biphenyl]-2-amine |
| Boc | *tert*-butoxycarbonyl |
| CDI | 1,1'-carbonyldiimidazole |
| CPME | cyclopentyl methylether |
| Cy | cyclohexyl |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCM | dichloromethane |
| DIEA or DIPEA | diisopropylethylamine |
| DMA | dimethylacetamide |

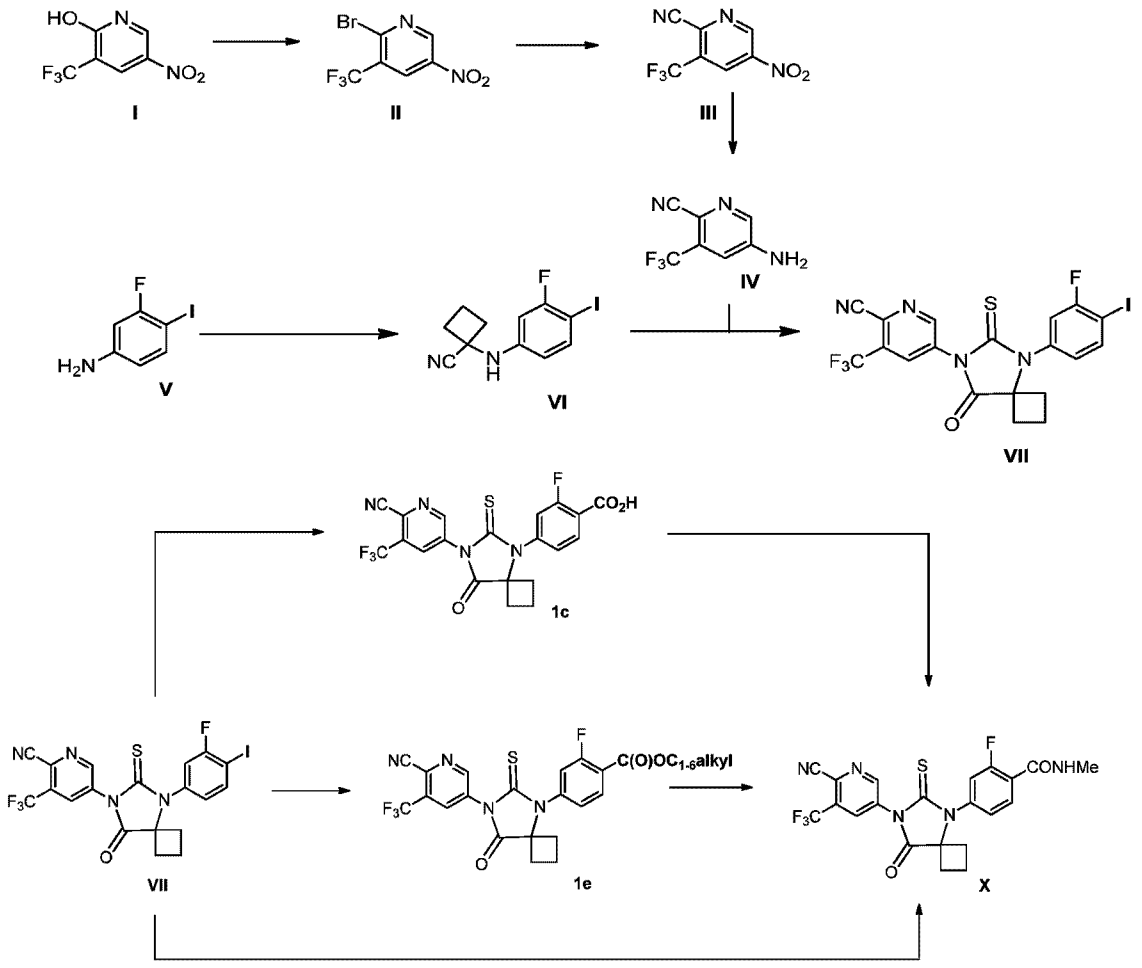
Abbreviations

| | |
|---|---|
| DMF | dimethylformamide |
| DMSO | methyl sulfoxide |
| dppf | 1,1′-bis(diphenylphosphino)ferrocine |
| h | hour(s) |
| HCl | hydrochloric acid |
| HPLC | high performance liquid chromatography |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methyl alcohol |
| mg | milligram |
| MTBE | methyl *tert*-butylether |
| NMP | *N*-methyl-2-pyrrolidone |
| $PdCl_2(dppf)\cdot CH_2Cl_2$ | 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex) |
| P(*o*-tol)$_3$ | tri(*o*-tolyl)phosphine |
| rt | room temperature |
| THF | tetrahydrofuran |
| 2-MeTHF | 2-methyl tetrahydrofuran |

General Schemes

The overall scheme for the present invention is illustrated in Scheme A, shown below.

**Scheme A**




In Scheme A, a compound (V) may be reacted with cyclobutanone and at least one molar equivalent of sodium cyanide; in a solvent such as acetic acid, or in a solvent system comprised, consisting, or consisting essentially of of at least one molar equivalent of an acid such as acetic acid or hydrochloric acid and a $C_{1-4}$alcoholic solvent such as methanol, ethanol, propanol, or butanol; at a temperature of about 0 °C to about 20 °C; to yield the corresponding compound (VI).

In one embodiment, the solvent is acetic acid.

In another embodiment, the solvent system is 90% acetic acid and 10% ethanol.

Compound (IV) may be reacted with a compound of formula (VI) in the presence of a thiocarbonylating agent selected from 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one, 1,1'-thiocarbonyl diimidazole, phenylthionochloroformate, beta-naphthyl thionochloroformate, 1,1'-thiocarbonylbis(pyridin-2(1*H*)-one), *O*,*O*-di(pyridin-2-yl)carbonothioate, 1,1'-thiocarbonylbis (1*H*-benzotriazole), or thiophosgene; in an organic solvent such as THF, 2-methyl-THF, acetonitrile, DMA, toluene, DMF, NMP, DMSO, or the like; at a temperature of about 0 °C to about 100 °C; to yield the corresponding compound (VII).

In one embodiment, the thiocarbonylating agent is 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one.

In another embodiment, the organic solvent is DMA.

Conversion to Compound (X) via Carboxylic Acid (1c)

(i) Compound (VII) may be converted to compound (X) via its corresponding carboxylic acid, compound (1c), by reacting compound (VII) with an organomagnesium halide selected from $C_{1-8}$alkylmagnesium halide or $C_{5-7}$cycloalkylmagnesium halide; in the presence or absence of a lithium halide such as lithium chloride, lithium bromide, or lithium iodide; followed by the addition of carbon dioxide gas; in an aprotic organic solvent selected from THF, 2-MeTHF, MTBE, CPME, or toluene; at a temperature of about 0 °C; to yield the corresponding carboxylic acid compound (1c).

More particularly, the $C_{1-8}$alkylmagnesium halide is a $C_{1-8}$alkylmagnesium chloride or $C_{1-8}$alkylmagnesium bromide, and the $C_{5-7}$cycloalkylmagnesium halide is a $C_{5-7}$cycloalkylmagnesium chloride or $C_{5-7}$cycloalkylmagnesium bromide.

In one embodiment, the $C_{1-8}$alkylmagnesium halide is selected from isopropylmagnesium chloride, *sec*-butylmagnesium chloride, *n*-pentylmagnesium chloride, hexylmagnesium chloride, ethylmagnesium chloride, ethylmagnesium bromide, *n*-butylmagnesium chloride, or isopropylmagnesium chloride.

In a further embodiment, the $C_{1-8}$alkylmagnesium halide is *n*-pentylmagnesium chloride; and the aprotic organic solvent is THF.

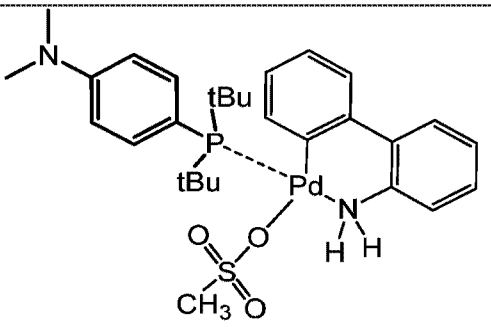
In a further embodiment, a lithium halide is absent.

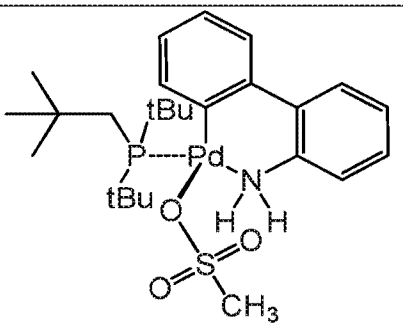
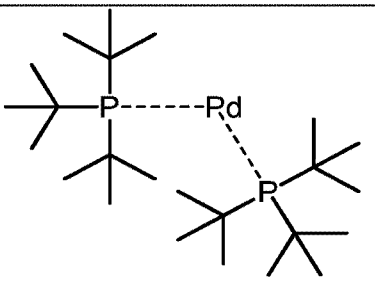
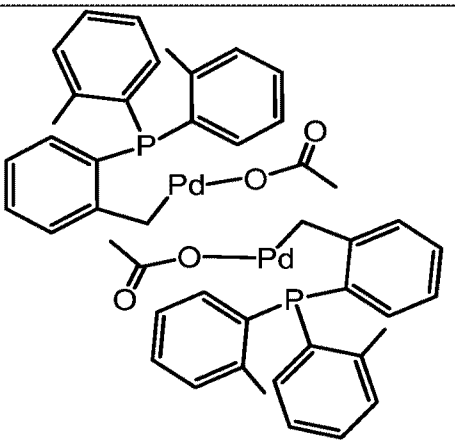
In another embodiment, the $C_{5-7}$cycloalkylmagnesium halide is cyclohexylmagnesium chloride.

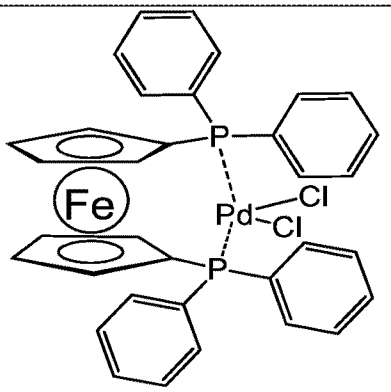
(ii) Alternatively, compound (VII) may be reacted under a carbon monoxide atmosphere, in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; in the presence of water; in a solvent such as methanol, ethanol, or the like; at a temperature of about 0 °C to about 100 °C; to yield the corresponding compound (1c).

It has been found that a variety of palladium catalysts and phosphorus ligands are suitable for this transformation. In an embodiment, the palladium catalyst is either a pre-formed palladium catalyst or a palladium-ligand catalyst complex that is formed *in situ*. When the palladium catalyst is a pre-formed palladium catalyst, it is selected from CAT1 to CAT5, shown in Table 1, and may be used for the above-described preparation of compound (1c).

Table 1. Pre-formed Palladium Catalysts

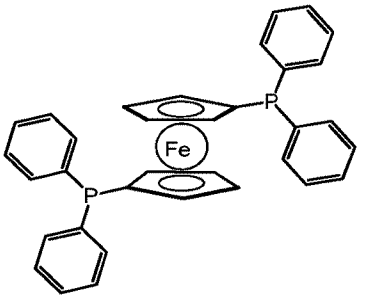
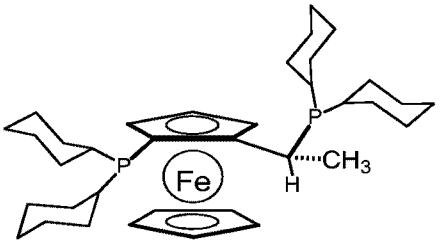
| Catalyst No. | Catalyst Name | Structure |
|---|---|---|
| CAT1 | Pd(OMs)(BA) (P(tBu$_2$-4-*N*,*N*-dimethylaniline)) |  |

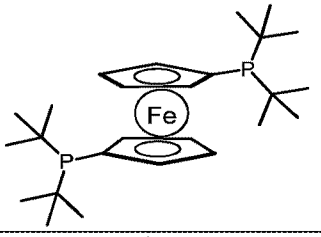
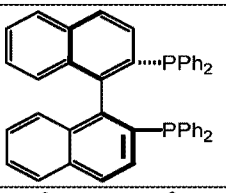
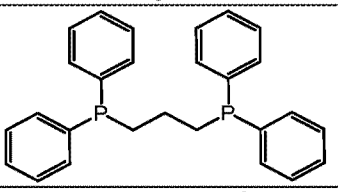
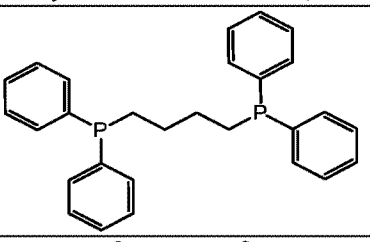
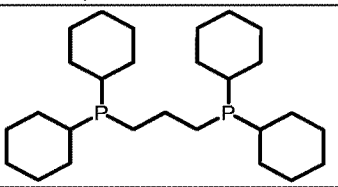
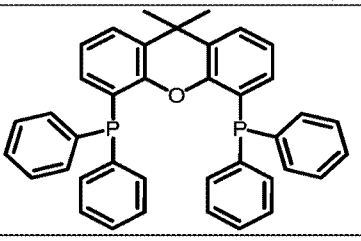
| Catalyst No. | Catalyst Name | Structure |
|---|---|---|
| CAT2 | Pd(OMs)(BA) (P($tBu_2$-neopentyl) |  |
| CAT3 | Pd(P($t$Bu$_3$)$_2$ |  |
| CAT4 | [Pd(OAc) (P($o$-Tol)$_3$]$_2$ |  |

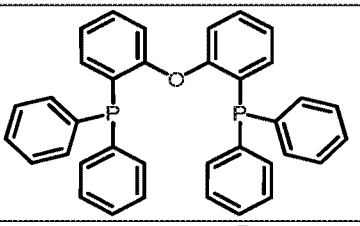
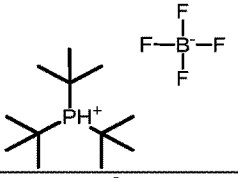
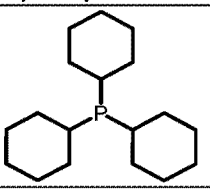
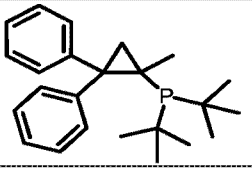
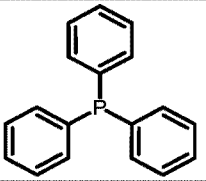
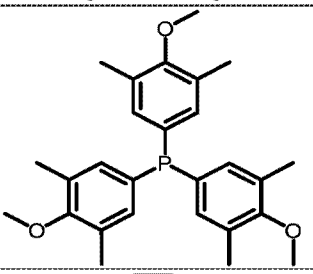
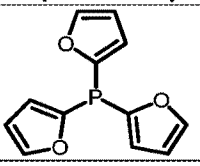
| Catalyst No. | Catalyst Name | Structure |
|---|---|---|
| CAT5 | $[PdCl_2(\mathbf{L3})]$ = $PCl_2(dppf)$ |  |

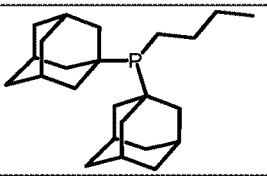
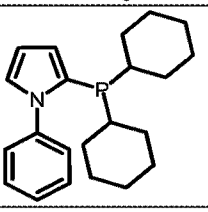
In another embodiment, one or more phosphorus ligands selected from L1 to L17, shown in Table 2, may be used in combination with either a pre-formed palladium catalyst (Table 1) or a palladium metal compound (Table 3), for the preparation of compound (1c).

Table 2. Phosphorus Ligands

| Ligand No. | Structure |
|---|---|
| L1 |  |
| L2 |  |

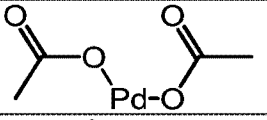
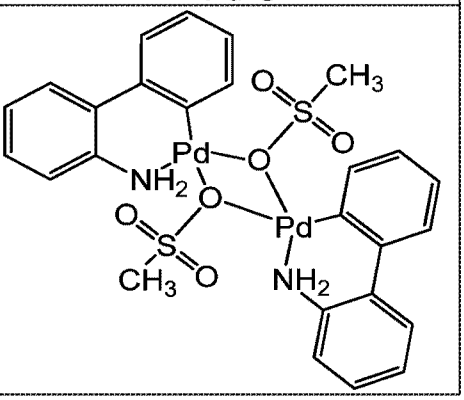
| Ligand No. | Structure |
|---|---|
| L3 |  |
| L4 |  |
| L5 |  |
| L6 |  |
| L7 |  |
| L8 |  |

| Ligand No. | Structure |
|---|---|
| L9 |  |
| L10 |  |
| L11 |  |
| L12 |  |
| L13 |  |
| L14 |  |
| L15 |  |

| Ligand No. | Structure |
|---|---|
| L16 |  |
| L17 |  |

In another embodiment, a palladium metal compound selected from M1 to M2, shown in Table 3 may be used.

Table 3. Palladium Metal Compounds

| Metal No. | Metal Cpd Name | Structure |
|---|---|---|
| M1 | palladium acetate |  |
| M2 | $[Pd(OMs)(BA)]_2$ |  |

In an embodiment, the palladium catalyst is comprised, consisting, or consisting essentially of the phosphorus ligand dppf (L1, Table 2) and the palladium metal compound palladium acetate (M1, Table 3).

Compound (1c) may then be treated with a coupling agent such as CDI; in an aprotic or protic solvent such as THF, toluene, or the like; at about room temperature; followed by the addition of methylamine; to yield the corresponding compound (X).

In one embodiment, methylamine is added as a solution in a protic or aprotic solvent. In a further embodiment, methylamine is added as a THF solution.

In another embodiment, methylamine is added in its gaseous state.

In yet another embodiment, methylamine is added as its methyl ammonium salt.

Conversion to Compound (X) via Ester (1e)

(i) Compound (VII) may also be converted to compound (X) via its corresponding $C_{1-6}$alkyl ester (1e), by reacting compound (VII) with an organomagnesium halide selected from a $C_{1-8}$alkylmagnesium halide or a $C_{5-7}$cycloalkylmagnesium halide; in the presence or absence of a lithium halide such as lithium chloride, lithium bromide, or lithium iodide; in an aprotic organic solvent selected from THF, 2-MeTHF, toluene, or the like; at a temperature of about -50 °C to about 22 °C; followed by the addition of a $C_{1-6}$alkyl chloroformate or $C_{1-6}$alkyl cyanoformate; to yield the corresponding ester of formula (1e).

More particularly, the $C_{1-8}$alkylmagnesium halide is a $C_{1-8}$alkylmagnesium chloride or $C_{1-8}$alkylmagnesium bromide, and the $C_{5-7}$cycloalkylmagnesium halide is a $C_{5-7}$cycloalkylmagnesium chloride or $C_{5-7}$cycloalkylmagnesium bromide.

In one embodiment, the $C_{1-8}$alkylmagnesium halide is selected from isopropylmagnesium chloride, *sec*-butylmagnesium chloride, cyclohexylmagnesium chloride, *n*-pentylmagnesium chloride, hexylmagnesium chloride, ethylmagnesium chloride, ethylmagnesium bromide, *n*-butylmagnesium chloride, or isopropylmagnesium chloride.

In another embodiment, the $C_{1-8}$alkylmagnesium halide is *n*-pentylmagnesium chloride and the aprotic organic solvent is THF or 2-MeTHF.

In a further embodiment, a lithium halide is absent.

(ii) Alternatively, compound (VII) may be reacted under suitable alkoxycarbonylation conditions, under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; with a base such as DIPEA, $K_2CO_3$, $K_3PO_4$, or $Cy_2NMe$; in a $C_{1-4}$alcoholic solvent selected from methanol,

ethanol, isopropyl alcohol, *n*-butyl alcohol, or *t*-butyl alcohol; to yield the corresponding compound of formula (1e).

It has been found that a variety of palladium catalysts and phosphorus ligands are suitable for this transformation. In an embodiment, the palladium catalyst is either a pre-formed palladium catalyst or a palladium-ligand catalyst complex that is formed *in situ*. When the palladium catalyst is a pre-formed palladium catalyst, it is selected from CAT1 to CAT5, shown in Table 1 (above), and may be used for the preparation of a compound of formula (1e).

In another embodiment, one or more phosphorus ligands selected from L1 to L17, shown in Table 2 (above), may be used in combination with either a pre-formed palladium catalyst (Table 1) or a palladium metal compound (Table 3), for the preparation of a compound of formula (1e).

In another embodiment, a palladium metal compound selected from M1 or M2 (Table 3, above) may be used, in combination with one or more phosphorus ligands selected from L1 to L17 from Table 2, for the above-described alkoxycarbonylation reaction.

Table 4 describes certain reaction conditions (**E1** to **E8**) for the conversion of compound (VII) to methyl ester (1e-1), wherein $C_{1-6}$alkyl of a compound of formula (1e) is methyl.

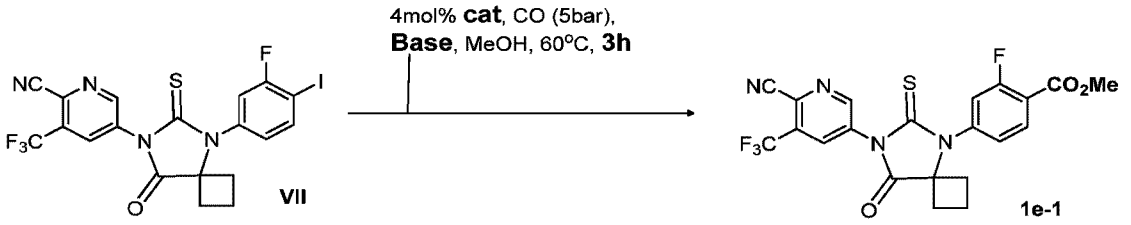



Table 4.

Conditions for Alkoxycarbonylation of Compound (VII) to Methyl Ester (1e-1)

| | Metal/Cat. | Ligand | Base | Conv. (%) | Yield (%) |
|---|---|---|---|---|---|
| **E1** | $Pd(P(tBu_3)_2$ | --- | DIPEA | 100.0 | 82.1 |

| | Metal/Cat. | Ligand | Base | Conv. (%) | Yield (%) |
|---|---|---|---|---|---|
| **E2** | $[Pd(OMs)BA)]_2$ | L10 | $Cy_2NMe$ | 99.0 | 72.5 |
| **E3** | $PdCl_2dppf$ | --- | $Cy_2NMe$ | 98.8 | 81.7 |
| **E4** | $PdCl_2dppf$ | --- | DIPEA | 98.7 | 84.8 |
| **E5** | $[Pd(OMs)BA)]_2$ | L17 | $Cy_2NMe$ | 98.4 | 83.8 |
| **E6** | $[Pd(OMs)BA)]_2$ | L13 | $Cy_2NMe$ | 92.0 | 72.8 |
| **E7** | $Pd(OAc)_2$ | L10 | $Cy_2NMe$ | 84.0 | 75.4 |
| **E8** | $Pd(OAc)_2$ | L16 | $Cy_2NMe$ | 78.8 | 73.0 |

In an embodiment, the process for the conversion of compound (VII) to a compound of formula (1e) is in the presence of the palladium catalyst $Pd(P(tBu_3)_2$ (CAT3, Table 1), and 1.2 equivalents of DIPEA.

In another embodiment, the palladium catalyst is comprised, consisting, consisting essentially of the phosphorus ligand L10 (Table 2) and the palladium metal compound $[Pd(OMs)(BA)]_2$ (M2, Table 3). In another embodiment, the organic base is $Cy_2NMe$.

In another embodiment, the palladium catalyst is comprised, consisting, or consisting essentially of of the phosphorus ligand dppf (L1, Table 2) and the palladium metal compound palladium acetate (M1, Table 3). In another embodiment, the organic base is $Cy_2NMe$.

In a further embodiment, the $C_{1-6}$alcoholic solvent is methanol.

A compound of formula (1e) may be treated with methylamine; in a protic or aprotic solvent such as THF, DMF, DMA, ethanol, or a mixture thereof; at a temperature of about 0 °C to about 60 °C; to yield the corresponding compound (X).

In an embodiment, methylamine is added as a THF solution.

In another embodiment, methylamine is added as a solution in MeOH.

In another embodiment, methylamine is added in its gaseous state.

Direct Conversion of Compound (VII) to Compound (X)

(i) Compound (VII) may be converted directly to compound (X) by reacting compound (VII) in the presence of molybdenum hexacarbonyl; optionally in the presence of one or more reagents such as norbornadiene, tetrabutylammonium bromide, or a base selected from triethylamine or DABCO; in an organic solvent selected from diglyme, dioxane, butyronitrile, propionitrile, or the like; followed by the addition of methylamine; at a temperature of from about 60 °C to about 140 °C; to yield the corresponding compound (X).

In one embodiment, the reagents norbornadiene, tetrabutylammonium bromide, and DABCO are present.

In another embodiment, the organic solvent is butyronitrile or diglyme.

(ii) Alternatively, compound (VII) may be reacted under suitable aminocarbonylation conditions; under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; in the presence of a base selected from DIPEA, $K_2CO_3$, $K_3PO_4$, $Cy_2NMe$, or excess methylamine; in the presence of methylamine; at a temperature of from about room temperature to about 100 °C; to yield the corresponding compound (X).

It has been found that a variety of palladium catalysts and phosphorus ligands are suitable for this transformation. In an embodiment, the palladium catalyst is either a pre-formed palladium catalyst or a palladium-ligand catalyst complex that is formed *in situ*. When the palladium catalyst is a pre-formed palladium catalyst, it is selected from CAT1 to CAT5, shown in Table 1 (above), and may be used for the preparation of compound (X).

In another embodiment, one or more phosphorus ligands selected from L1 to L17, shown in Table 2 (above), may be used in combination with either a pre-formed palladium catalyst (Table 1) or a palladium metal compound (Table 3), for the preparation of compound (X).

In another embodiment, a palladium metal compound selected from M1 or M2 (Table 3, above) may be used, in combination with one or more phosphorus ligands selected from L1 to L17 (Table 2), for the above-described aminocarbonylation reaction.

Table 5 describes certain reaction conditions (**G1** to **G7**) for the conversion of compound (VII) to Compound (X).

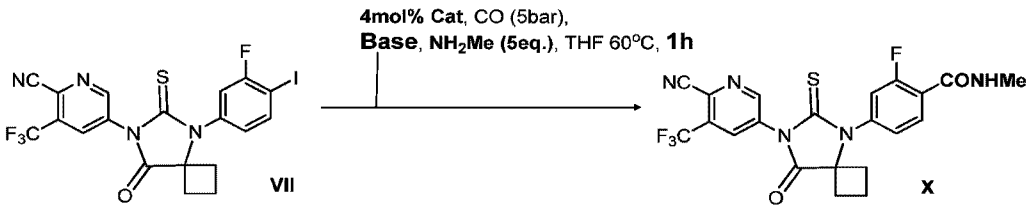



Table 5.

Conditions for Aminocarbonylation of Compound (VII) to Compound (X)

| | Metal/Cat. Precursor | Ligand | Base | Conv. [%] | Yield |
|---|---|---|---|---|---|
| **G1** | $Pd(P(tBu_3)_2$ | --- | DIPEA | 100 | 95 |
| **G2** | $Pd(OAc)_2$ | L10 | $Cy_2NMe$ | 100 | 93.9 |
| **G3** | $Pd(OAc)_2$ | L16 | $Cy_2NMe$ | 100 | 93.1 |
| **G4** | $[Pd(OMs)BA)]_2$ | L10 | $Cy_2NMe$ | 100 | 91.8 |
| **G5** | $[Pd(OMs)BA)]_2$ | L16 | $Cy_2NMe$ | 100 | 88.5 |
| **G6** | $Pd(OAc)_2$ | L16 | $K_3PO_4$ | 100 | 83.7 |
| **G7** | $Pd(OAc)_2$ | L17 | $Cy_2NMe$ | 95.1 | 83.5 |

In one embodiment, the palladium catalyst is $Pd(P(tBu_3)_2$ (CAT3, Table 1), and the organic base is 1.2 equivalents of DIPEA.

In another embodiment, the palladium catalyst is comprised, consisting or consisting essentially of the phosphorus ligand L10 (Table 2) and the palladium metal compound $Pd(OAc)_2$ (M1, Table 3). In a further embodiment, the base is $Cy_2NMe$.

In one embodiment, methylamine is added as a solution in a protic or aprotic solvent.

In another embodiment, methylamine is added as a THF solution.

In another embodiment, methylamine is added in its gaseous state.

In another embodiment, methylamine is added as a solution in methanol.

In yet another embodiment, methylamine is added as its methyl ammonium hydrochloride salt.

In another embodiment, the organic solvent is THF.

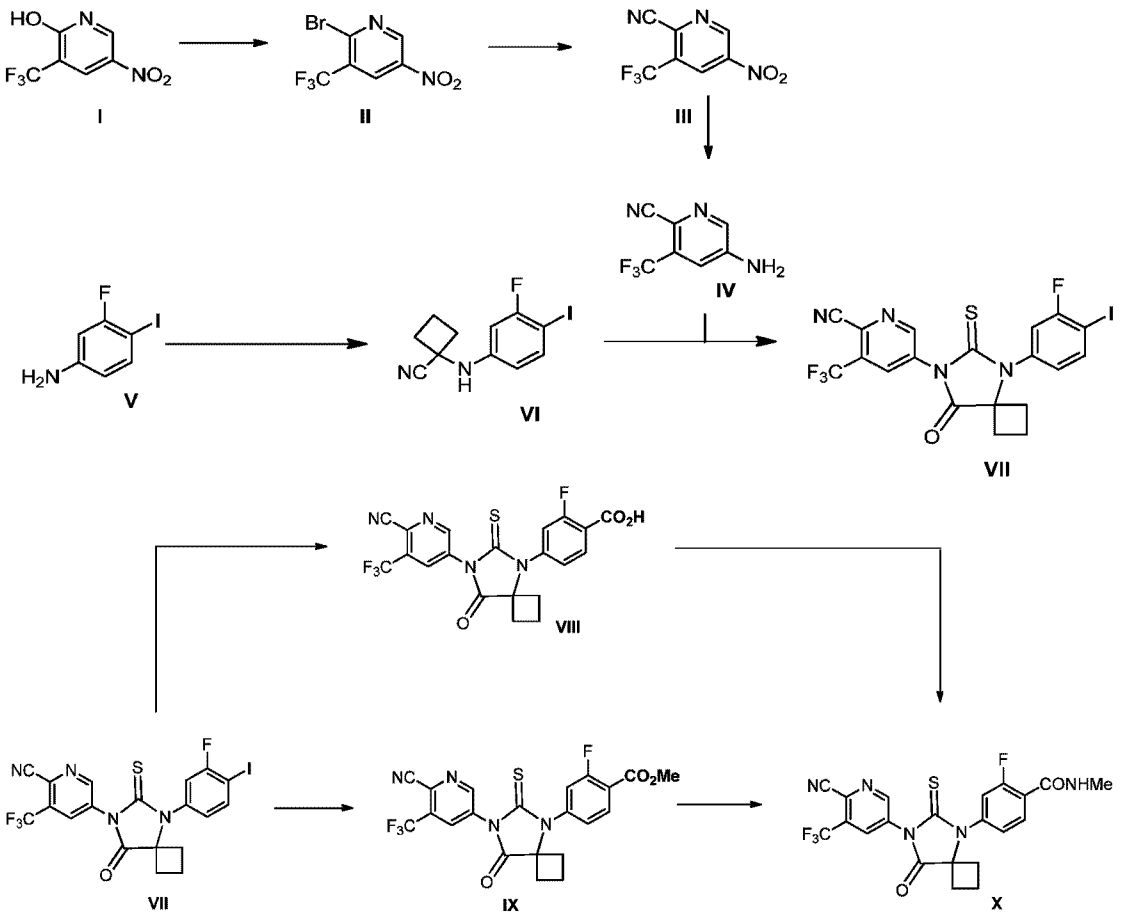
One skilled in the art will further recognize that the reaction or process step(s) as herein described (or claimed) are allowed to proceed for a sufficient period of time, at a suitable temperature or range of temperatures, until the reaction is complete, as determined by any method known to one skilled in the art, for example, chromatography (e.g. HPLC, TLC, etc.). In this context a "completed reaction or process step" means that the reaction mixture contains a decreased amount of the starting material(s) / reagent(s) and an increased amount of the desired product(s), as compared to the amounts of each present at the beginning of the reaction.

## Specific Examples

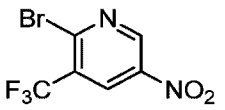
The following Examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

In the Examples that follow, some synthesis products are listed as having been isolated as a residue. It will be understood by one of ordinary skill in the art that the term "residue" does not limit the physical state in which the product was isolated and may include, for example, a solid, an oil, a foam, a gum, a syrup, and the like.

## Example 1



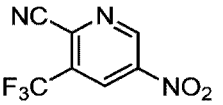
Step A. Preparation of Compound II.



A vessel was charged with 19 g of compound (I), 5 g of triethylamine hydrobromide, 49 g of xylenes and 67 g DMF. A solution of 26 g of phosphorous oxybromide in 16 g of xylene was dosed into the reaction mixture. The reaction mixture was heated to 100 °C for 3 h. The mixture was then cooled to 70 °C. To this mixture was added 75 g of a solution of NaOH (10M). After phase separation at room temperature, the

organic layer was washed with a 84 g of an aqueous solution of NaOH (10M) followed by 84 g of an aqueous solution of NaCl (25 %). The organic phase was carried forward into the next step without further purification. Isolation by crystallization from heptane was performed for characterization purposes of compound (II). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.36, 8.75.

Step B. Preparation of Compound (III).



III

To the previous solution of compound (II) in xylenes was added 8.7 g of sodium cyanide and 6.8 g of copper (I) iodide and 45 g of butyronitrile. The mixture was heated to 120 °C for 20 h. The reaction mixture was cooled, washed twice with an aqueous solution of sodium carbonate (10%). The organic phase was carried forward into the next step. Isolation was performed for characterization purposes of compound (III). $^1$H NMR (300 MHz, DMSO-$d_6$) δ 149.3, 145.4, 133.9, 131.9, 130.1, 119.5, 114.0.

Step C. Preparation of Compound (IV).

Preparation of modified catalyst slurry.

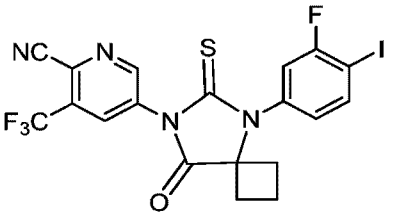
In a 20 mL beaker glass 0.156 g (0.129 mL, 50 % w/w) of $H_3PO_2$ was added to a slurry of 1.00 g 5 % Pt/C catalyst F101 R/W (from Evonik AG, contains ~60 % water) and 4.0 mL of deionized water. After 15 minutes while stirring with a magnetic stirring bar, 58 mg of $NH_4VO_3$ was added and the slurry was again stirred for 15 minutes.

Hydrogenation.

A 100 mL autoclave was charged with a solution of 10.0 g of compound (III) (46.1 mmol) in 26.7 mL of xylenes and 13.3 mL of butyronitrile. To this solution, the modified catalyst slurry was added with the aid of 2 mL of deionized water. The autoclave was closed, then inertized by pressurizing 3 times with nitrogen to 10 bar and 3 times hydrogen to 10 bar. The reactor pressure was set to 5.0 bar hydrogen, stirring was started (hollow

shaft turbine stirrer, 1200 rpm) and the mixture heated up to 70 °C within 50 min. As soon as 70 °C was reached, the hydrogen uptake ceased. After stirring for another 40 min, the heating was stopped and the autoclave was allowed to cooling. The slurry was filtered through a fiberglass filter and washed in portions using 40 mL of xylenes at 20-23 °C. Compound (IV) was crystallized from the solution upon distillation of the butyronitrile solvent. $^1$H NMR (300 MHz, DMSO-$d_6$) δ 8.20 (d, J=2.4Hz, 1H), 7.31 (d, J=2.6Hz, 1H), 7.04 (s, NH).

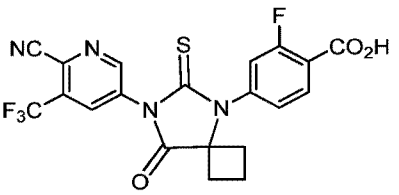
Step D. Preparation of Compound (VII).




VII

To a reactor containing compound (VI) (25 g) and compound (IV) (14 g) was added 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one (18 g) and toluene (316 mL). The reaction mixture was stirred and heated to 100 °C for 20 h. A solvent switch from toluene to DMA (8 L/kg final composition) was performed, then EtOH (400 mL) was added. The mixture was then heated to 70 °C before addition of HCl (2 M, 160 mL). After stirring for 2 h, the reaction was cooled down to 0 °C. The precipitate was collected by filtration, rinsed with EtOH/$H_2O$ (100 mL, 1:1), and dried to give compound (VII) (24 g, 63%). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.09 (d, J=2.1Hz, 1H), 8.35 (d, J=2.1Hz, 1H), 8.01 (dd, J=8.3, 6.8Hz, 1H), 7.07 (dd, J=7.9, 2.3Hz, 1H), 6.94 (dd, JJ=8.0, 2.0Hz, 1H), 2.72 (m, 2H), 2.58 (m, 2H), 2.30 (m, 1H), 1.74 (m, 1H).

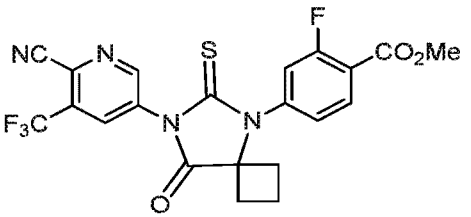
Step E. Preparation of Compound (VIII).



VIII

A reactor was charged with a solution of 5 g of compound (VII) in 50 mL of anhydrous THF and stirring begun. The reaction solution was cooled to an internal temperature of 0 °C. A solution of *n*-pentylmagnesium chloride (1 eq) was added slowly to maintain a reaction temperature of 0 °C. After 30 min, carbon dioxide gas was added into the stirred reaction mixture. Upon consumption of the starting material, the reaction mixture was added to a solution of aqueous acetic acid (10 %) to yield compound (VIII) (75 %). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.11 (d, 1H), 8.37 (d, 1H), 8.20 (m, 1H), 7.25 (m, 2H), 5.30 (s, 1H), 2.75 (m, 2H), 2.61 (m, 2H), 2.31 (m, 1H), 1.74 (m, 1H).

Step F. Preparation of Compound (IX).



IX

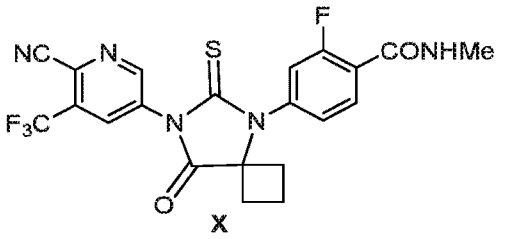
Method A. A pressure reactor was charged with Compound (VII) (1 g), palladium acetate (10 mol%), dppf (10 mol%), and diisopropylamine (1 eq) and methanol (10 mL). The reaction was placed under carbon monoxide (4 bar) and heated for 4 h at 60 °C. The reaction was allowed to cool to ambient temperature, diluted with dichloromethane (5 mL), then washed with a 3% cysteine aqueous solution. The organic layer was separated, concentrated, and dried to yield compound (IX) (85 %). $^1$H NMR (300 MHz, $CDCl_3$) δ 9.10 (d, $J$ = 1.9 Hz, 1H), 8.36 (d, $J$ =1.9 Hz, 1H), 8.20 (m, 1H), 7.20 (m, 2H), 4.00 (s, 3H),

2.75 (m, 2H), 2.58 (m, 2H), 2.30 (m, 1H), 1.76 (m, 1H); $^{13}$C NMR ($CDCl_3$, JMOD) δ 179.6, 174.2, 163.3, 159.2, 153.4 (ArH), 140.9, 135.5 (ArH), 132.9 (ArH), 128.9, 126.5 (ArH), 118.9(ArH), 114.2, 67.7, 52.6, 31.1, 13.4.

Method B. A reactor was charged with 2.5 g of compound (VII) in 25 mL 2-methyl-THF. The mixture was stirred under Argon at -15 °C. A solution of *n*-pentylmagnesium chloride in THF (2M, 2.4 mL) was dosed over 1 h. After 15 min of stirring, methyl chloroformate (1.1 eq, 0.40 mL) was added dropwise and the temperature was then allowed to warm to 15 °C. The reaction was quenched with a solution of 10% AcOH in water (20 mL). After phase separation, the organic layer was washed with water and then concentrated to yield compound (IX) in 77 % yield.

Method C. A reactor was charged with 2 g of compound (VII) in 20 mL of THF. The mixture was stirred under Argon at 50 °C. A solution of isopropylmagnesium chloride lithium chloride complex in THF (1.3M, 3.4 mL) was dosed over 10 min. After 5 min of stirring, methyl cyanoformate (1.25 eq, 0.37 mL) was added dropwise and the temperature was then allow to warm to 15 °C. The reaction was quenched with a solution of 10% AcOH in water (20 mL). After the phase separation, the organic layer was washed with water and then concentrated to yield compound (IX) in 75% yield.

Step G. Preparation of Compound (X).

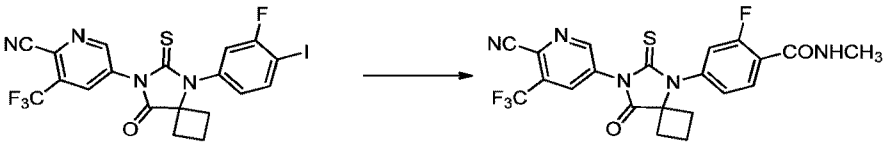



X

A reactor was charged with compound (IX) (0.3 g) and a solution of methylamine in ethanol (10 eq) and stirring begun. The reaction was stirred at ambient temperature. Upon consumption of compound (IX), the reaction was concentrated, re-dissolved in toluene, and washed with aqueous HCl (2M) until all base was neutralized. The toluene phase was then concentrated to give compound (X) (80 %). $^1$H NMR (300 MHz, DMSO) δ 9.22 (d, $J$ = 1.9 Hz, 1H), 8.76 (d, $J$ =1.9 Hz, 1H), 8.50 (d, $J$ =4.5Hz, 1H), 7.84 (t, $J$

=2x8.0Hz, 1H), 7.48 (dd, $J$ =10.5, 1.8Hz, 1H), 7.39 (dd, $J$ =8.2, 1.8Hz, 1H), 4.00 (s, 3H), 2.75 (m, 2H), 2.58 (m, 2H), 2.30 (m, 1H), 1.76 (m, 1H).

Example 2




VII X

Method A. In a 10 mL test tube, compound (VII) (0.3 g, 0.55 mmol), molybdenum hexacarbonyl (0.145 g, 0.55 mmol), norbornadiene (0.05 g, 0.545 mmol), tetrabutylammonium bromide (0.177 g, 0.55 mmol) and DABCO (0.185 g, 1.65 mmol) were charged under nitrogen, followed by 3 mL of diglyme. The mixture was heated with stirring under a nitrogen atmosphere to 140 °C. Methylamine hydrochloride (0.05 g, 0.61 mmol) was added, and the mixture was stirred at 140 °C for 1 h to yield compound (X) (13 %).

Method B. In a 10 mL test tube, compound (VII) (0.3 g, 0.55 mmol), molybdenum hexacarbonyl (0.145 g, 0.55 mmol), norbornadiene (0.05 g, 0.545 mmol), tetrabutylammonium bromide (0.177 g, 0.55 mmol) and DABCO (0.185 g, 1.65 mmol) were charged under nitrogen, followed by 3 mL of butyronitrile. The mixture was heated with stirring under a nitrogen atmosphere to 140 °C. Methylamine hydrochloride (0.05 g, 0.61 mmol) was added in 3 portions over 30 min, and the mixture was stirred at 118 °C for 1 h to yield compound (X) (43 %).

Method C. A 30 mg (0.059 mmol) portion of Pd(t-$Bu_3P)_2$ was placed in a 10 mL Schlenk flask, which was subsequently set under an inert atmosphere (Argon). Then 3 mL of degassed THF was added and the solution stirred for 5 min at ambient temperature. In a second 20 mL Schlenk flask, 0.8 g of compound (VII) (1.464 mmol) was inertized and 4.3 mL degassed THF, 3.7 mL (7.32 mmol, 2M in THF) N-methylamine, and 0.37 mL dicyclohexylmethylamine (1.75 mmol) were added. Both the substrate solution and the catalyst solution were transferred via cannula into the 50 mL autoclave, which was

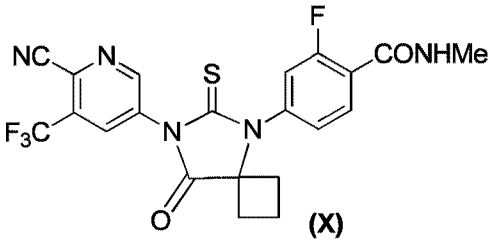
previously set under an inert atmosphere of Argon. The reactor was sealed and purged with Argon, and finally the Argon was replaced by 5 bar CO (three purge cycles). The reaction was stirred and heated to 60 °C for 2 h.

While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations and/or modifications as come within the scope of the following claims and their equivalents.

## CLAIMS

What is claimed is:

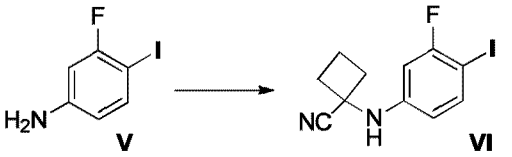
1. A process for the preparation of compound (X):




(X)

comprising:

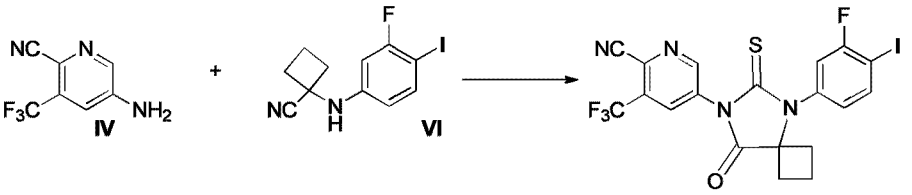
step (1a):




V VI (1a)

reacting compound (V) with cyclobutanone in the presence of sodium cyanide; in acetic acid, or a solvent system comprised of an alcoholic solvent and a protic acid; at a temperature of about 0 °C to about 20 °C; to yield the compound (VI);

step (1b):



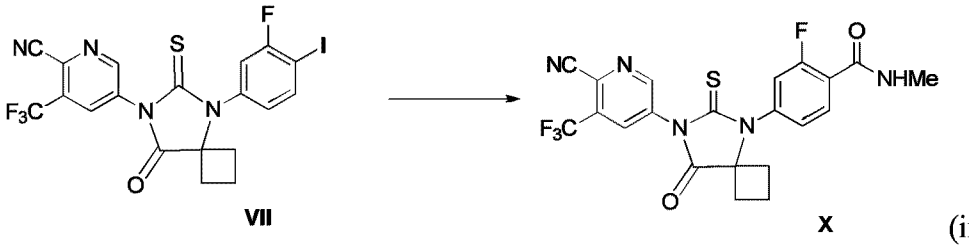

IV VI VII (1b)

reacting compound (IV) and compound (VI) in the presence of a thiocarbonylating agent; in an organic solvent; at a temperature of about 0 °C to about 100 °C; to yield the compound (VII); and

step (ix):



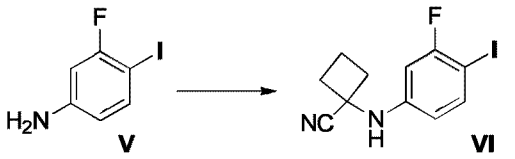
Date Reçue/Date Received 2023-03-01




(ix)

converting compound (VII) to compound (X).

2. The process of claim 1, wherein step (1a) comprises




(1a)

reacting compound (V) with cyclobutanone in the presence of at least one molar equivalent of sodium cyanide; in acetic acid, or a solvent system comprised of at least one molar equivalent of acetic acid or hydrochloric acid and a $C_{1-4}$alcoholic solvent selected from the group consisting of methanol, ethanol, propanol, and butanol; at a temperature of about 0 °C to about 20 °C; to yield the compound (VI).

3. The process of claim 2, wherein the solvent system is acetic acid.

4. The process of claim 2, wherein the solvent system is 90% acetic acid and 10% ethanol.

5. The process of claim 1, wherein:

the thiocarbonylating agent is 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one, 1,1'-thiocarbonyl diimidazole, phenylthionochloroformate, beta-naphthyl thionochloroformate, 1,1'-thiocarbonylbis(pyridin-2(1*H*)-one), *O,O*-di(pyridin-2-yl)carbonothioate, 1,1'-thiocarbonylbis (1*H*-benzotriazole), or thiophosgene; and the organic solvent is THF, 2-methyl-THF, acetonitrile, DMA, toluene, DMF, NMP, or DMSO.

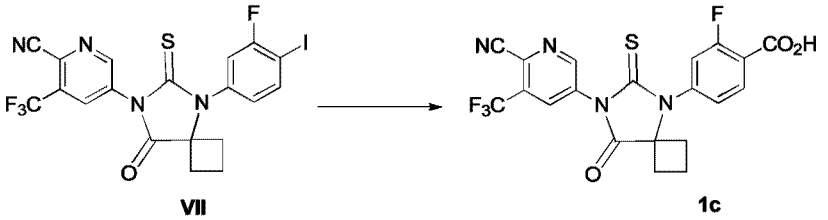
6. The process of claim 5, wherein the thiocarbonylating agent is 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one.

7. The process of claim 6, wherein the organic solvent is DMA.



Date Reçue/Date Received 2023-03-01

8. The process of claim 1, wherein step (1x) comprises the conversion of compound (VII) to compound (X) via the carboxylic acid compound (1c),




(1c)

wherein the carboxylic acid compound (1c) is formed by reacting compound (VII) with an organomagnesium halide; in the presence or absence of a lithium halide; followed by the addition of carbon dioxide gas; in an aprotic organic solvent; at a temperature of about 0 °C; to yield the carboxylic acid compound (1c).

9. The process of claim 8, comprising reacting compound (VII) with an organomagnesium halide selected from the group consisting of a $C_{1-8}$alkylmagnesium halide and a $C_{5-7}$cycloalkylmagnesium halide; in the presence or absence of a lithium halide selected from the group consisting of lithium chloride, lithium bromide, and lithium iodide; followed by the addition of carbon dioxide gas; in an aprotic organic solvent selected from the group consisting of THF, 2-MeTHF, MTBE, CPME, and toluene; at a temperature of about 0 °C; to yield the carboxylic acid compound (1c).

10. The process of claim 9, wherein the $C_{1-8}$alkylmagnesium halide is a $C_{1-8}$alkylmagnesium chloride or $C_{1-8}$alkylmagnesium bromide.

11. The process of claim 10, wherein the $C_{1-8}$alkylmagnesium halide is selected from the group consisting of isopropylmagnesium chloride, *sec*-butylmagnesium chloride, *n*-pentylmagnesium chloride, hexylmagnesium chloride, ethylmagnesium chloride, ethylmagnesium bromide, *n*-butylmagnesium chloride, and isopropylmagnesium chloride.

12. The process of claim 11, wherein the organomagnesium halide is *n*-pentylmagnesium chloride and the aprotic solvent is THF.

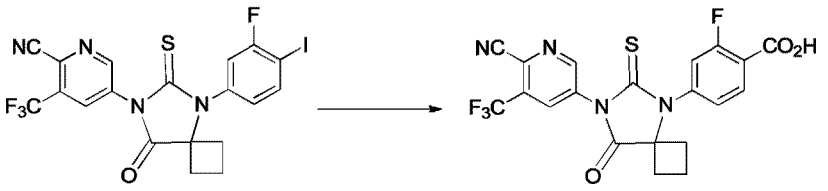
13. The process of claim 9, wherein the $C_{5-7}$cycloalkylmagnesium halide is a $C_{5-7}$cycloalkylmagnesium chloride or $C_{5-7}$cycloalkylmagnesium bromide.



Date Reçue/Date Received 2023-03-01

14. The process of claim 13, wherein the $C_{5-7}$cycloalkylmagnesium halide is cyclohexylmagnesium chloride.

15. The process of claim 1, wherein step (1x) comprises the conversion of compound (VII) to compound (X) via the carboxylic acid compound (1c),

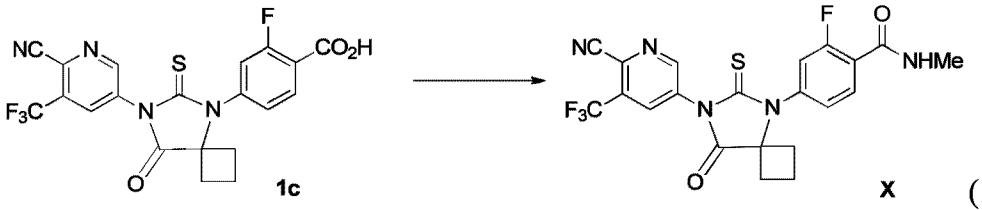



(1c)

wherein the carboxylic acid compound (1c) is formed by reacting compound (VII) under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; with an organic base; in the presence of water; in an organic solvent; at a temperature of about 0 °C to about 100 °C; to yield the carboxylic acid compound (1c).

16. The process of claim 15, wherein the palladium catalyst is comprised of a phosphorus ligand that is dppf and a palladium metal compound that is palladium acetate.

17. The process of claim 15, wherein step (1x) comprises the conversion of the carboxylic acid compound (1c) to compound (X), by




(1d)

reacting the carboxylic acid compound (1c) with a coupling agent; in an aprotic or protic solvent; at about room temperature; followed by the addition of methylamine; to yield the compound (X).

18. The process of claim 17, wherein the coupling agent is CDI and the aprotic or protic solvent is THF or toluene.

19. The process of claim 18, wherein methylamine is added as a THF solution.

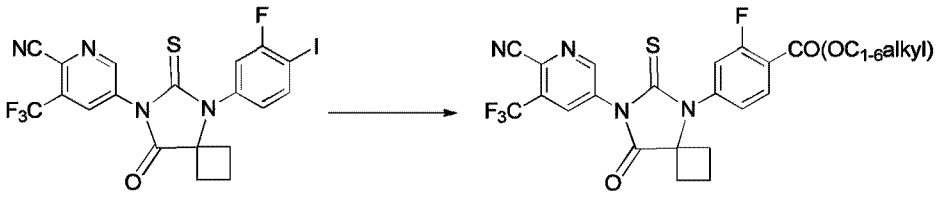


Date Reçue/Date Received 2023-03-01

20. The process of claim 18, wherein methylamine is added in its gaseous state.

21. The process of claim 18, wherein methylamine is added as its methyl ammonium salt.

22. The process of claim 1, wherein step (1x) comprises the conversion of compound (VII) to compound (X) via an ester compound (1e),




(1e)

wherein the ester compound (1e) is formed by reacting compound (VII) with an organomagnesium halide; in the presence or absence of a lithium halide; in an aprotic organic solvent; at a temperature of about -50 °C to about room temperature; followed by the addition of an $C_{1-6}$alkyl chloroformate or $C_{1-6}$alkyl cyanoformate; to yield the ester compound (1e).

23. The process of claim 22, wherein the organomagnesium halide is a $C_{1-8}$alkylmagnesium halide or a $C_{5-7}$cycloalkylmagnesium halide; the lithium halide is lithium chloride, lithium bromide, and lithium iodide; and the aprotic organic solvent is THF, 2-MeTHF, or toluene.

24. The process of claim 23, wherein the $C_{1-8}$alkylmagnesium halide is a $C_{1-8}$alkylmagnesium chloride or $C_{1-8}$alkylmagnesium bromide.

25. The process of claim 24, wherein the $C_{1-8}$alkylmagnesium halide is selected from the group consisting of *sec*-butylmagnesium chloride, cyclohexylmagnesium chloride, *n*-pentylmagnesium chloride, hexylmagnesium chloride, ethylmagnesium chloride, ethylmagnesium bromide, *n*-butylmagnesium chloride, and isopropylmagnesium chloride.

26. The process of claim 25, wherein the $C_{1-8}$alkylmagnesium halide is *n*-pentylmagnesium chloride and the aprotic organic solvent is THF or 2-MeTHF.

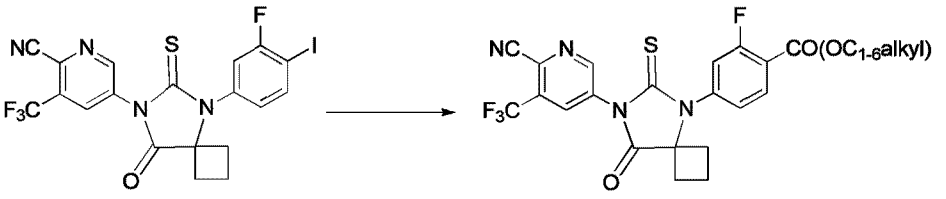


Date Reçue/Date Received 2023-03-01

27. The process of claim 23, wherein the $C_{5-7}$cycloalkylmagnesium halide is a $C_{5-7}$cycloalkylmagnesium chloride or $C_{5-7}$cycloalkylmagnesium bromide.

28. The process of claim 27, wherein the $C_{5-7}$cycloalkylmagnesium halide is cyclohexylmagnesium chloride.

29. The process of claim 1, wherein step (1x) comprises the conversion of compound (VII) to compound (X) via the ester compound (1e),



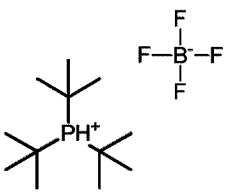

(1e)

wherein the ester compound (1e) is formed by reacting compound (VII) under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; with a base; in a $C_{1-6}$alcoholic solvent; at a temperature of about room temperature to about 100 °C; to yield the ester compound (1e).

30. The process of claim 29, wherein the base is DIPEA, $K_2CO_3$, $K_3PO_4$, or $Cy_2NMe$ and the $C_{1-4}$alcoholic solvent is methanol, ethanol, isopropyl alcohol, *n*-butyl alcohol, or *t*-butyl alcohol.

31. The process of claim 30, wherein the palladium catalyst is $Pd(P(tBu)_3)_2$ and the base is 1.2 equivalents of DIPEA.

32. The process of claim 30, wherein the palladium catalyst is comprised of a phosphorus ligand that is L10and a palladium metal compound that is $[Pd(OMs)(BA)]_2$; in the presence of $Cy_2NMe$:




L10.

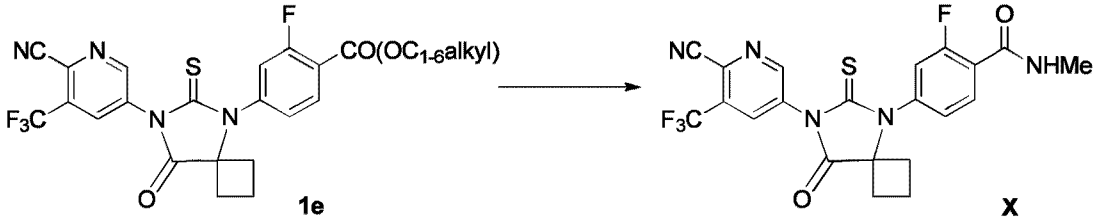


Date Reçue/Date Received 2023-03-01

33. The process of claim 30, wherein the palladium catalyst is comprised of a phosphorus ligand that is dppf and a palladium metal compound that is palladium acetate; in the presence of DIPEA.

34. The process of claim 30 wherein the $C_{1-4}$alcoholic solvent is methanol.

35. The process of claim 1, wherein step (1x) comprises the conversion of compound (VII) to compound (X) via the ester compound (1e), by




treating the ester compound (1e) with methylamine; in a protic or aprotic solvent; at a temperature of about 0 °C to about 60 °C; to yield the compound (X).

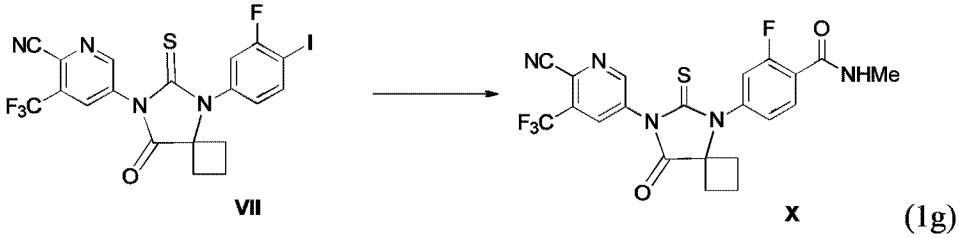
36. The process of claim 35, wherein the protic or aprotic solvent is selected from the group consisting of THF, DMF, DMA, and ethanol, or a mixture thereof.

37. The process of claim 36, wherein the methylamine is added as a THF solution.

38. The process of claim 36, wherein the methylamine is added as a MeOH solution.

39. The process of claim 36, wherein the methylamine is added in its gaseous state.

40. The process of claim 1, wherein step (1x) comprises the conversion of compound (VII) directly to compound (X), by




(1g)

reacting compound (VII) in the presence of molybdenum hexacarbonyl; optionally in the presence of one or more reagents selected from the group consisting of norbornadiene, tetrabutylammonium bromide, and a base selected from triethylamine or



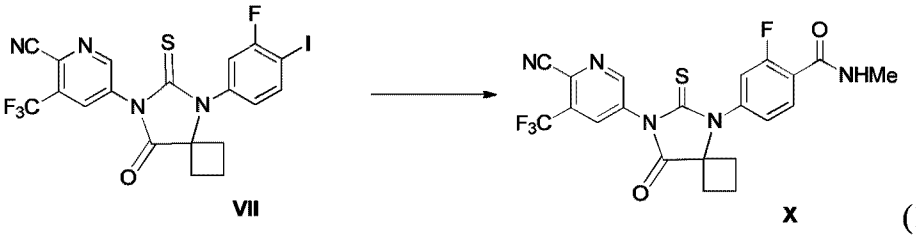
Date Reçue/Date Received 2023-03-01

DABCO; in an organic solvent selected from the group consisting of diglyme, dioxane, butyronitrile, and propionitrile; followed by the addition of methylamine; at a temperature of about 60 °C to about 140 °C; to yield the compound (X).

41. The process as in claim 40, wherein norbornadiene, tetrabutylammonium bromide, and DABCO are present.

42. The process as in claim 41, wherein the organic solvent is butyronitrile or diglyme.

43. The process as in claim 1, wherein step (1x) comprises the conversion of compound (VII) directly to compound (X),




VII X (1g)

by reacting compound (VII) under a carbon monoxide atmosphere; in the presence of a palladium catalyst; in the presence of one or more phosphorus ligands; in the presence of a base; in the presence of methylamine; in an organic solvent; at a temperature of about room temperature to about 100 °C; to yield the compound (X).

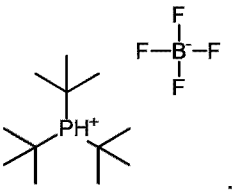
44. The process as in claim 43, wherein the base is DIPEA, $K_2CO_3$, $K_3PO_4$, $Cy_2NMe$, or excess methylamine; in the presence of methylamine; in an organic solvent; at a temperature of about room temperature to about 100 °C; to yield the compound (X).

45. The process as in claim 44, wherein the palladium catalyst is $Pd(P(tBu_3))_2$and the base is DIPEA.

46. The process as in claim 44, wherein the palladium catalyst is comprised of the phosphorus ligand that is L10, and the palladium metal compound that is $Pd(OAc)_2$; in the presence of $Cy_2NMe$:



Date Reçue/Date Received 2023-03-01



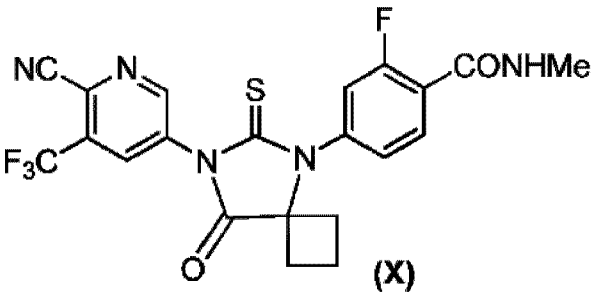
47. The process as in claim 44, wherein methylamine is added as a THF solution.

48. The process as in claim 44, wherein methylamine is added as a MeOH solution.

49. The process as in claim 44, wherein methylamine is added in its gaseous state.

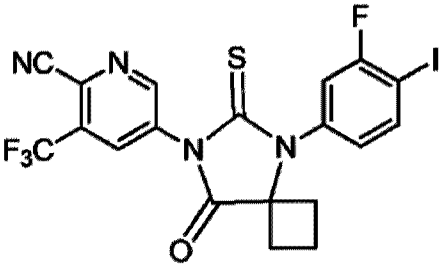
50. The process as in claim 44, wherein methylamine is added as its methyl ammonium hydrochloride salt.

51. A process for preparing compound (X):



(X)

comprising converting compound (VII) to compound (X):



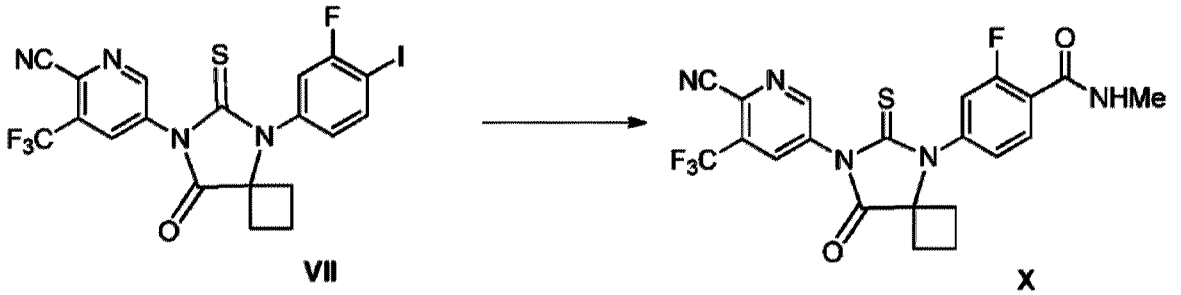
VII

by (i) reacting compound (VII) with molybdenum hexacarbonyl in an organic solvent, optionally in presence of one or more of norbornadiene, tetrabutylammonium bromide, triethylamine or DABCO, followed by the addition of methylamine to yield the compound (X); or



Date Reçue/Date Received 2023-03-01

(ii) reacting compound (VII) with carbon monoxide in a reaction mixture comprising a palladium catalyst, one or more phosphorus ligands, methyl amine, and one or more of DIPEA, potassium carbonate, potassium phosphate, or $Cy_2NMe$, or excess methyl amine to yield the compound (X):



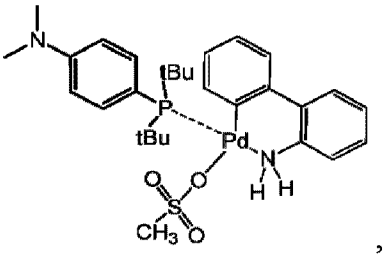

52. The process of claim 51, wherein the solvent in (i) is diglyme, dioxane, butyronitrile, or propionitrile.

53. The process of claim 52, wherein compound (VII) is reacted in the presence of norbornadiene, tetrabutylammonium bromide, and DABCO.

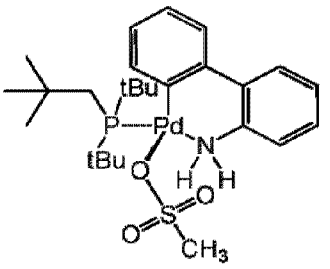
54. The process of claim 51, wherein the palladium catalyst is added to the reaction mixture as a pre-formed palladium catalyst or is generated *in situ*.

55. The process of claim 51, wherein the palladium catalyst is:

Pd(OMs)([1,1'-biphenyl]-2-amine)(P(t-$Bu_2$-4-*N,N*-dimethylaniline))

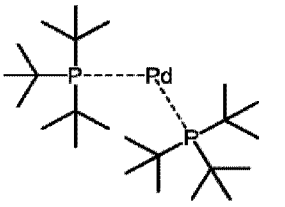


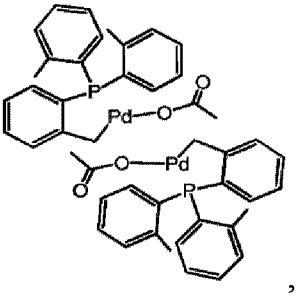

Pd(OMs)([1,1'-biphenyl]-2-amine)(P(t-$Bu_2$-neopentyl)

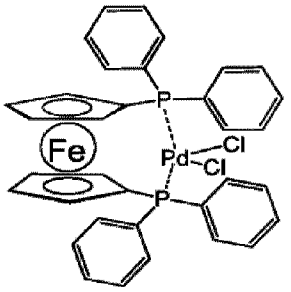




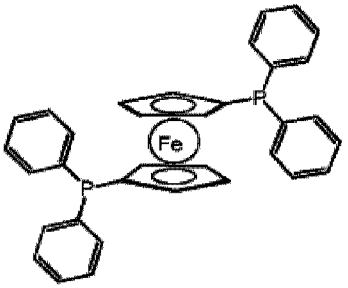
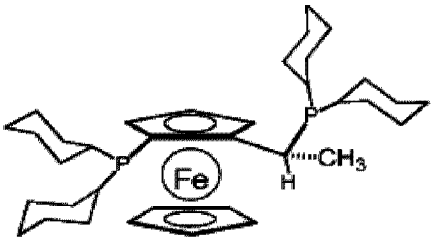

Date Reçue/Date Received 2023-03-01

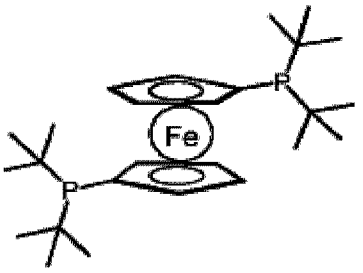
$Pd(P(t\text{-}Bu)_3)_2$  ,

$Pd(OAc)(P(o\text{-}Tol)_3)_2$  , or

$PdCl_2(dppf)$  .

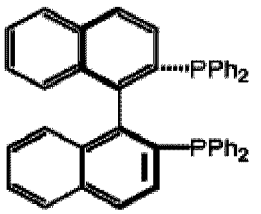
56. The process of claim 53, wherein the palladium catalyst is generated *in situ* by the reaction of a palladium catalyst or palladium metal compound with one or more of:

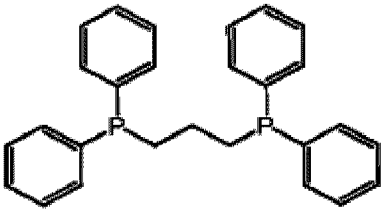
 ,  ,

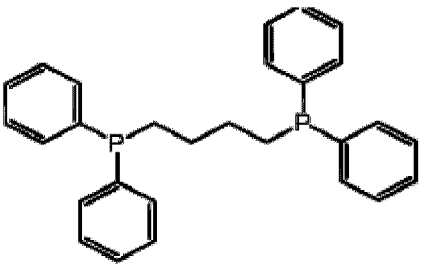
 ,

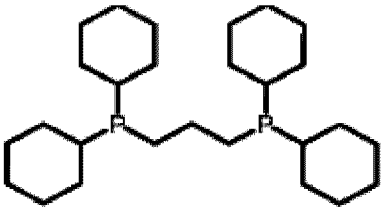


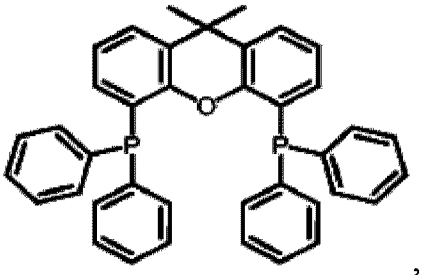
Date Reçue/Date Received 2023-03-01

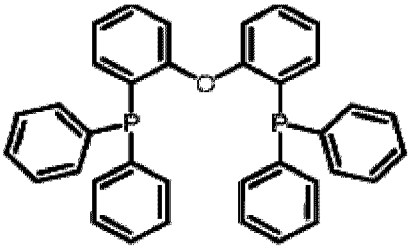


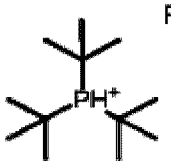
,


,


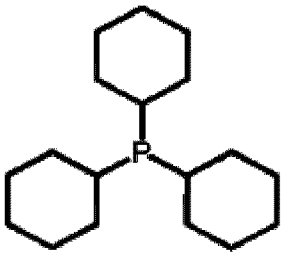
,


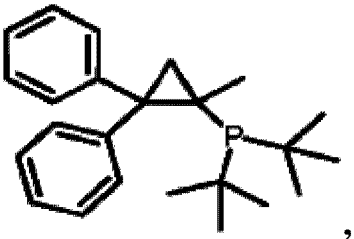
,


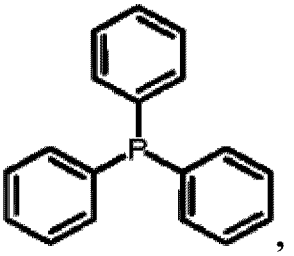
,


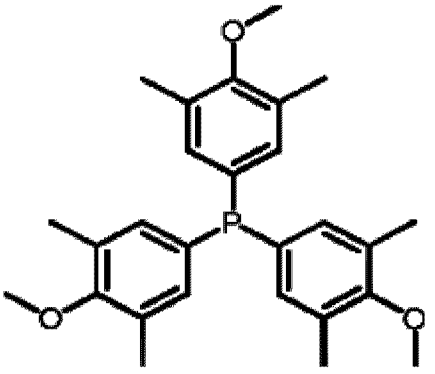
,


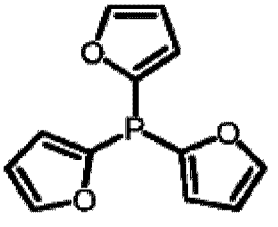
,

,


,


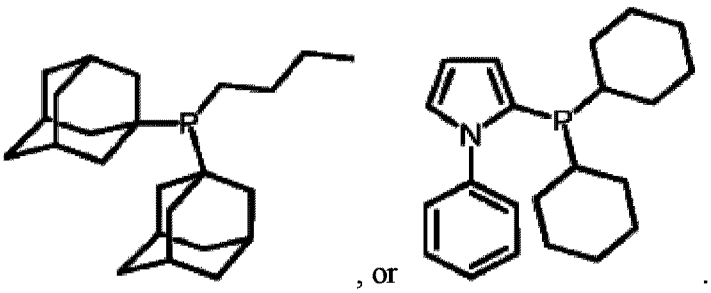
,


,


,

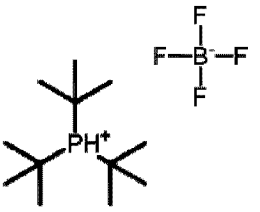


Date Reçue/Date Received 2023-03-01



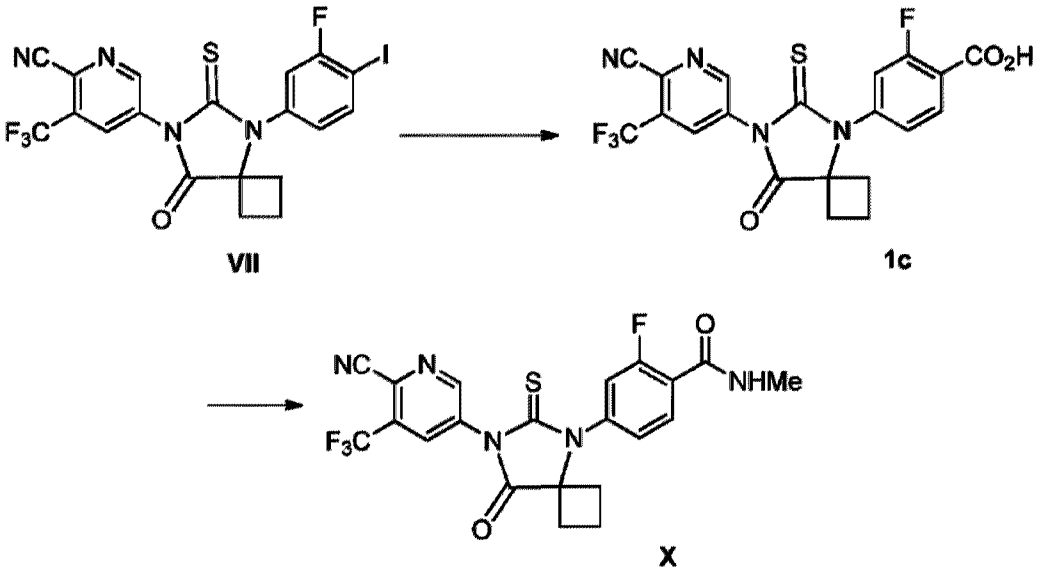
, or .

57. The process of claim 53, wherein the palladium catalyst is $Pd(P(t\text{-}Bu)_3)_2$ and is generated *in situ* by the reaction of $Pd(OAc)_2$ with L10 in the presence of $Cy_2NMe$:



L10 .

58. The process of claim 51, wherein the process comprises converting compound (VII) to carboxylic acid compound (1c), and then converting carboxylic acid compound (1c) to compound (X):



VII 1c X .



Date Reçue/Date Received 2023-03-01

59. The process of claim 58, comprising reacting compound (VII) with an organomagnesium halide in an aprotic solvent, optionally in the presence of a lithium halide, followed by reacting the resulting mixture with carbon dioxide to yield the carboxylic acid compound (1c).

60. The process of claim 59, wherein the organomagnesium halide is a $C_{1-8}$alkylmagnesium halide or a $C_{5-7}$cycloalkylmagnesium halide; wherein the lithium halide is lithium chloride, lithium bromide, or lithium iodide; and the aprotic organic solvent is tetrahydrofuran, 2-methyl-tetrahydrofuran, methyl *tert*-butylether (MTBE), cyclopentyl methylether (CPME), or toluene.

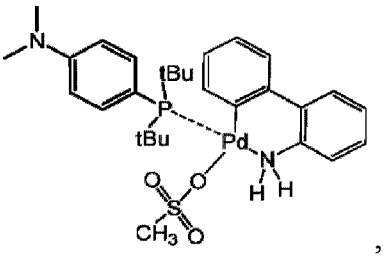
61. The process of claim 60, wherein the $C_{1-8}$alkylmagnesium halide is a $C_{1-8}$alkylmagnesium chloride or $C_{1-8}$alkylmagnesium bromide and the $C_{5-7}$cycloalkylmagnesium halide is a $C_{5-7}$cycloalkylmagnesium chloride or a $C_{5-7}$cycloalkylmagnesium bromide.

62. The process of claim 60, wherein the $C_{1-8}$alkylmagnesium halide is isopropylmagnesium chloride, sec-butylmagnesium chloride, n-pentylmagnesium chloride, hexylmagnesium chloride, ethylmagnesium chloride, ethylmagnesium bromide, n-butylmagnesium chloride, or isopropylmagnesium chloride and the $C_{5-7}$cycloalkylmagnesium halide is cyclohexylmagnesium chloride.

63. The process of claim 58, comprising reacting compound (VII) with carbon monoxide in a mixture comprising a palladium catalyst, with an organic base in alcoholic solvent comprising water to yield the carboxylic acid compound (1c).

64. The process of claim 63, wherein the palladium catalyst is:

Pd(OMs)([1,1'-biphenyl]-2-amine)(P(t-$Bu_2$-4-*N,N*-dimethylaniline))

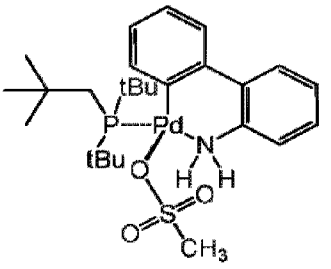



,



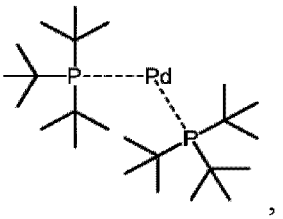
Date Reçue/Date Received 2023-03-01

Pd(OMs)([1,1'-biphenyl]-2-amine)(P(t-Bu$_2$-neopentyl)



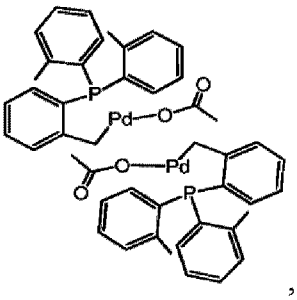
,

Pd(P(t-Bu)$_3$)



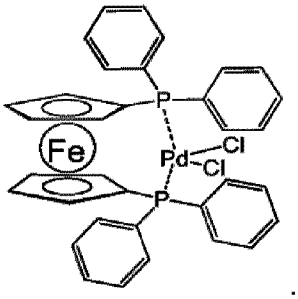
,

Pd(OAc)(P(o-Tol)$_3$)$_2$,



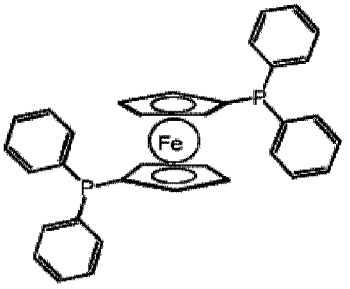
, or

$PdCl_2$(dppf)

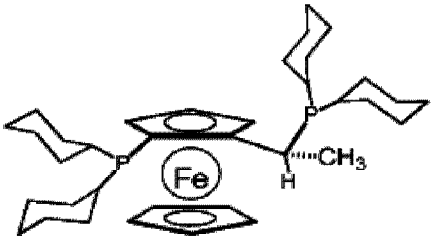


.

65. The process of claim 63, wherein the palladium catalyst is generated *in situ* by the reaction of a palladium catalyst or palladium metal compound with one or more of:



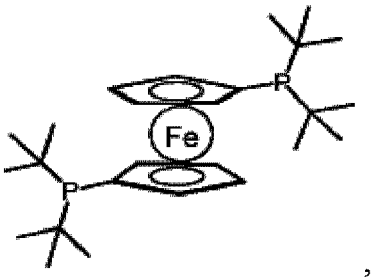
,

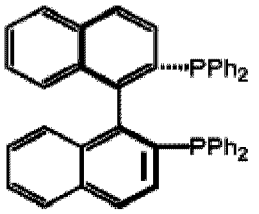


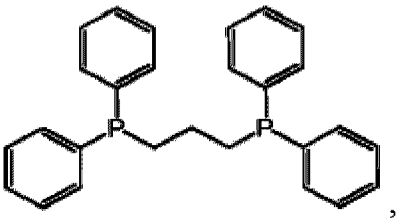
,

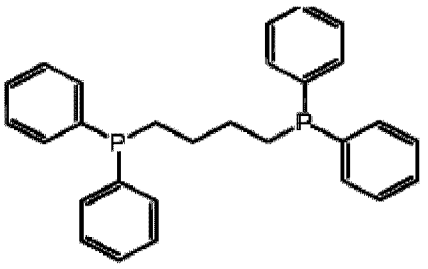


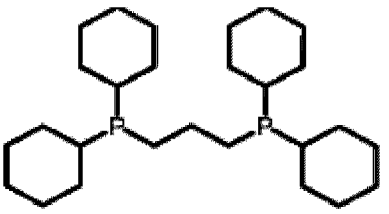
Date Reçue/Date Received 2023-03-01

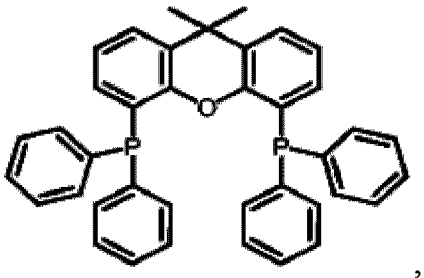


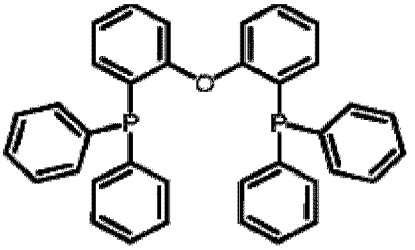
,


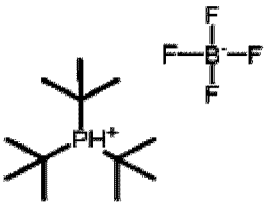
,


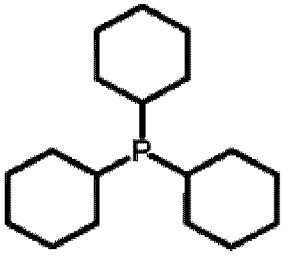
,


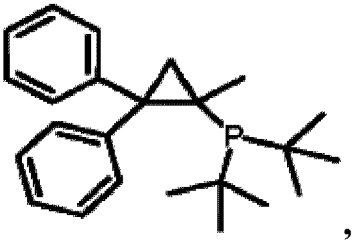
,


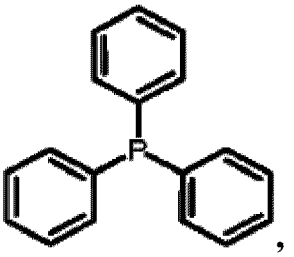
,


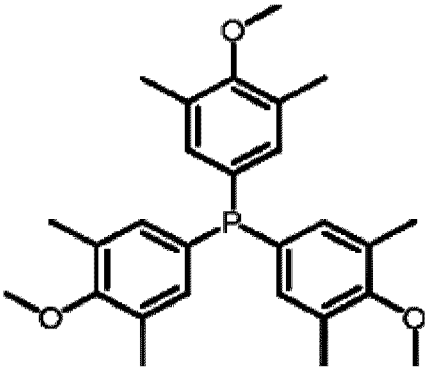
,


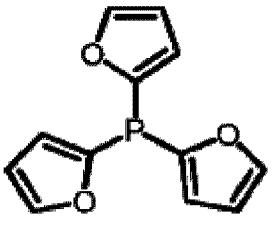
,


,


,


,


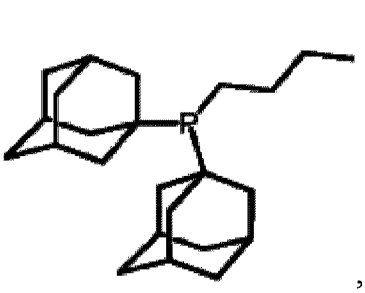
,


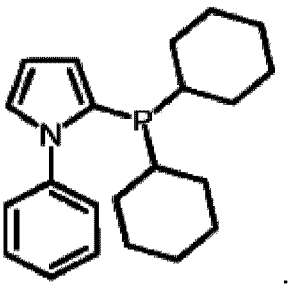
,


,



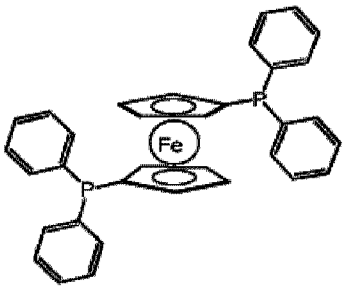
Date Reçue/Date Received 2023-03-01




, or 


.

66. The process of claim 63, wherein the palladium catalyst is generated *in situ* by the reaction of palladium acetate and dppf:




(dppf).

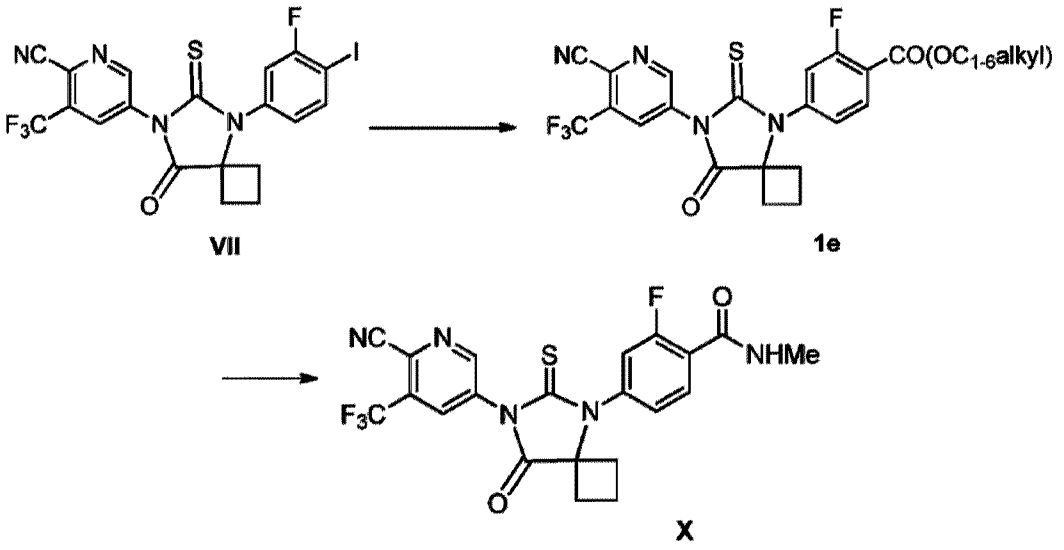
67. The process of claim 58, wherein the carboxylic acid compound (1c) is converted to compound (X) by reacting the carboxylic acid compound (1c) with methylamine in a solvent, in the presence of a coupling agent, to yield compound (X).

68. The method of claim 67, wherein the coupling agent is 1,1'-carbonyldiimidazole (CDI) and the solvent is tetrahydrofuran or toluene.

69. The process of claim 51, wherein the process comprises converting compound (VII) to compound (1e), and then converting compound (1e) to compound (X):



Date Reçue/Date Received 2023-03-01




70. The process of claim 69, comprising reacting compound (VII) with an organomagnesium halide in an aprotic solvent, optionally in the presence of a lithium halide, followed by reacting the resulting mixture with a $C_{1-6}$alkyl chloroformate or a $C_{1-6}$alkyl cyanoformate to yield the compound (1e).

71. The process of claim 70, wherein the organomagnesium halide is a $C_{1-8}$alkylmagnesium halide or a $C_{5-7}$cycloalkylmagnesium halide; wherein the lithium halide is lithium chloride, lithium bromide, or lithium iodide; and the aprotic organic solvent is tetrahydrofuran, 2-methyl-tetrahydrofuran, or toluene.

72. The process of claim 71, wherein the $C_{1-8}$alkylmagnesium halide is a $C_{1-8}$alkylmagnesium chloride or $C_{1-8}$alkylmagnesium bromide and the $C_{5-7}$cycloalkylmagnesium halide is a $C_{5-7}$cycloalkylmagnesium chloride or a $C_{5-7}$cycloalkylmagnesium bromide.

73. The process of claim 71, wherein the $C_{1-8}$alkylmagnesium halide is isopropylmagnesium chloride, sec-butylmagnesium chloride, n-pentylmagnesium chloride, hexylmagnesium chloride, ethylmagnesium chloride, ethylmagnesium bromide, n-butylmagnesium chloride, or isopropylmagnesium chloride and the $C_{5-7}$cycloalkylmagnesium halide is cyclohexylmagnesium chloride.

74. The process of claim 71, wherein the alkylmagnesium halide is n-pentylmagnesium chloride, the aprotic solvent is tetrahydrofuran or 2-methyl-tetrahydrofuran, the lithium halide is



Date Reçue/Date Received 2023-03-01

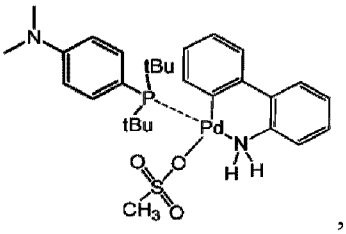
absent, and the reaction is conducted at a temperature in a range of from about -50°C to about 22°C.

75. The process of claim 69, comprising reacting the compound (VII) with carbon monoxide in a $C_{1-4}$alcoholic solvent comprising a base and a palladium catalyst to yield the compound (1e).

76. The process of claim 75, wherein the $C_{1-4}$alcoholic solvent is methanol, ethanol, isopropanol, n-butyl alcohol, or *t*-butyl alcohol and the base is DIPEA, $K_2CO_3$, $K_3PO_4$, or $Cy_2NMe$.

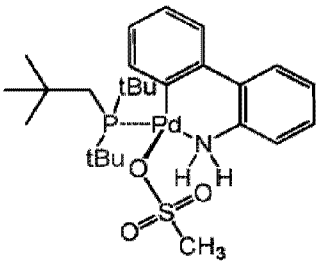
77. The process of claim 75, wherein the palladium catalyst is:

Pd(OMs)([1,1'-biphenyl]-2-amine)(P(t-$Bu_2$-4-*N,N*-dimethylaniline))



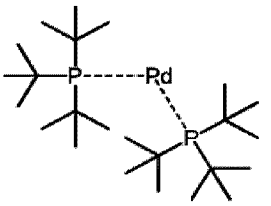
,

Pd(OMs)([1,1'-biphenyl]-2-amine)(P(t-$Bu_2$-neopentyl)



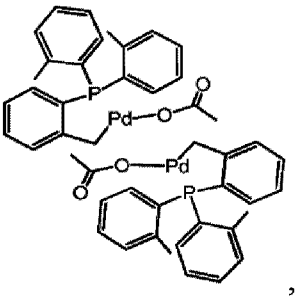
,

Pd(P(t-Bu)$_3$)



,

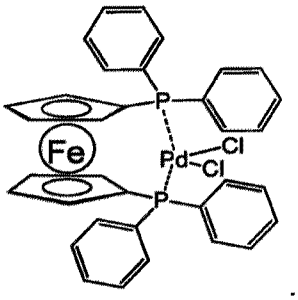
Pd(OAc)(P(o-Tol)$_3$)$_2$,



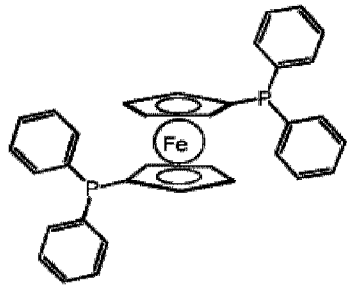
, or

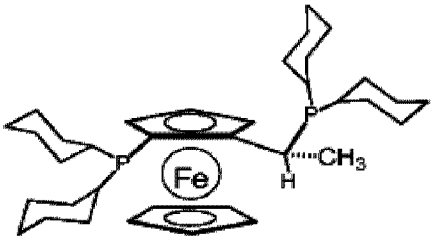


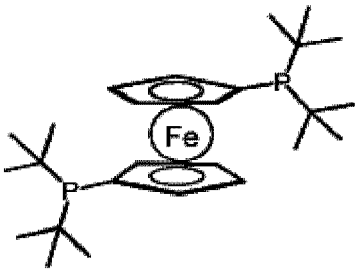
Date Reçue/Date Received 2023-03-01

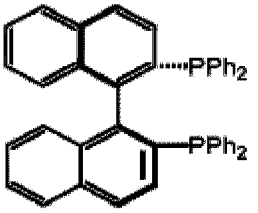
$PdCl_2(dppf)$ 

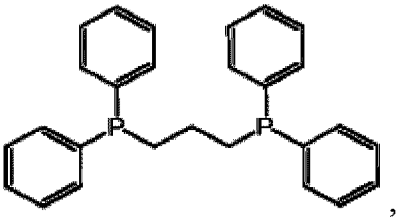
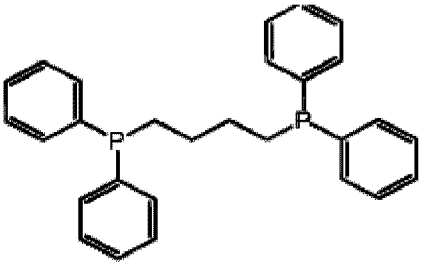
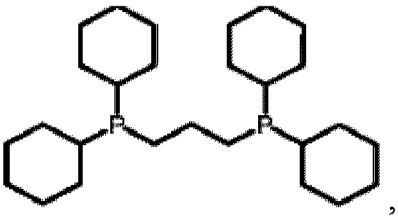
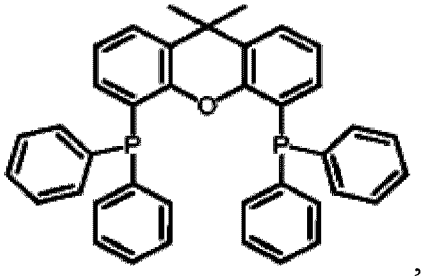
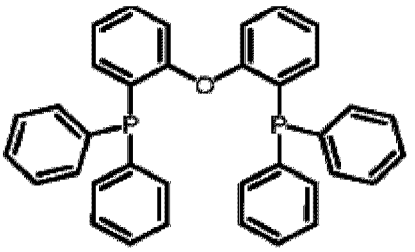
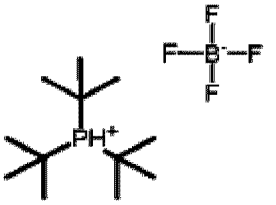

78. The process of claim 75, wherein the palladium catalyst is generated *in situ* by the reaction of a palladium catalyst or palladium metal compound with one or more of:



,


,


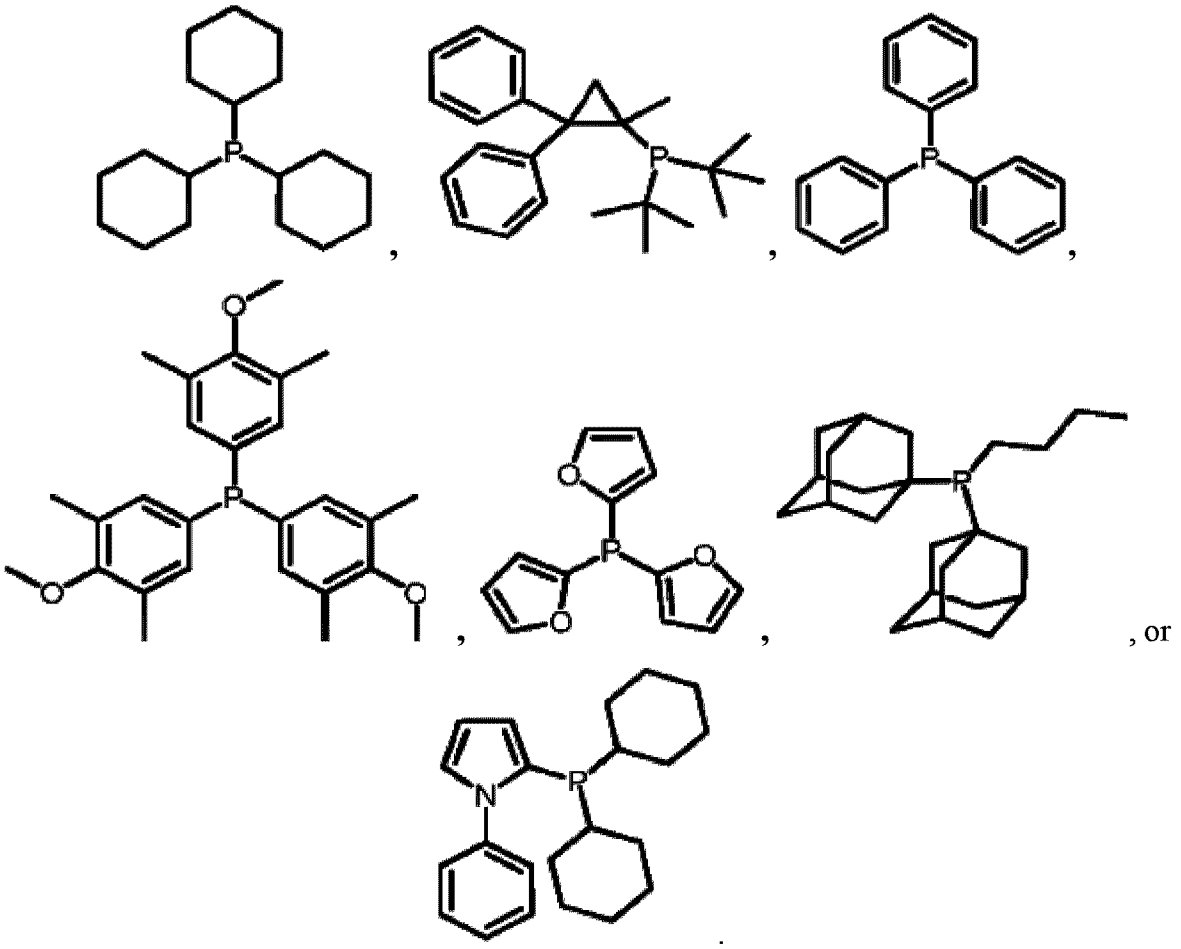
,


,

,

,

,

,

,


,

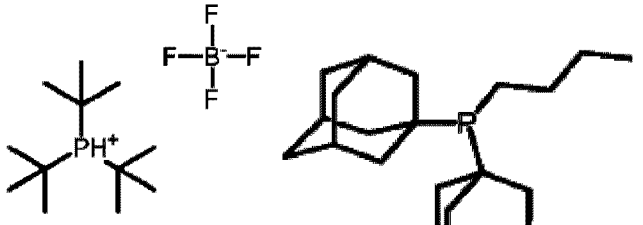


Date Reçue/Date Received 2023-03-01



79. The process of claim 75, wherein the palladium catalyst is $Pd(P(t\text{-}Bu)_3)_2$ or $PdCl_2(dppf)$.

80. The process of claim 75, wherein the palladium catalyst is generated *in situ* by the reaction of $Pd(OAc)_2$ with L10 or L16 in the presence of $Cy_2NMe$:



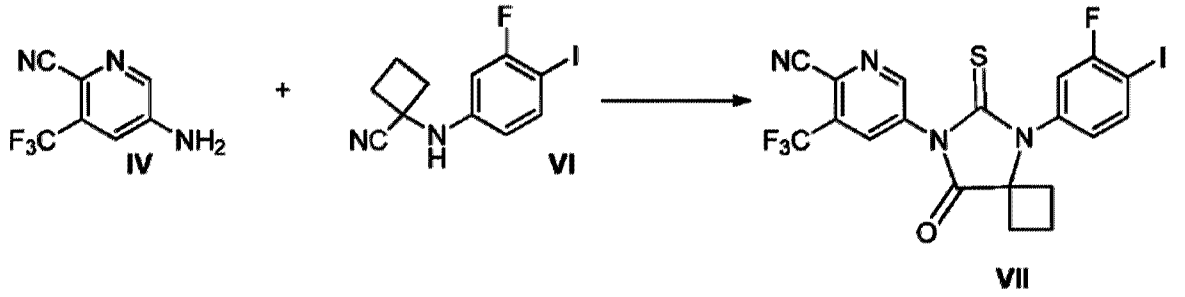
L10 (L16).

81. The process of claim 75, wherein the palladium catalyst is generated *in situ* by the reaction of palladium acetate and dppf.



Date Reçue/Date Received 2023-03-01

82. The process of claim 51, further comprising reacting compound (IV) with compound (VI) to form compound (VII)

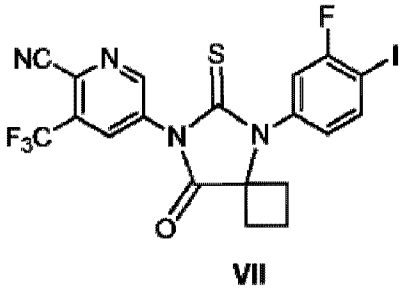



83. The process of claim 82, comprising reacting compound (IV) and compound (VI) in the presence of a thiocarbonylating agent that is 1-(2-oxopyridine-l-carbothioyl)pyridin-2-one, 1,1'-thiocarbonyl diimidazole, phenylthionochloroformate, beta-naphthyl thionochloroformate, 1,1'-thiocarbonylbis(pyridin-2(1*H*)-one), *O,O*-di(pyridin-2-yl)carbonothioate, 1,1'-thiocarbonylbis(1*H*-benzotriazole), or thiophosgene; in an organic solvent that is selected from the group consisting of THF, 2-methyl-THF, acetonitrile, DMA, toluene, DMF, NMP, and DMSO; at a temperature of about 0 °C to about 100 °C; to yield the compound (VII).

84. The process of claim 83, wherein the thiocarbonylating agent is 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one.

85. The process of claim 83, wherein the organic solvent is DMA.

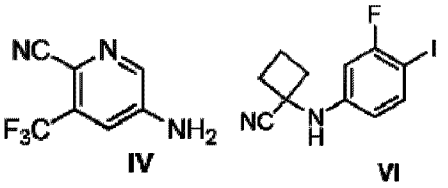
86. A process for preparing compound (VII):




reacting compound (IV) and compound (VI) in the presence of a thiocarbonylating agent; in an organic solvent; to yield the compound (VII):



Date Reçue/Date Received 2023-03-01




87. The process of claim 86, wherein the thiocarbonylating agent is 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one, 1,1'-thiocarbonyl diimidazole, phenylthionochloroformate, beta-naphthyl thionochloroformate, 1,1'-thiocarbonylbis(pyridin-2(1H)-one), O,O-di(pyridin-2-yl)carbonothioate, 1,1'-thiocarbonylbis(1H-benzotriazole), or thiophosgene.

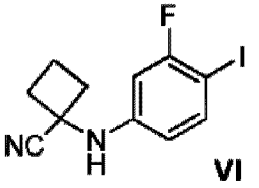
88. The process of claim 86, wherein the organic solvent comprises THF, 2-methyl-THF, acetonitrile, DMA, toluene, DMF, NMP, and DMSO.

89. The process of claim 86, wherein the reacting is done at a temperature in a range of from about 0 °C to about 100 °C.

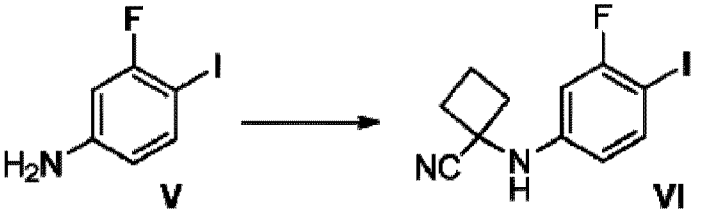
90. The process of any one of claims 86 to 89, wherein the thiocarbonylating agent is 1-(2-oxopyridine-1-carbothioyl)pyridin-2-one.

91. The process of any one of claims 86 to 89, wherein the organic solvent is DMA.

92. A compound of structure (VI):




93. A process for preparing the compound (VI) of claim 92, the process comprising:

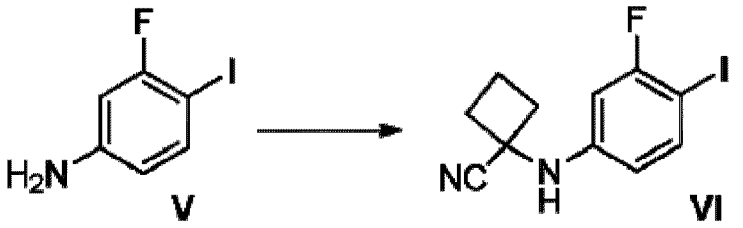





Date Reçue/Date Received 2023-03-01

reacting compound (V) with cyclobutanone in the presence of sodium cyanide: in acetic acid, or a solvent system comprised of an alcoholic solvent and a protic acid; at a temperature of about 0 °C to about 20 °C; to yield the compound (VI).

94. The process of claim 93, comprising:

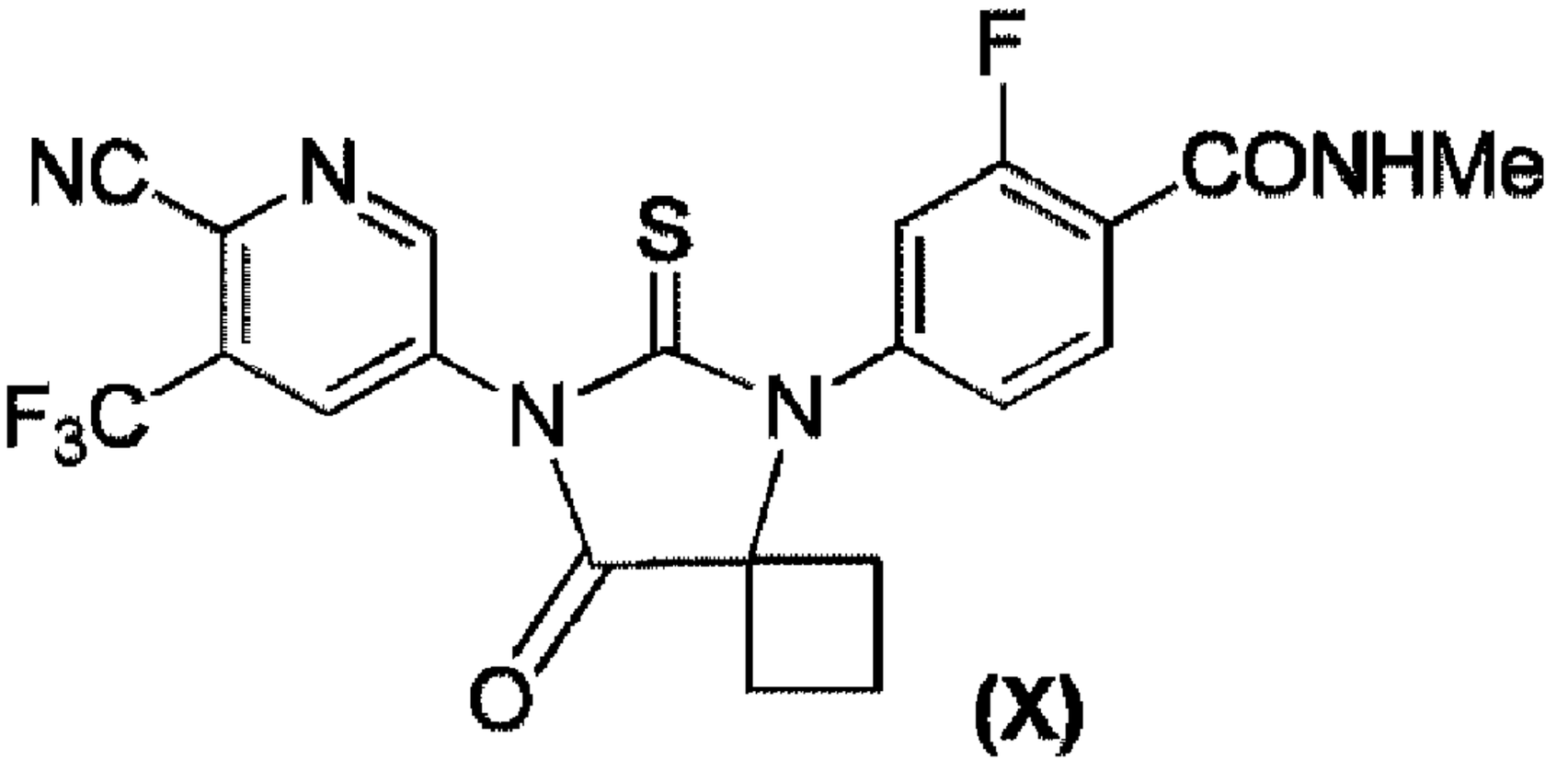



reacting compound (V) with cyclobutanone in the presence of at least one molar equivalent of sodium cyanide; in acetic acid, or a solvent system comprised of at least one molar equivalent of acetic acid or hydrochloric acid and a $C_{1-4}$ alcoholic solvent; at a temperature of about 0 °C to about 20 °C; to yield the compound (VI).

95. The process of claim 93 or 94, wherein the solvent system is acetic acid.



Date Reçue/Date Received 2023-03-01




(X)