PROCESSES AND COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application 62/804,391 filed on February 12, 2019. The disclosure of this prior application is considered part of the disclosure of this application and is hereby incorporated by reference it its entirety.

FIELD OF THE INVENTION

[0002] Useful processes of preparation and intermediates useful for the preparation of Compound 1, a selective estrogen receptor alpha (ERα) modulator/degrader (SERM/SERD), having utility for the treatment of ER+ cancers including breast cancer are described.

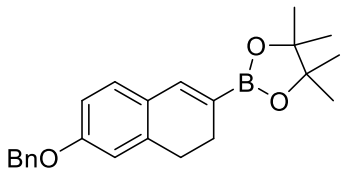
BACKGROUND

[0003] Breast cancer is the second leading cause of cancer-related death in women, with an estimated 246,660 newly diagnosed cases and 40,450 deaths in the United States alone in 2016. Breast cancer is a heterogeneous disease divided into three subtypes based on expression of three receptors: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her2). Overexpression of ERs is found in many breast cancer patients. ER-positive (ER+) breast cancers comprise two-thirds of all breast cancers. Other than breast cancer, estrogen and ERs are associated with, for example, ovarian cancer, colon cancer, prostate cancer and endometrial cancer.

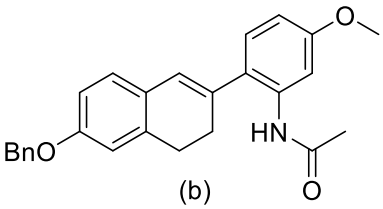
[0004] Compound 1 has demonstrated promising mixed activity as a selective estrogen receptor alpha (ERα) modulator/degrader (SERM/SERD) against ER+ breast cancer, acting as a SERM at low doses and a SERD at high doses. In response to the growing demand for Compound 1, more efficient syntheses are required to provide increased quantities of Compound 1 to be used in additional clinical studies and potential future commercial use.

SUMMARY

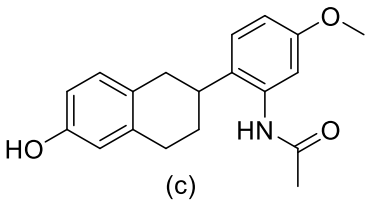
[0004a] In one aspect of the present disclosure, there is provided a compound selected from: ~~(a) (g)~~



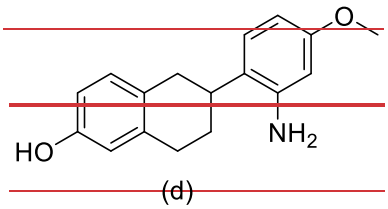
(a)



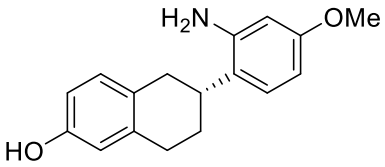
(b)



(c)

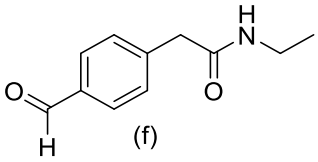


(d)

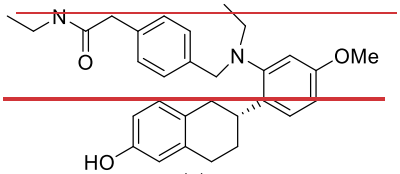


(e)

and



(f)



(g)

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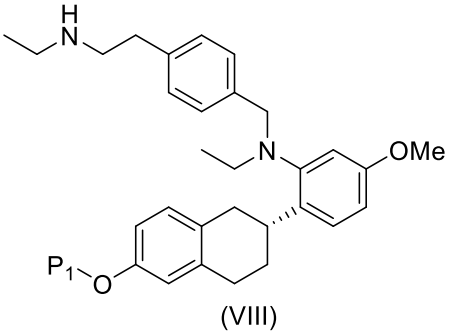
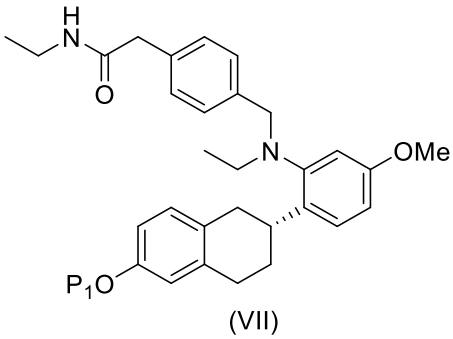
[0004b] In another aspect of the present disclosure, there is provided a process of preparing a compound of formula (VIII)



(VIII)

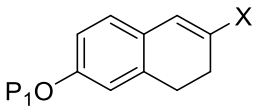
,

comprising the reduction of a compound of formula (VII)



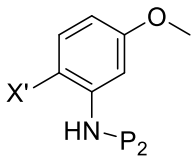
(VII)

wherein said compound of formula (III) is prepared by the coupling of a compound of formula (I)



(I)

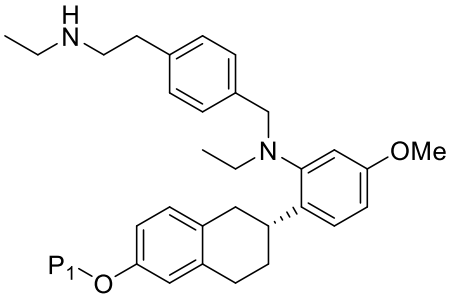
with a compound of formula (II)



(II)

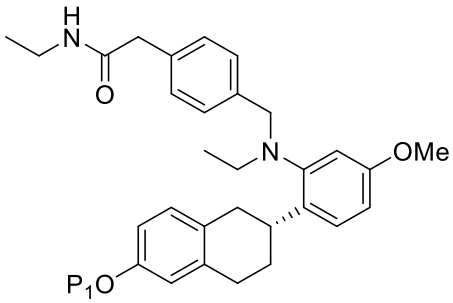
and wherein P_1 is H, or a phenol protecting group; R_b is H or Et; P_2 is (C=O)-CH_3; X is a halogen, transition metal-containing functional group, or boron-containing functional group~~compound~~; and X' is a halogen, transition metal-containing functional group, or boron-containing functional group; and wherein said X and X' are suitable for cross-coupling of compound (I) with compound (II).

[0004c] In a further aspect of the present disclosure, there is provided a process of preparing a compound of formula (VIII):



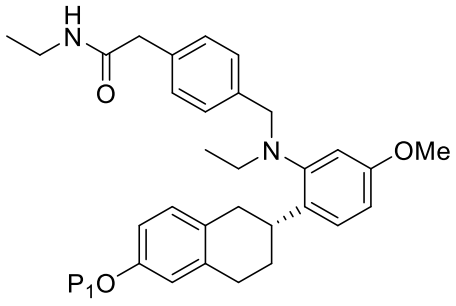
(VIII)

comprising the reduction of a compound of formula (VII):



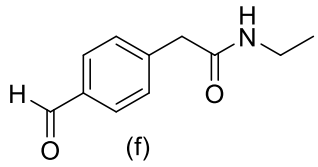
(VII)

wherein P_1 is H or a phenol protecting group~~.~~:



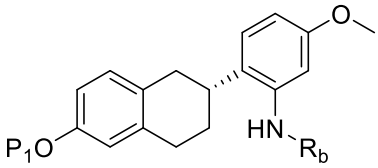
(VII)

comprising the reaction of a compound of formula (f);



(f)

with a compound of formula (VI)



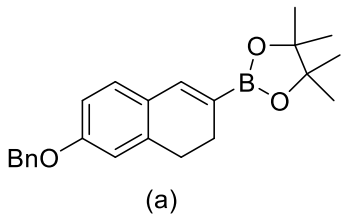
(VI),

in the presence of a reducing agent wherein Rb is H or Et.

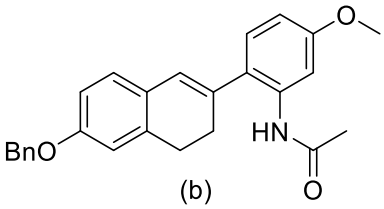
[0005] In certain examples, compounds (a)-(g) are useful in the preparation of a selective estrogen receptor modulator/degrader as disclosed herein.

CLAIMS:

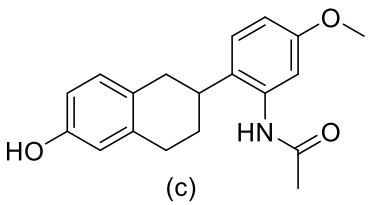
1. A compound selected from: ~~(a) (g)~~



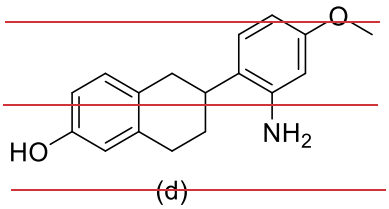
(a)



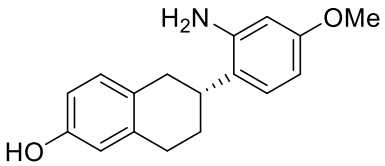
(b)



(c)

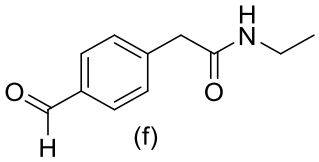


(d)



(e)

and



(f)

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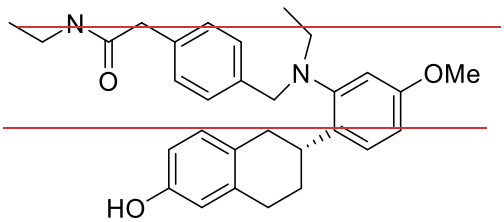
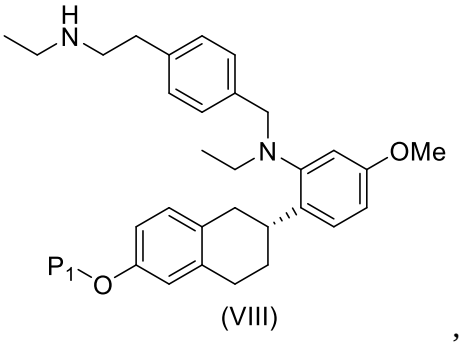


(g)

2. A compound of claim 1 having formula (e) ~~or (g)~~ wherein said compound is present in an enantiomeric excess of >50%.

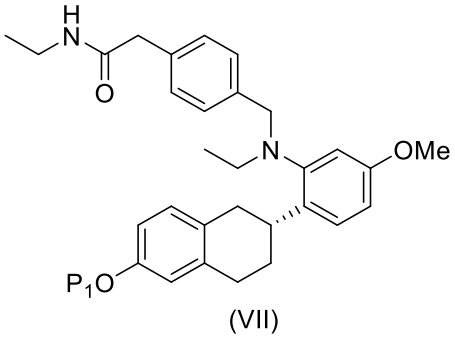
3. A process of preparing a compound of formula (VIII)



(VIII)

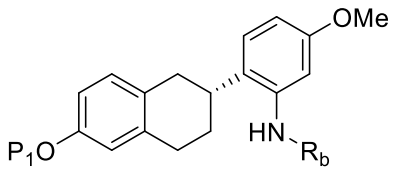
,

comprising the reduction of a compound of formula (VII)



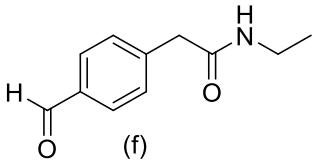
(VII)

wherein said compound of formula (VII) is prepared by a reductive amination of a compound of formula (VI)



(VI)

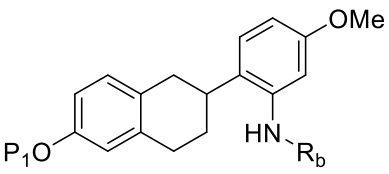
in the presence of a compound of formula (f)



(f)

,

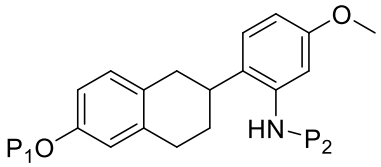
wherein said compound of formula (VI) is prepared by contacting a compound of formula (V)



(V)

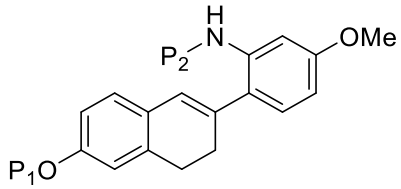
with a chiral acid to form an enantiomerically enriched salt, crystallizing the enantiomerically enriched salt, and freeing the compound of formula (VI),

wherein said compound of formula (V) is prepared by treatment of a compound of formula (IV) with a reducing agent;



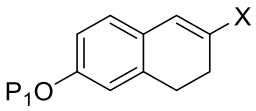
(IV)

wherein said compound of formula (IV) is prepared by reduction of a compound of formula (III)



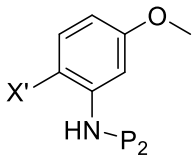
(III)

wherein said compound of formula (III) is prepared by the coupling of a compound of formula (I)



(I)

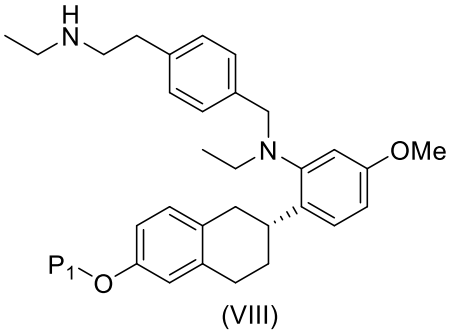
with a compound of formula (II)



(II)

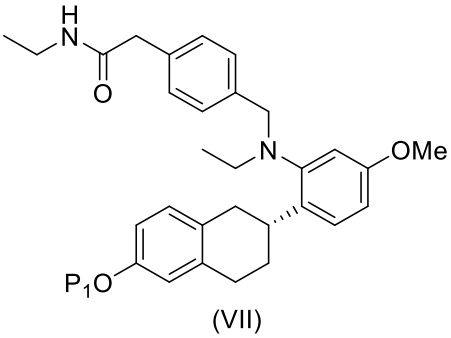
and wherein P_1 is H, or a phenol protecting group; R_b is H or Et; P_2 is (C=O)-CH_3; X is a halogen, transition metal-containing functional group, or boron-containing functional group~~compound~~; and X' is a halogen, transition metal-containing functional group, or boron-containing functional group; and wherein said X and X' are suitable for cross-coupling of compound (I) with compound (II).

4. A process of preparing a compound of formula (VIII):



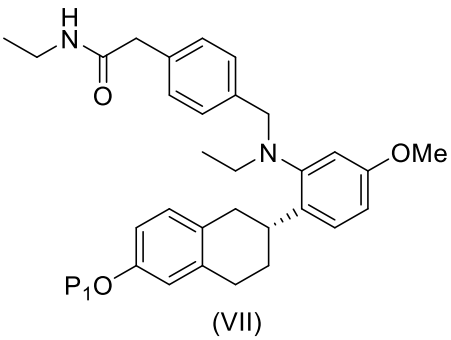
(VIII)

comprising the reduction of a compound of formula (VII):



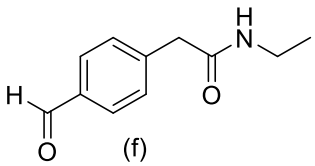
(VII)

wherein P_1 is H or a phenol protecting group;



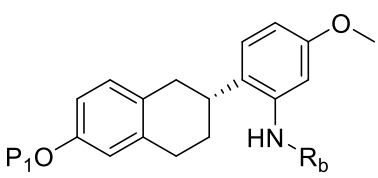
(VII)

comprising the reaction of a compound of formula (f);



(f)

with a compound of formula (VI)

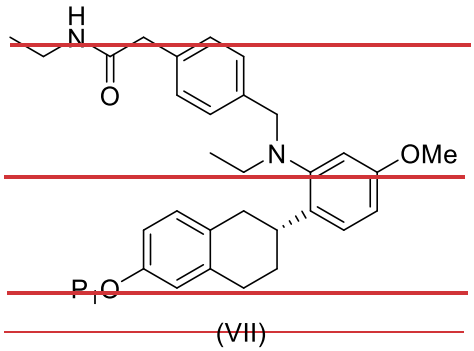


(VI),

in the presence of a reducing agent wherein Rb is H or Et.

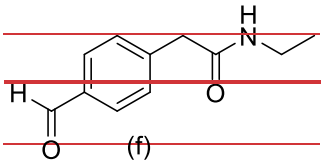
5. The process of claim 4, conducted in the presence of AlH_3, AlH_2Cl, $AlHCl_2$, $NaBH_4$, $LiAlH_4$, $LiBH_4$, $LiEt_3BH$, BH_3, $BH_3.THF$, $CH_3CH_2C(O)OBH_3Na$, $Zn(OAc)_2/(EtO)_3SiH$, $Mg/TiCL_4$, (HBpin)/tris(4,4-dimethyl-2-oxazolinyl)phenylborateMgMe or combinations thereof.

~~6. The process of claim 4, further comprising a process for preparing a compound of formula (VII):~~



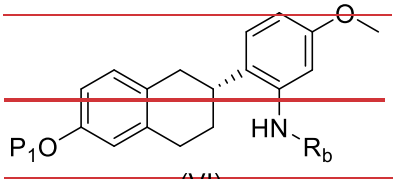
~~(VII)~~

~~comprising the reaction of a compound of formula (f):~~



~~(f)~~

~~with a compound of formula (VI)~~

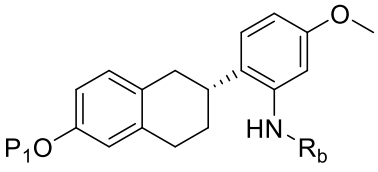


~~(VI)~~ ,

~~in the presence of a reducing agent wherein R_b is H or Et.~~

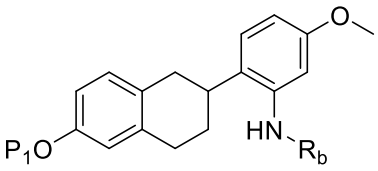
6~~7~~. The process of claim ~~6~~4 wherein the reducing agent used to react Compound (f) with a compound of Formula VI is ~~$NaBH_n(OAc)_n$ is~~ $NaBH(OAc_{ac})_3$.

8~~7~~. The process of claim 4~~6~~, further comprising a process for increasing the enantiomer excess of a compound of formula (VI):



(VI)

comprising contacting a compound of formula (V) with a chiral acid to form an enantiomerically enriched salt,



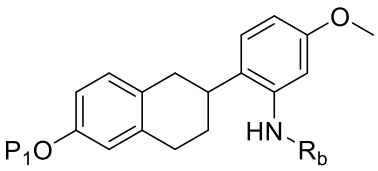
(V)

crystallizing the enantiomerically enriched salt, and freeing the compound of formula (VI).

89. The process of claim ~~8~~7, wherein said enantiomeric excess of the compound of formula (VI) is >50%.

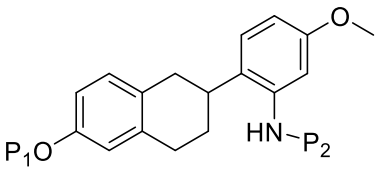
910. The process of claim ~~8~~7 or claim ~~9~~8, wherein said processes uses a (+) or (-) chiral acid selected from Aspartic acid, O-Acetyl-Mandelic acid, cis-2-Benzamidocyclohexanecarboxylic acid, 1,1'-Binapthyl-2,2'-diyl hydrogen phosphate, Camphoric acid, 10-Camphorsulfonic acid, trans-1,2-Cyclohexanedicarboxylic acid, Dibenzoyl-Tartaric acid, Diacetyl-tartaric acid, Di-p-toluoyl-tartaric acid, N-(3,5-Dinitrobenzoyl)-α-phenylglycine, Diacetyl-tartaric anhydride, Diacetyl-tartaric acid, Glutamic acid, Malic acid, Mandelic acid, N-(α-methylbenzyl)phthalamic acid, 2-(6-Methoxy-2-napthyl)propionic acid, Pyroglutamic acid, Quinic acid and Tartaric acid, or combinations thereof.

1011. The process of claim 7~~8~~, further comprising a process of preparing a compound of formula (V):



(V)

comprising the reaction of a compound of formula (IV):



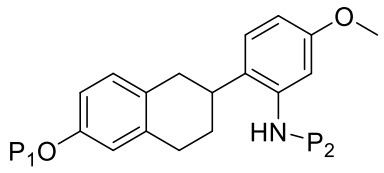
(IV)

with an acid, base, nucleophile or reducing agent wherein P_2 is an amino-protecting group.

1112. The process of claim 1011, wherein the compound of formula (IV) is treated with a hydride-containing reducing agent.

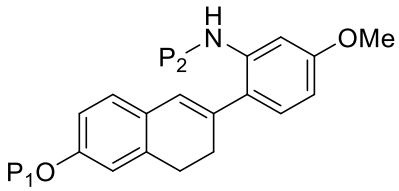
1213. The process of claim 1011 wherein R_b is H; and P_2 is an amino-protecting group and the compound according to formula (IV) is treated with an acid, base or nucleophile.

1314. The process of claim 1110, further comprising a process of preparing a compound of formula (IV):



(IV)

comprising the reduction of a compound of formula (III):

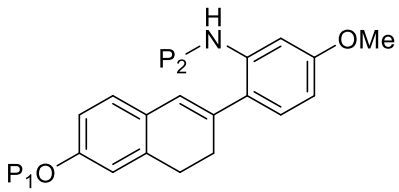


(III)

in the presence of a reducing agent.

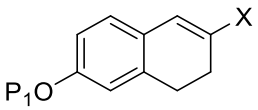
1415. The process of claim 1413, wherein P_1 is H, (C=O)-C_1-C_8 alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C_1-C_5 alkyl)$_3$, Si(aryl)$_2$(C_1-C_5 alkyl) or CH_2Aryl; and P_2 is ~~H, Et,~~ (C=O)-C_1-C_8 alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C_1-C_8 alkyl, (C=O)-O-aryl, (C=O)-O-heteroaryl, (C=O)-O-C_1-C_8 alkylaryl, or -(C=O-(CH_2)$_n$-C=O).

1516. The process of claim 1314, further comprising a process of preparing a compound of formula (III):



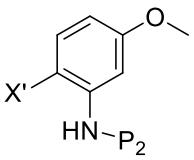
(III)

comprising the reaction of a compound of formula (I):



(I)

with a compound of formula (II):



(II)

in the presence of a base and a transition metal catalyst;

wherein

X is a halogen, transition metal-containing functional group, or boron-containing functional group~~compound~~; and

X' is a halogen, transition metal-containing functional group, or boron-containing functional group, wherein said X and X' are suitable for cross-coupling of compound (I) with compound (II).

~~17~~16. The process of claim 15~~16~~, wherein P_1 is H, or a protecting group selected from (C=O)-C_1-C_8 alkyl, (C=O)-aryl, (C=O)-heteroaryl, Si(C_1-C_5 alkyl)$_3$, Si(aryl)$_2$(C_1-C_5 alkyl) and CH_2Aryl;

P_2 is ~~H, Et,~~ (C=O)-C_1-C_8 alkyl, (C=O)-aryl, (C=O)-heteroaryl, (C=O)-O-C_1-C_8 alkyl, (C=O)-O-aryl, (C=O)-O-heteroaryl, (C=O)-O-C_1-C_8 alkylaryl, or (C=O-(CH_2)$_n$-C=O)-;

X is B(OR)$_2$, B(-O-(C(R_a)$_2$)$_n$-O-), Cl, Br, I, OSO_2CF_3 or OSO_2(aryl);

X' is B(OR)$_2$, B(-O-(C(R_a)$_2$)$_n$-O-), Cl, Br, I, OSO_2CF_3 or OSO_2(aryl);

each R is independently H, C_{1-3} alkyl or aryl;

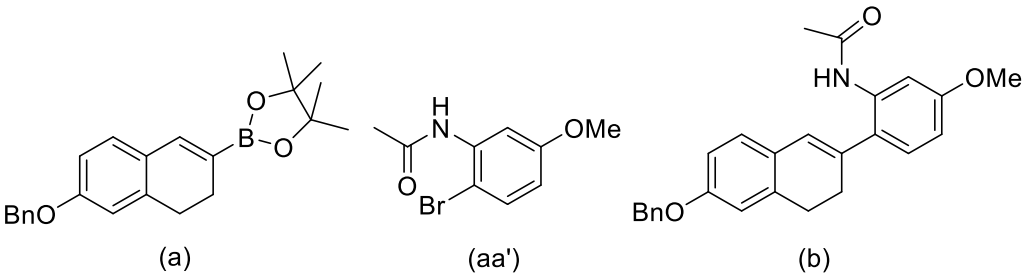
each R_a is independently C_{1-3} alkyl or aryl; and

each n is independently an integer of 2 or 3,

wherein when X is B(OR)$_2$ or B(-O-(C(R_a)$_2$)$_n$-O-), X' is Cl, Br, I, OSO_2CF_3 or OSO_2(aryl).

17~~18~~. The process of claim 15~~16~~ or claim 16~~17~~, conducted in the presence of a transition metal catalyst selected from the group consisting of Pd(OAc)$_2$, Pd(PPh_3)$_4$, $PdCl_2$(PPh_3)$_2$, Pd(dppf)Cl_2, Pd_2(Dba)$_3$, Cu(0), Pd(PCy_3)$_2$, and any combinations thereof.

18~~19~~. The process of any one of claims 3, or 15-17~~1-5~~, wherein the compounds of formulas (I), (II) and (III) are (a), (aa') and (b):



(a) (aa') (b)