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IODONIUM CYCLOPHANES FOR SECURE ARENE FUNCTIONALIZATION

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(54) IODONIUM CYCLOPHANES FOR SECURE ARENE FUNCTIONALIZATION

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None
See application file for complete search history.

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(57) **ABSTRACT**

This disclosure relates to compounds, reagents, and methods useful in the synthesis of aryl fluorides, for example, in the preparation of ^{18}F labeled radiotracers. For example, this disclosure provides universal "locked" aryl substituents that result in StereoElectronic Control of Unidirectional Reductive Elimination (SECURE) from diaryliodonium salts. The reagents and methods provided herein may be used to access a broad range of compounds, including aromatic compounds, heteroaromatic compounds, amino acids, nucleotides, and synthetic compounds.

83 Claims, 1 Drawing Sheet

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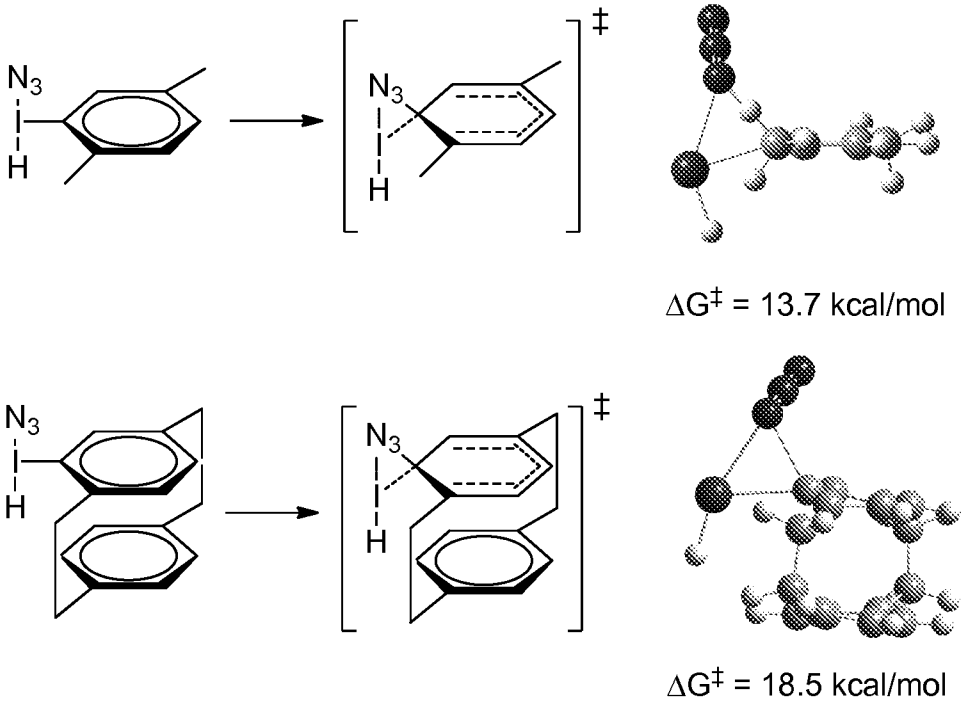

N3
H
‡
ΔG‡ = 13.7 kcal/mol
ΔG‡ = 18.5 kcal/mol

IODONIUM CYCLOPHANES FOR SECURE ARENE FUNCTIONALIZATION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. §119(e) to U.S. Provisional Application Ser. No. 61/301,491, filed on Feb. 4, 2010, which is incorporated by reference in its entirety herein.

TECHNICAL FIELD

This disclosure relates to compounds, reagents, and methods useful in the synthesis of aryl fluorides, for example, in the preparation of ^{18}F labeled radiotracers. The reagents and methods provided herein may be used to access a broad range of compounds, including aromatic compounds, heteroaromatic compounds, amino acids, nucleotides, and synthetic compounds.

BACKGROUND

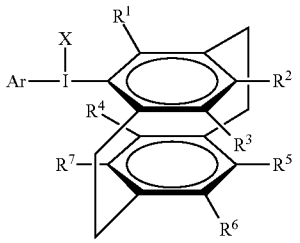
Aryl fluorides are structural moieties in natural products as well as a number of therapeutically important compounds, including positron emission tomography (PET) tracers and pharmaceuticals. Therefore methods and reagents for producing such aryl fluorides, for example efficient methods for producing aryl fluorides, are desirable.

SUMMARY

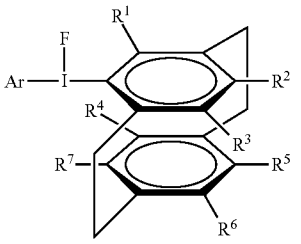
Provided herein are methods of preparing substituted aryl and heteroaryl ring systems using iodonium cyclophane compounds, salts, and intermediates. For example, iodonium cyclophane salts and iodonium cyclophane fluorides, as provided herein, can undergo decomposition to prepare an aryl fluoride. In the thermal decomposition of unsymmetrial diaryliodonium salts, the identity of the aryl iodide reductively eliminated it typically dictated by electronic effects; for example, the electron-rich aryl iodide and the functionalized electron-poor aromatic compound are formed predominantly (see, for example, WO 2010/048170, which is incorporated by reference herein). This disclosure provides universal "locked" aryl substituents that result in StereoElectronic Control of Unidirectional Reductive Elimination (SECURE) from diaryliodonium salts. Since electronic effects cannot be used exclusively to achieve this end, steric and/or stereoelectronic effects can be exploited to gain regiocontrol of reductive elimination.

Provided herein are aryl ligands on iodine that can generate a highly strained reductive elimination transition state. This strained transition state is created through the introduction of significant steric congestion above and/or below the aromatic ring in conjunction with little steric congestion in the plane of the ring. For example, [2.2]paracyclophane iodine(III) salts are described herein.

In some embodiments, the iodonium cyclophane compound can be a compound of Formula (1):



or Formula (4):



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

X is either a moiety wherein the pKa of the acid H—X is less than 12 or a leaving group;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_m$, —SR^8, —SOR^8, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$, $NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and $(L)_p$-Z, or one or more of R^2 and R^3, R^4 and R^7, and R^5 and R^6 come together to form a fused cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring system;

each m, n, and p are independently an integer from 0 to 10;

each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

L is a linker; and

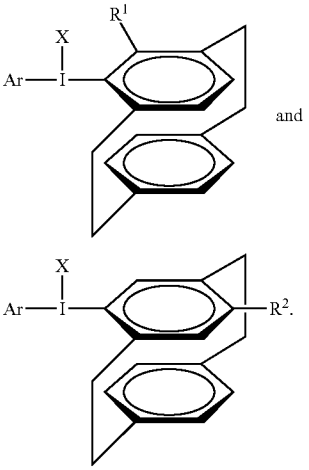
Z is a solid support.

The X moiety can be one wherein the pKa of the acid H—X is less than 12. In some embodiments, X is selected from the group consisting of halide, aryl carboxylate, alkyl carboxylate, phosphate, phosphonate, phosphonite, azide, thiocyanate, cyanate, phenoxide, triflate, trifluoroethoxide, thiolates, and stabilized enolates. For example, X can be selected from the group consisting of: fluoride, chloride, bromide, iodide, triflate, trifluoroacetate, benzoate, acetate, phenoxide, trifluoroethoxide, cyanate, azide, thiocyanate, thiolates, phosphates, and stabilized enolates. In some embodiments, X can comprise a radioactive isotope. For example, X can be F or a radioactive isotope of F (i.e., ^{18}F).

In some cases, X is a leaving group. For example, X can be selected from the group consisting of: triflate, mesylate, nonaflate, hexaflate, tosylate, nosylate, brosylate, perfluoroalkyl sulfonate, tetraphenylborate, hexafluorophosphate, trifluoroacetate, tetrafluoroborate, perchlorate, perfluoroalkylcarboxylate, chloride, bromide, and iodide.

The aryl rings on the cyclophane moiety can be substituted or unsubstituted. In some embodiments, R^1 is selected from the group consisting of: —(C_1-C_{10})alkyl, —(C_1-C_{10})ha-

loalkyl, (C_2-C_{10})alkenyl, (C_2-C_{10})alkynyl, —O—(C_1-C_{10})alkyl, —C(O)—O—(C_1-C_{10})alkyl, aryl, and heteroaryl. For example, R^1 can be —O—(C_1-C_{10})alkyl (e.g., OCH_3). In some embodiments, R^2 is —O—(C_1-C_{10})alkyl (e.g., OCH_3). For example, a compound of Formula (1) can be chosen from:

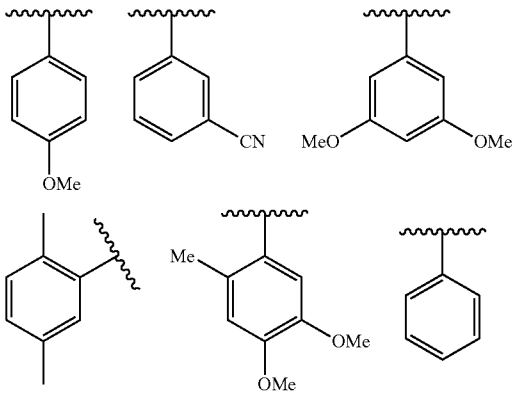


and

In some embodiments, one or more of R^2-R^7 is $(L)_p$-Z. L and Z can be covalently or noncovalently bound to one another.

The compounds described herein can be used with a variety of aryl and heteroaryl ring systems. In some embodiments, Ar is an electron rich aryl or heteroaryl ring system, for example, Ar—H can be more easily oxidized than benzene. In some embodiments, Ar is chosen from a phenylalanine derivative, tyrosine derivative, typtophan derivative, histidine derivative, and estradiol derivative. The Ar moiety can be present as a racemic mixture, enantiomerically pure, or as a mixture thereof. In some embodiments, the Ar moiety is enantiomerically enriched. For example, the Ar moiety can be present in an enantiomeric excess of at least 75%, an enantiomeric excess of at least 95%, or an enantiomeric excess of at least 98%.

In some embodiments, Ar can be selected from the group consisting of:



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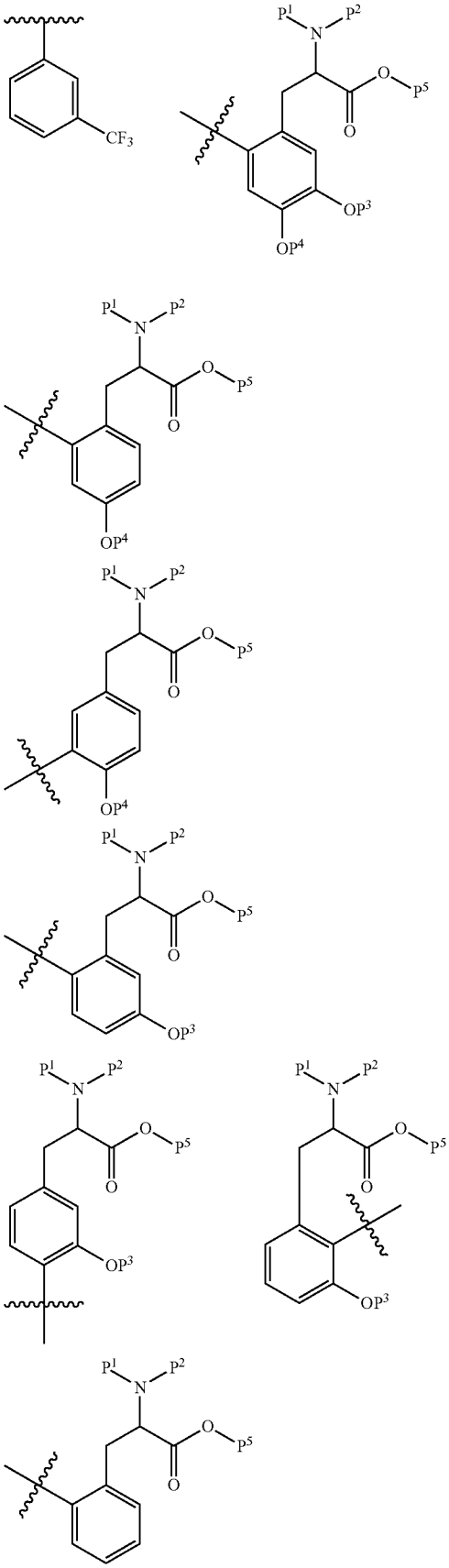

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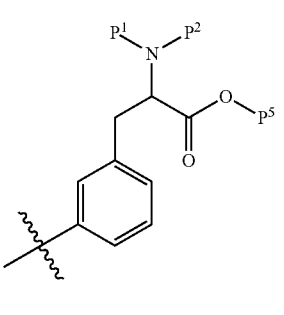

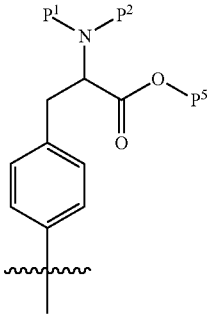

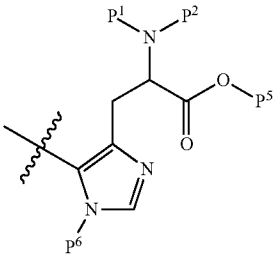

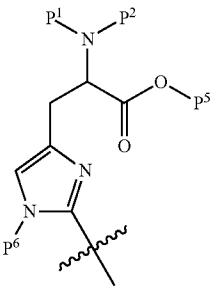

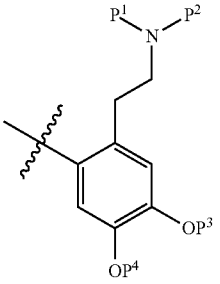

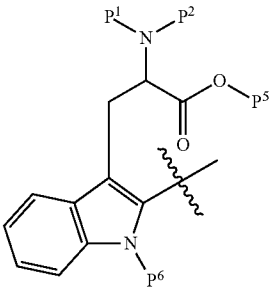

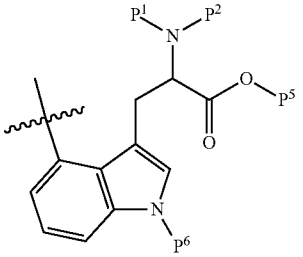

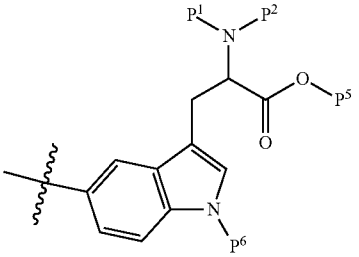

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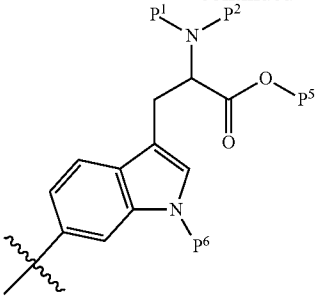

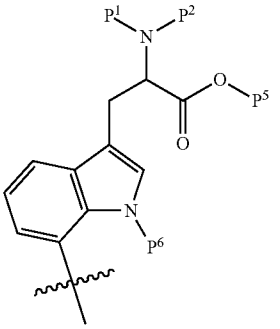

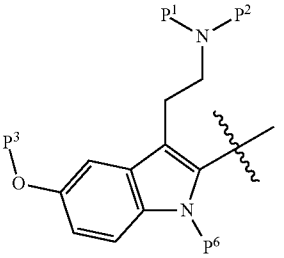

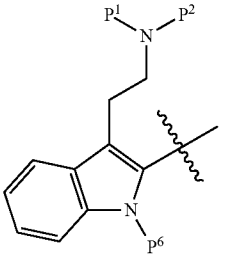

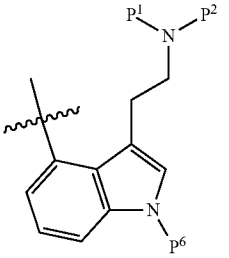

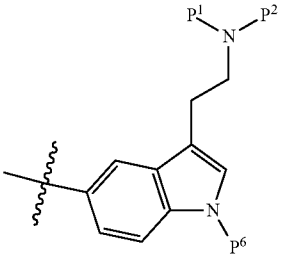

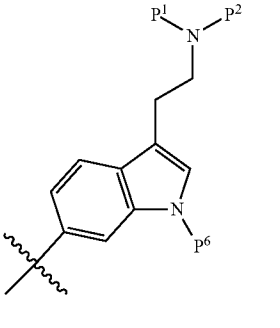

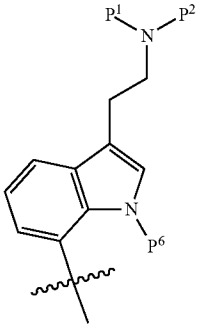

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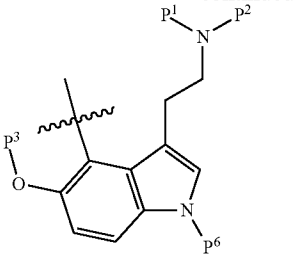

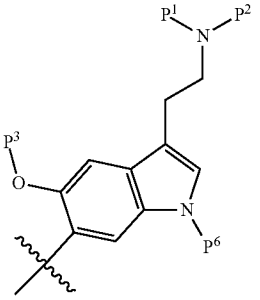

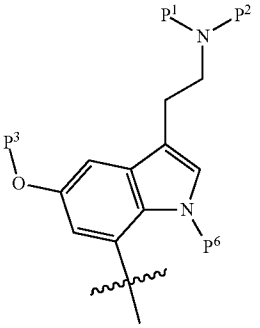

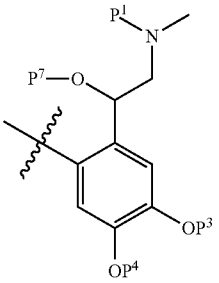

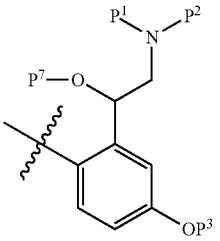

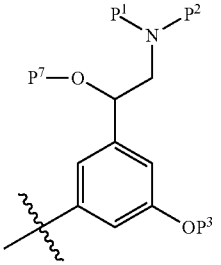

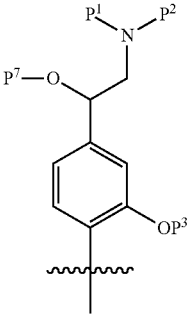

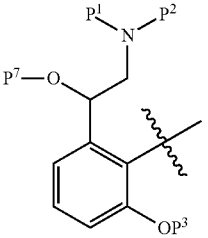

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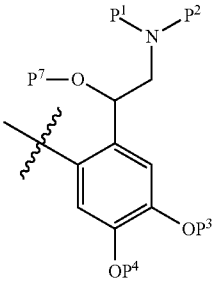

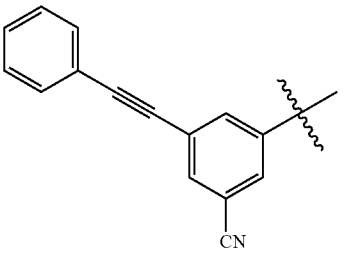

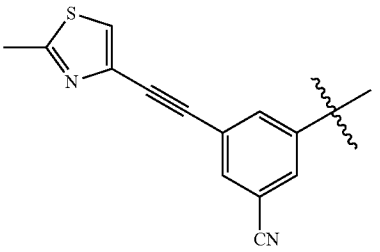

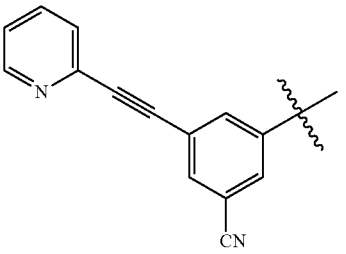

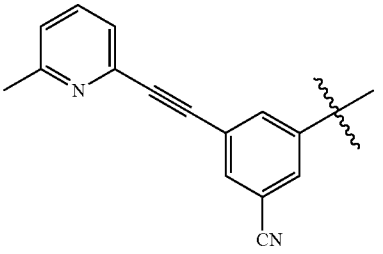

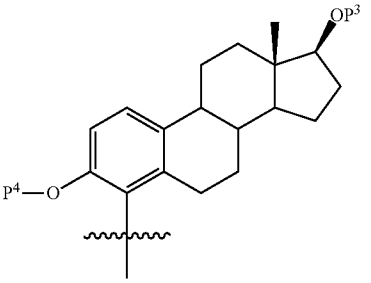

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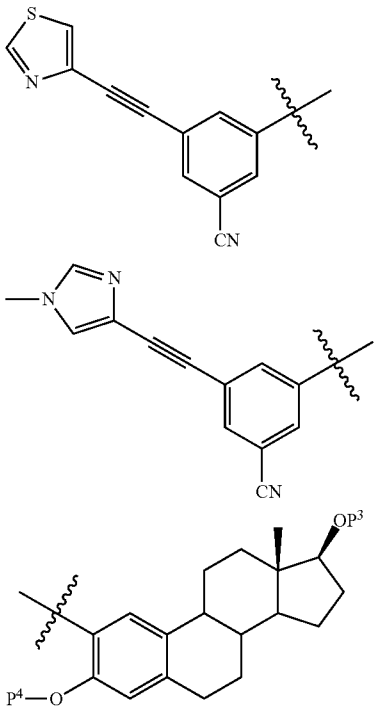


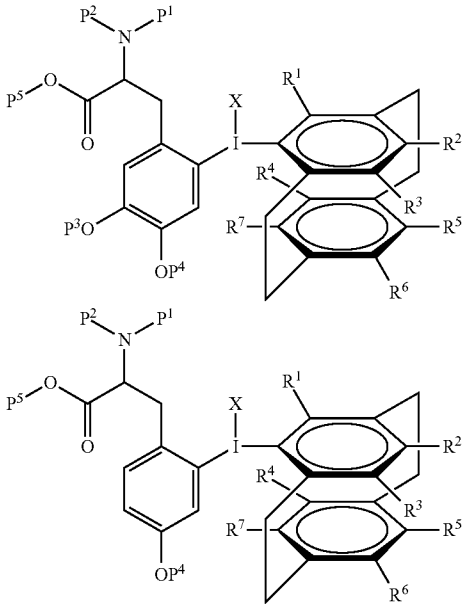
wherein:

each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

In some embodiments, the compound of Formula (1) is chosen from:



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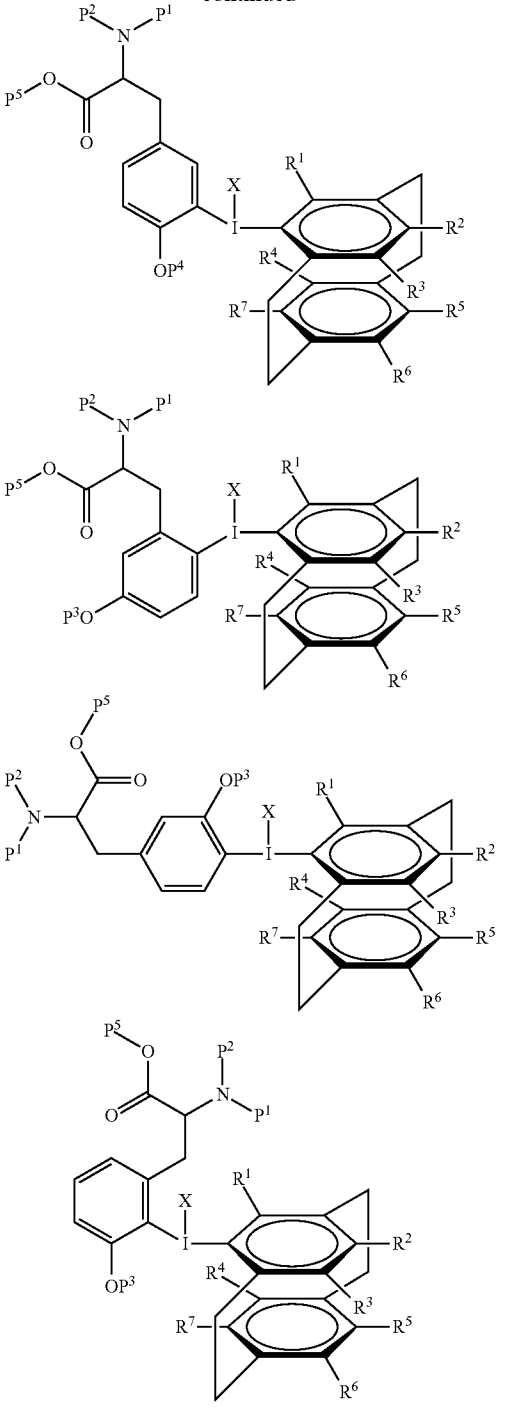


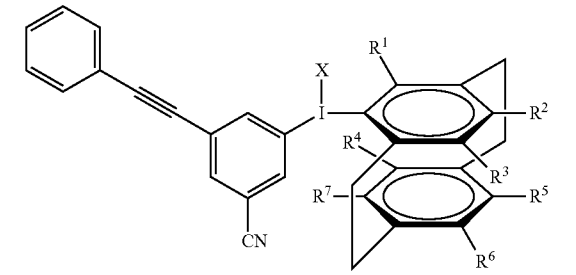
wherein:

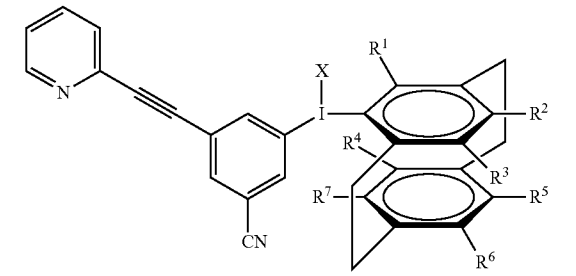
each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

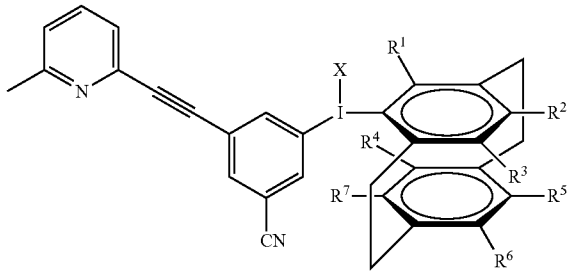
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

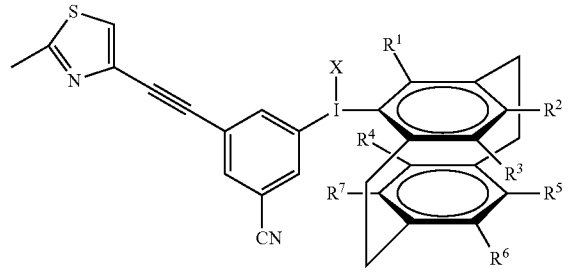
P^5 is a carboxylic acid protecting group.

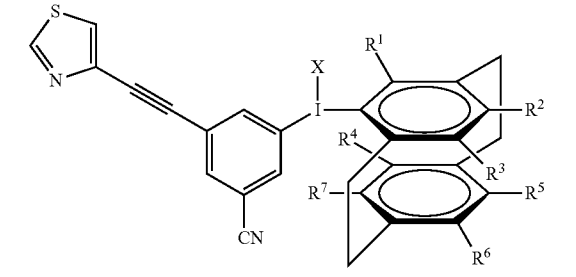
In some embodiments, the compound of Formula (1) is selected from the group consisting of:

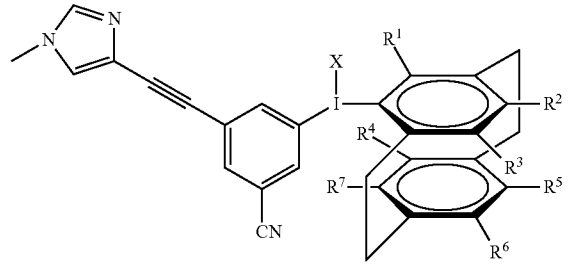




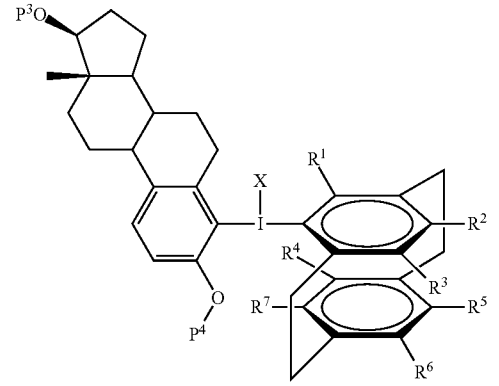


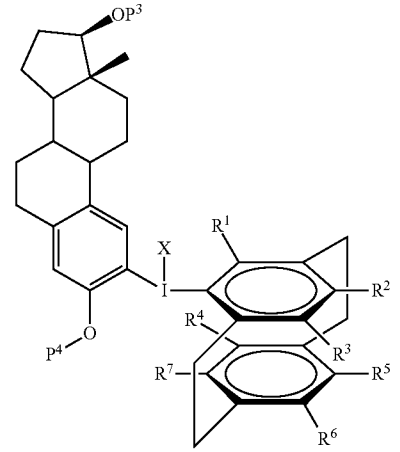






In some embodiments, the compound of Formula (1) is selected from the group consisting of:



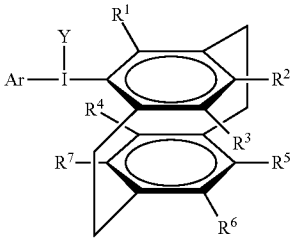


wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

In any of the above embodiments, X can be F. For example, X can be ^{18}F.

In some embodiments, a compound of Formula (1) can be a compound of Formula (3):



wherein Y is a leaving group. For example, Y can be selected from the group consisting of: triflate, mesylate, nonaflate, hexaflate, tosylate, nosylate, brosylate, perfluoroalkyl sulfonate, tetraphenylborate, hexafluorophosphate, trifluoroacetate, tetrafluoroborate, perchlorate, perfluoroalkylcarboxylate, chloride, bromide, and iodide.

Further provided herein is a method of making a compound of Formula (2):

Ar—X or

Formula (5):

Ar—F

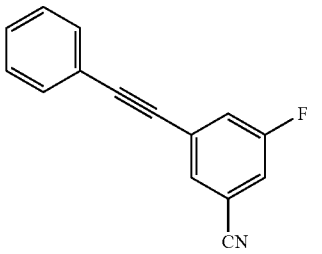
wherein Ar is a substituted or unsubstituted aryl or heteroaryl ring system; and X is a moiety whether the pKa of the acid H—X is less than 12, as described above. The method includes heating a solution comprising a compound MX (e.g., MF), wherein M is a counter ion and X is as defined above, and a compound of Formula (3).

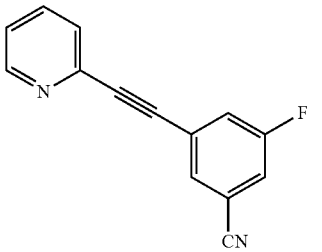
In some embodiments, the solution comprising MX or MF and a compound of Formula (3) can further include a non-polar solvent. The non-polar solvent can be, for example, benzene, toluene, o-xylene, m-xylene, p-xylene, ethyl benzene, carbon tetrachloride, hexane, cyclohexane, fluorobenzene, chlorobenzene, nitrobenzene, or mixtures thereof. In some embodiments, the solution comprising MX or MF and a compound of Formula (3) can further include a polar solvent. The polar solvent can be, for example, acetonitrile, acetone, dichloromethane, ethyl acetate, tetrahydrofuran, dimethylformamide, 1,2-difluorobenzene, benzotrifluoride, or mixtures thereof.

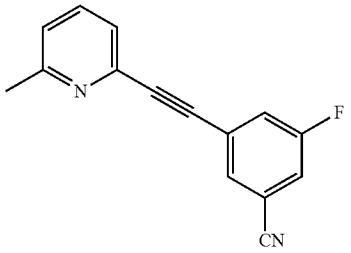
In some embodiments, the method further comprises filtering the solution to remove insoluble material prior to heating. In some cases, the solvent is removed from the filtrate prior to heating. In some embodiments, the method further comprises removing salt by chromatography prior to heating (for example, removing salt using gel permeation chromatography).

Heating of the solution can be done at a temperature ranging from about 25° C. to about 250° C. In some embodiments, the heating occurs for from about 1 second to about 25 minutes. Heating can be accomplished by any reasonable method, for example, by a flash pyrolysis method, a conventional heating method, or by a microwave method.

Non-limiting examples of a compound of Formula (2) or (5) include:







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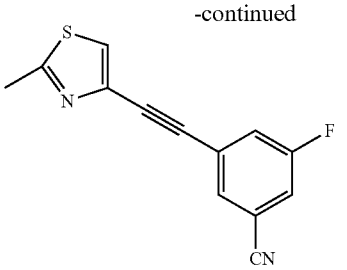
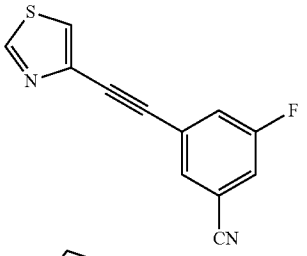
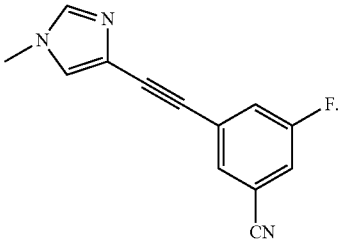
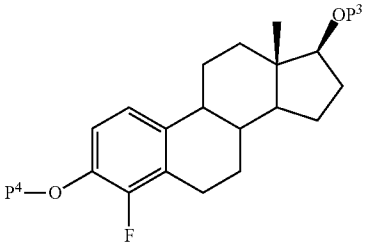
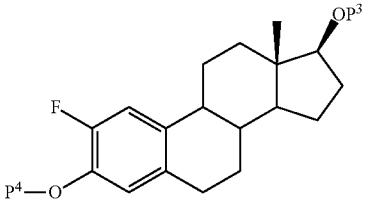






In some embodiments, the compound of Formula (2) or (5) can be chosen from:

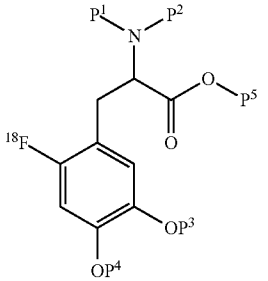




wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

In some embodiments, the compound of Formula (2) or (5) is:



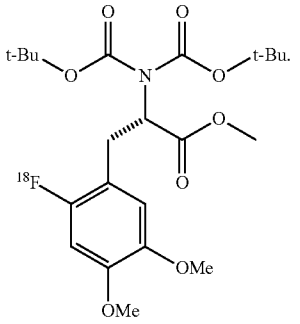
wherein:

each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

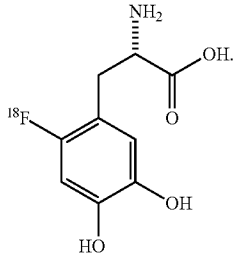
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

For example, the compound can be:



In some embodiments, the compound of formula (2) or (5) is:



Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used to practice the invention, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

These and other features, aspects and advantages of the present teachings will become better understood with reference to the following description, examples and appended claims.

DESCRIPTION OF DRAWINGS

FIG. **1** shows the calculated transition state structures and activation barriers for a (2,5-dimethylphenyl) and [2.2]paracyclophan-4-yl iodonium salt.

DETAILED DESCRIPTION

Provided herein are methods of preparing substituted aryl and heteroaryl ring systems using iodonium cyclophane compounds and intermediates. For example, iodonium cyclophane salts and iodonium cyclophane fluorides, as provided herein, can undergo decomposition to prepare an aryl fluoride. In the thermal decomposition of unsymmetrial diaryliodonium salts, the identity of the aryl iodide reductively eliminated it typically dictated by electronic effects; for example, the electron-rich aryl iodide and the functionalized electron-poor aromatic compound are formed predominantly (see, for example, WO 2010/048170, which is incorporated by reference herein). This disclosure provides universal "locked" aryl substituents that result in StereoElectronic Control of Unidirectional Reductive Elimination (SECURE) from diaryliodonium salts. Since electronic effects cannot be used exclusively to achieve this end, steric and/or stereoelectronic effects can be exploited to gain regiocontrol of reductive elimination.

DEFINITIONS

As used herein, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise.

In general, the term "aryl" includes groups having at least 5 carbon atoms which form a ring structure and have an aromatic character, including 5- and 6-membered single-ring aromatic groups, such as benzene and phenyl. Furthermore, the term "aryl" includes polycyclic aryl groups, e.g., tricyclic, bicyclic, such as naphthalene and anthracene.

The term "heteroaryl" includes groups having at least 5 atoms which form a ring structure and have an aromatic character, including 5- and 6-membered single-ring aromatic groups, that have from one to four heteroatoms, for example, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "heteroaryl" includes polycyclic heteroaryl groups, e.g., tricyclic, bicyclic, such as benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, indazole, or indolizine.

The term "substituted" means that an atom or group of atoms formally replaces hydrogen as a "substituent" attached to another group. For aryl and heteroaryl groups, the term "substituted", unless otherwise indicated, refers to any level of substitution, namely mono, di, tri, tetra, or penta substitution, where such substitution is permitted. The substituents are independently selected, and substitution may be at any chemically accessible position.

The compounds provided herein may encompass various stereochemical forms and tautomers. The compounds also encompasses diastereomers as well as optical isomers, e.g. mixtures of enantiomers including racemic mixtures, as well as individual enantiomers and diastereomers, which arise as a consequence of structural asymmetry in certain compounds. Separation of the individual isomers or selective synthesis of the individual isomers is accomplished by application of various methods which are well known to practitioners in the art.

As used herein, chemical structures which contain one or more stereocenters depicted with bold and dashed bonds, i.e., ⁞| are meant to indicate absolute stereochemistry of the stereocenter(s) present in the chemical structure. As used herein, bonds symbolized by a simple line do not indicate a stereopreference. Unless otherwise indicated to the contrary, chemical structures, which include one or more stereocenters, illustrated herein without indicating absolute or relative stereochemistry encompass all possible steroisomeric forms of the compound (e.g., diastereomers, enantiomers) and mixtures thereof Structures with a single bold or dashed line, and

at least one additional simple line, encompass a single enantiomeric series of all possible diastereomers.

The term "optically enriched" or "enantiomerically enriched" as used herein refers to the presence of an enantiomeric excess of either an R or an S isomer at a given stereocenter of a molecule in a composition. "Enantiomeric excess" is defined as |F(R)−F(S)| for a mixture of (R) and (S) enantiomers, with the composition given as the mole fractions F(R) and F(S), where F(R)+F(S)=1. The percent enantiomeric excess is given by 100|F(R)−F(S)|). Enantiomeric excess is frequently abbreviated as ee. In some embodiments, the ee for each species of a genus is independent of the other members of the genus.

The term "electron rich", as used herein, refers to an aryl or heteroaryl ring system which is more easily oxidized than benzene. For example the aryl or heteroaryl ring system may be substituted with one or more substituents having a Hammett σ_p value of less than zero.

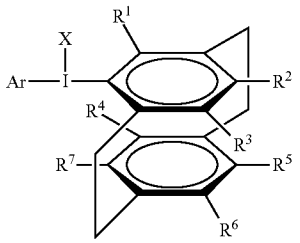
The term "fluorine", unless explicitly stated otherwise, includes all fluorine isotopes. Multiple fluorine isotopes are known, however, only ^{19}F is stable. The radioisotope ^{18}F has a half-life of 109.8 minutes and emits positrons during radioactive decay. The relative amount of ^{18}F present at a designated site in a compound of this disclosure will depend upon a number of factors including the isotopic purity of ^{18}F labeled reagents used to make the compound, the efficiency of incorporation of ^{18}F in the various synthesis steps used to prepare the compound, and the length of time since the ^{18}F has been produced. When a position is designated specifically as ^{18}F in the methods and compounds of the present disclosure, the position is understood to have at least about 0.01%, at least about 0.1%, at least about 1%, at least about 2%, at least about 3%, at least about 4%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, or at least about 85% ^{18}F incorporation at that site.

Compounds

Provided herein are aryl ligands on iodine that can generate a highly strained reductive elimination transition state. This strained transition state is created through the introduction of significant steric congestion above and/or below the aromatic ring in conjunction with little steric congestion in the plane of the ring. On such ligand is [n.n]cyclophane. Cyclophanes, as described herein, are a hydrocarbon consisting of an aromatic unit (e.g., a benzene ring) and an aliphatic chain that forms a bridge between two non-adjacent positions of the aromatic ring. For example, [2.2]paracyclophane iodine(III) salts are described herein, but those of skill in the art will appreciate that other cyclophanes, e.g., [2.2]metacyclophane or [2.2] orthocyclophane, can also be used in the compounds and methods described herein. In addition, cyclophanes are chiral and the cyclophane moieties provided herein may be enantiomerically pure, racemic, or a mixture thereof.

One example of a [2.2]paracyclophane iodine(III) salt is a compound of Formula

(1)



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

X is either a moiety wherein the pKa of the acid H—X is less than 12 or a leaving group;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_m$, —SR^8, —SOR^8, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$, $NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and $(L)_p$-Z, or one or more of R^2 and R^3, R^4 and R^7, and R^5 and R^6 come together to form a fused cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring system;

each m, n, and p are independently an integer from 0 to 10;

each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

L is a linker; and

Z is a solid support.

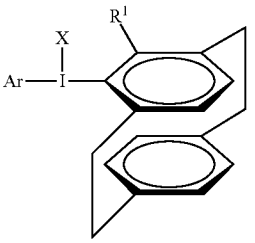
The X moiety can be selected from atoms and compounds in which the pKa of the acid H—X (i.e., the conjugate acid of X) is less than about 12. In some cases, X comprises a radioactive isotope (e.g., ^{18}F, ^{123}I, ^{131}I, ^{32}P, and ^{33}P). In some embodiments, X can be chosen from halide, aryl carboxylate, alkyl carboxylate, phosphate, phosphonate, phosphonite, azide, thiocyanate, cyanate, phenoxide, triflate, trifluoroethoxide, thiolates, and stabilized enolates. For example, X can be fluoride, chloride, bromide, iodide, trifluoroacetate, benzoate, and acetate. In some embodiments, X is fluoride. In some embodiments, X is a radioactive isotope of fluoride (^{18}F).

X can also be any suitable leaving group. In some embodiments, X is a weakly coordinating anion (i.e., an anion that coordinates only weakly with iodine). For example, X can be the conjugate base of a strong acid, for example, any anion for which the pKa of the conjugate acid (H—X) is less than about 1. For example, X can be triflate, mesylate, nonaflate, hexaflate, toluene sulfonate(tosylate), nitrophenyl sulfonate (nosylate), bromophenyl sulfonate(brosylate), perfluoroalkyl sulfonate (e.g., perfluoro C_{2-10} alkyl sulfonate), tetraphenylborate, hexafluorophosphate, trifluoroacetate, perfluoroalkylcarboxylate, tetrafluoroborate, perchlorate, hexafluorostibate, hexachlorostibate, chloride, bromide, or iodide. In some embodiments, a slightly more basic leaving group such as acetate or benzoate may be used.

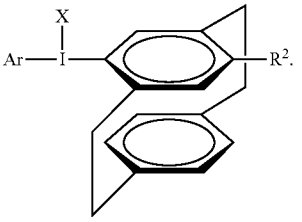
The aryl rings that form the cyclophane moeity may be substituted or unsubstituted as described above. In some embodiments, at least one aryl ring is substituted with at least one substituent having a Hammett σ_p value of less than zero (see, for example, "A survey of Hammett substituent constants and resonance and field parameters", Corwin. Hansch, A. Leo, R. W. Taft *Chem. Rev.*, 1991, 91 (2), pp 165-195). For example, R^1 can be selected from —$(C_1$-$C_{10})$alkyl, $(C_2$-$C_{10})$ alkenyl, $(C_2$-$C_{10})$alkynyl, —C(O)—O—$(C_1$-$C_{10})$alkyl, aryl,

and heteroaryl. In some embodiments, R^1 can be —O—(C_1-C_{10})alkyl, for example, R^1 can be OCH_3. Similarly, in some embodiments, R^2 can be —O—(C_1-C_{10})alkyl, for example, R^2 can be OCH_3. For example, the compound of Formula (1) can be a compound of Formula (1A) or (1B):

(1A)



(1B)



In some embodiments, adjacent R moieties (e.g., R^2 and R^3, R^4 and R^7, and/or R^5 and R^6) can come together to form a fused cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring system. For example, the cyclophane can include substituted or unsubstituted napthyl or anthracyl rings as the upper and/or lower aromatic ring moieties.

In some cases, the cyclophane ligand can be substituted with a solid support, Z. A "solid support" may be any suitable solid-phase support which is insoluble in any solvents to be used but which can be covalently or noncovalently bound (e.g., to the cyclophane ligand or to an optional linker). Examples of suitable solid supports include polymers such as polystyrene (which may be block grafted, for example with polyethylene glycol), polyacrylamide, or polypropylene or glass or silicon coated with such a polymer. The solid support may be in the form of small discrete particles such as beads or pins, or as a coating on the inner surface of a reaction vessel, for example a cartridge or a microfabricated vessel. See, for example, U.S. 2007/0092441. In some embodiments, the supports can be sealed into HPLC columns.

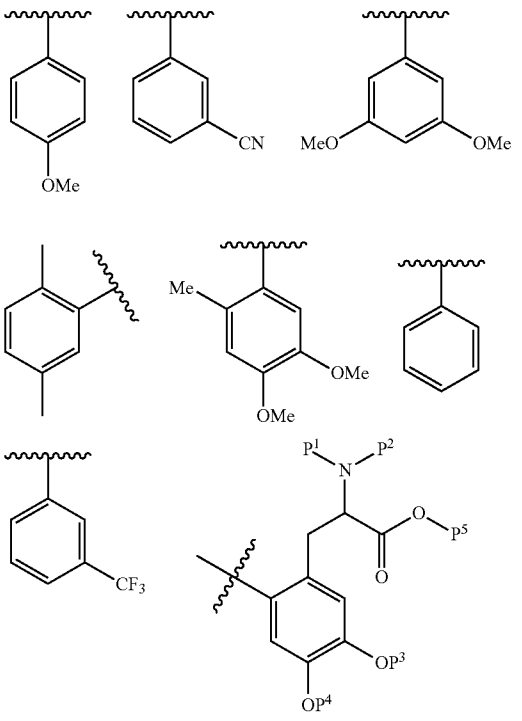
In some embodiments, the solid support is covalently or noncovalently bound to the cyclophane ligand through the use of a linker, L. A "linker" can be any suitable organic group which serves to space the ligand from the solid support structure so as to maximize reactivity. In some embodiments, L and Z are covalently bound to one another. For example, a linker can include a C_{1-20} alkyl or a C_{1-20} alkoxy, attached to the solid support, for example, a resin can be linked by an amide ether or a sulphonamide bond. The linker may also be a polyethylene glycol (PEG) linker. Examples of such linkers are well known to those skilled in the art of solid-phase chemistry. In some cases the linker and solid support are noncovalently bound to one another. Examples of noncovalent means for conjugation of a linker and a solid support include, e.g., ionic bonding, hydrophobic interactions, ligand-nucleotide binding, chelating agent/metal ion pairs or specific binding pairs such as avidin/biotin, streptavidin/biotin, anti-fluorescein/fluorescein, anti-2,4-dinitrophenol (DNP)/DNP, anti-peroxidase/peroxidase, anti-digoxigenin/digoxigenin or, more generally, receptor/ligand.

In some embodiments, a fluorous tag ($C_nF_{(2n+1)}$) can be used as a linker to immobilize a compound of Formula (1) on a fluorous support. For example, such immobilization can be accomplished by using a fluorophobic solvent such as acetonitrile. Examples of fluorous supports include powdered polyfluorinated resins (PTFE or PFA (DuPont)) or heavily fluorinated silica gels (FluoroFlash (Fluorous Technologies)). In some embodiments, a linker can comprise a fluorous alcohol as the source of the tag. This tag can be linked to the cyclophane ligand through any suitable organic linkage, for example, an alkyl group, polyethylene glycol (PEG) ethers, or mixtures of aliphatic, aromatic, and PEG linkers. In some embodiments, the length of the perfluoroalkyl chain on the linker can range from C_6F_{13} to $C_{20}F_{41}$. In addition, multiple fluorous tags may be incorporated into the same iodonium salt.

The compounds described herein can be used with a variety of aryl and heteroaryl ring systems. Accordingly, the Ar moiety can be any aryl or heteroaryl ring system in which substitution by X (e.g., F such as ^{18}F) is desired. In some embodiments, the Ar moiety is enantiomerically enriched. For example, the Ar moiety can be present in an enantiomeric excess of at least 75%, at least 95%, or at least 98%. In some embodiments, Ar is enantiomerically pure.

Ar can be an electron rich aryl or heteroaryl ring system, such as a ring system where Ar—H is more easily oxidized than benzene. In some embodiments, Ar is chosen from a phenylalanine derivative, tyrosine derivative, typtophan derivative, histidine derivative, and estradiol derivative.

In some embodiments, Ar can be selected from the group consisting of:



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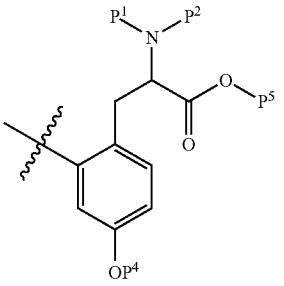

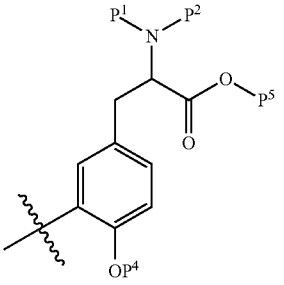

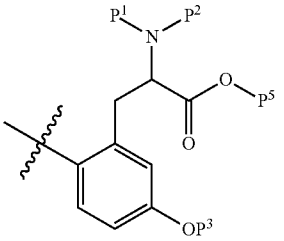

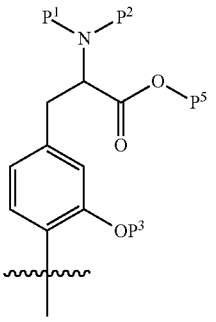

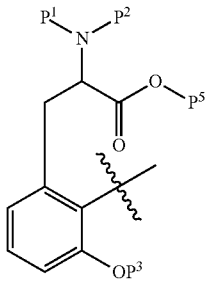

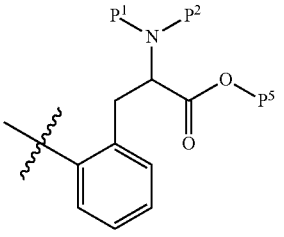

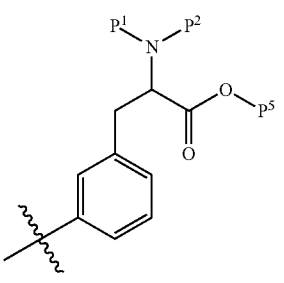

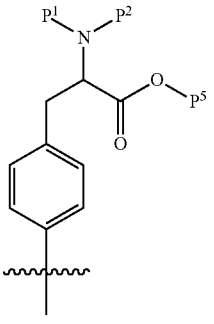

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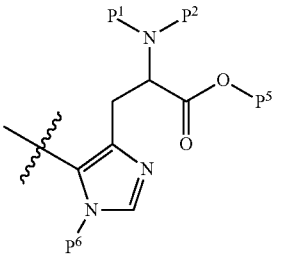

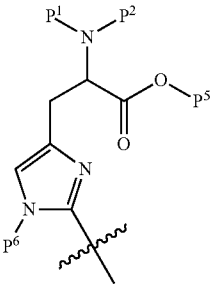

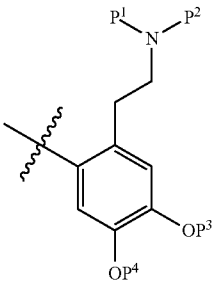

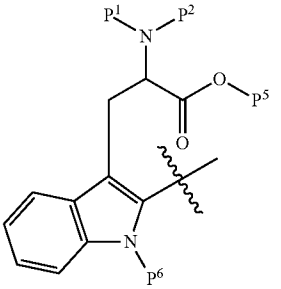

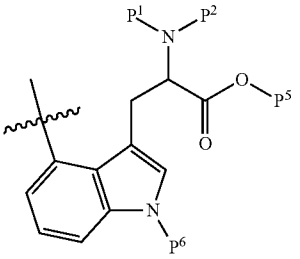

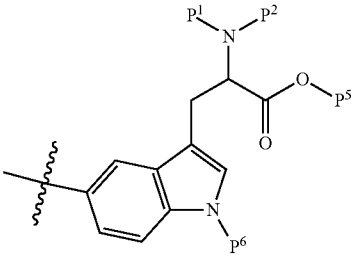

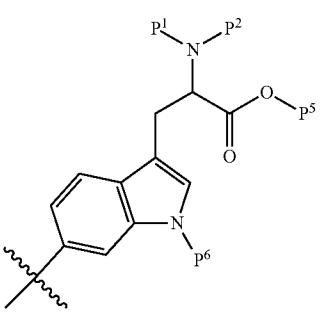

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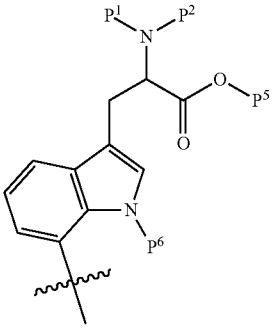

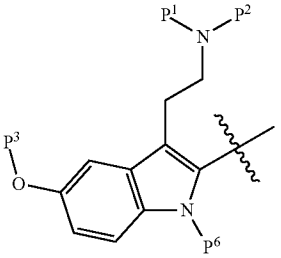

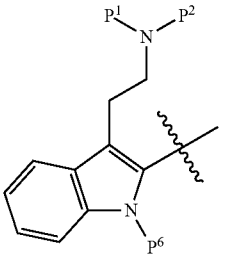

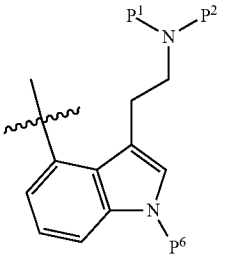

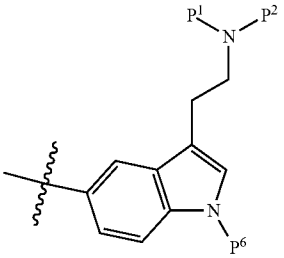

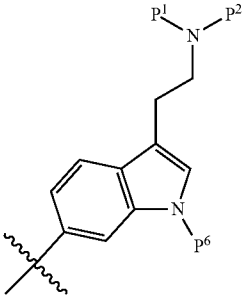

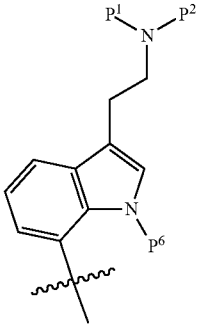

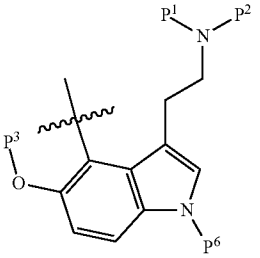

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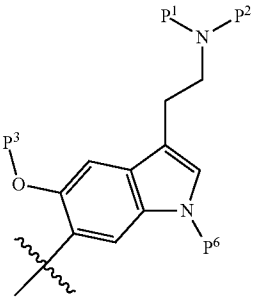

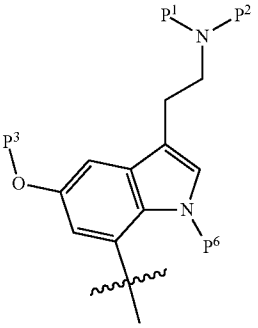

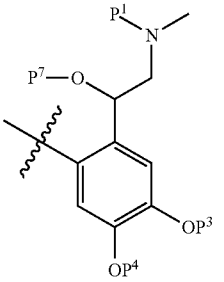

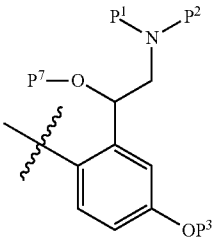

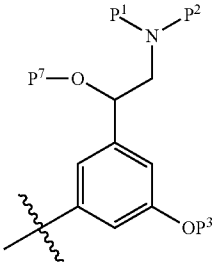

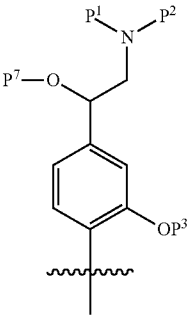

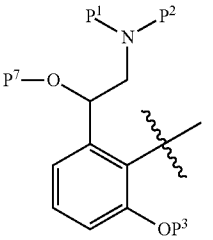

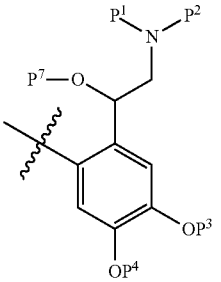

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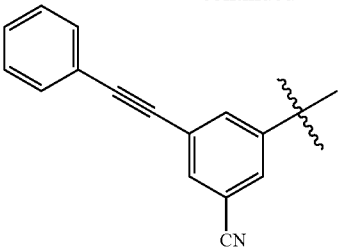

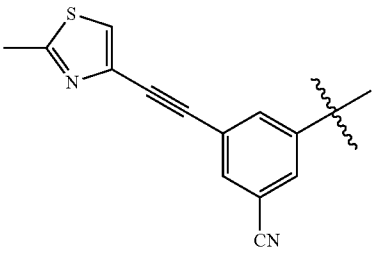

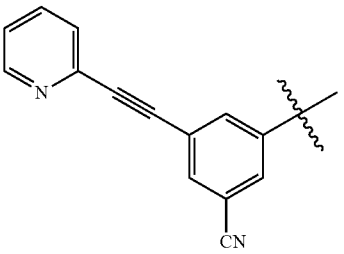

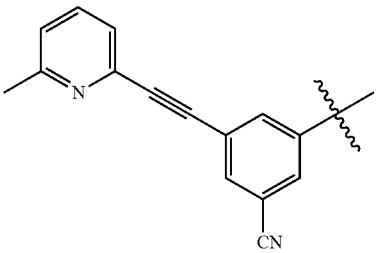

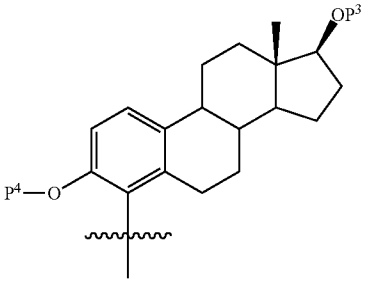

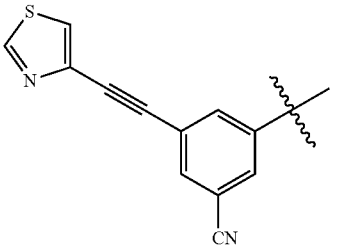

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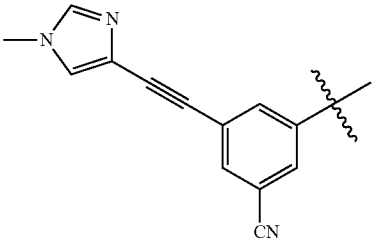
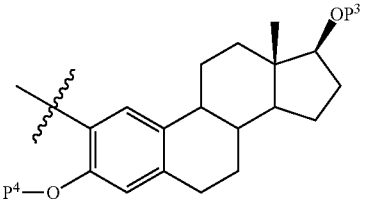




wherein:

each of P^1, P^2 and P^6 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

each of P^3, P^4, and P^7 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

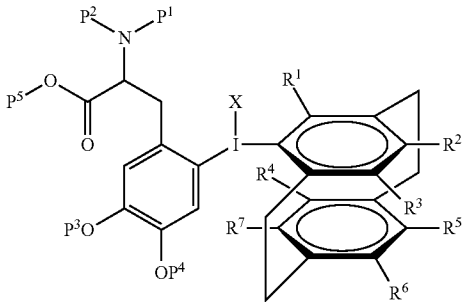
P^5 is a carboxylic acid protecting group.

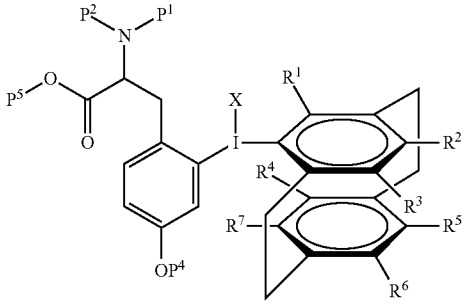
Protecting groups as described herein can be a temporary substituent which protects a potentially reactive functional group from undesired chemical transformations. The choice of the particular protecting group employed is well within the skill of one of ordinary skill in the art. A number of considerations can determine the choice of protecting group including, but not limited to, the functional group being protected, other functionality present in the molecule, reaction conditions at each step of the synthetic sequence, other protecting groups present in the molecule, functional group tolerance to conditions required to remove the protecting group, and reaction conditions for the thermal decomposition of the compounds provided herein. The field of protecting group chemistry has been reviewed (Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 2.sup.nd ed.; Wiley: N.Y., 1991).

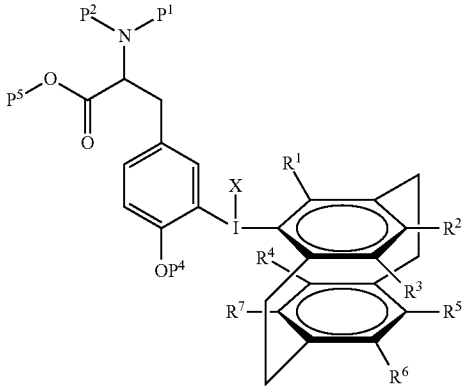
A nitrogen protecting group can be any temporary substituent which protects an amine moiety from undesired chemical transformations. Examples of such protecting groups include, but are not limited to allylamine, benzylamines (e.g., bezylamine, p-methoxybenzylamine, 2,4-dimethoxybenzylamine, and tritylamine), acetylamide, trichloroacetammide, trifluoroacetamide, pent-4-enamide, phthalimides, carbamates (e.g., methyl carbamate, t-butyl carbamate, benzyl carbamate, allyl carbamates, 2,2,2-trichloroethyl carbamate, and 9-fluorenylmethyl carbamate), imines, and sulfonamides (e.g., benzene sulfonamide, p-toluenesulfonamide, and p-nitrobenzenesulfonamide).

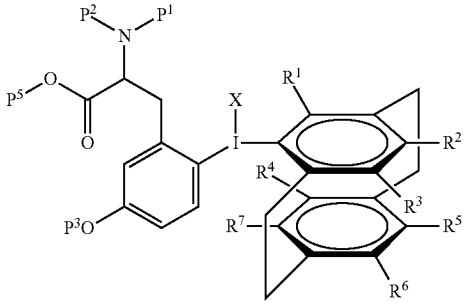
An oxygen protecting group can be any temporary substituent which protects a hydroxyl moiety from undesired chemical transformations. Examples of such protecting groups include, but are not limited to esters (e.g., acetyl, t-butyl carbonyl, and benzoyl), benzyl (e.g., benzyl, p-methoxybenzyl, and 2,4-dimethoxybenzyl, and trityl), carbonates (e.g., methyl carbonate, allyl carbonate, 2,2,2-trichloroethyl carbonate and benzyl carbonate) ketals, and acetals, and ethers.

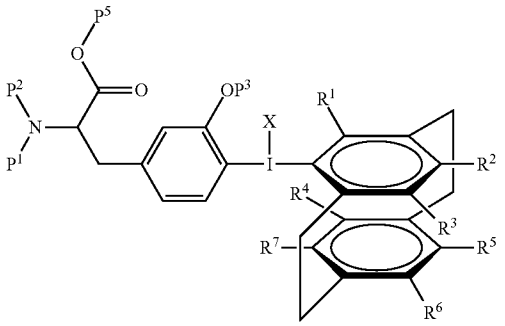
In some embodiments, the compound of Formula (1) can be selected from the group consisting of:











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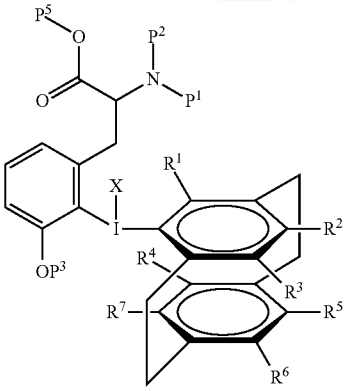


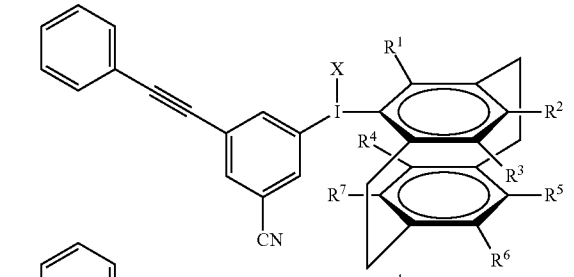
wherein:

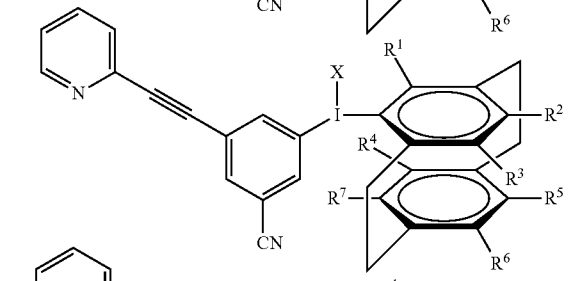
each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

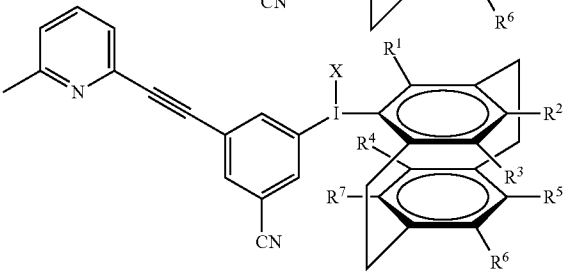
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

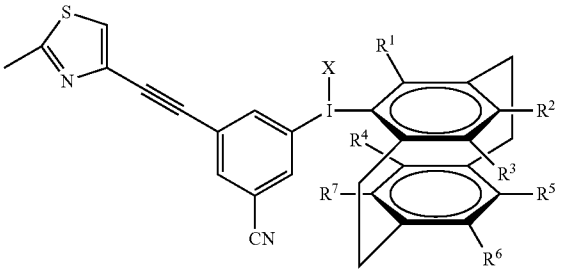
P^5 is a carboxylic acid protecting group.

In some cases, the compound of Formula (1) is selected from the group consisting of:









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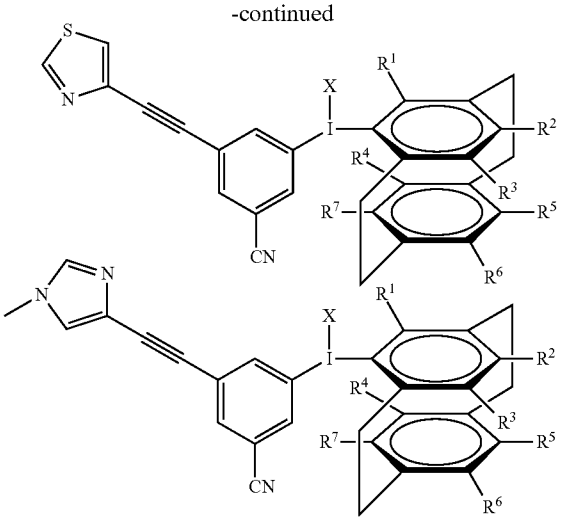
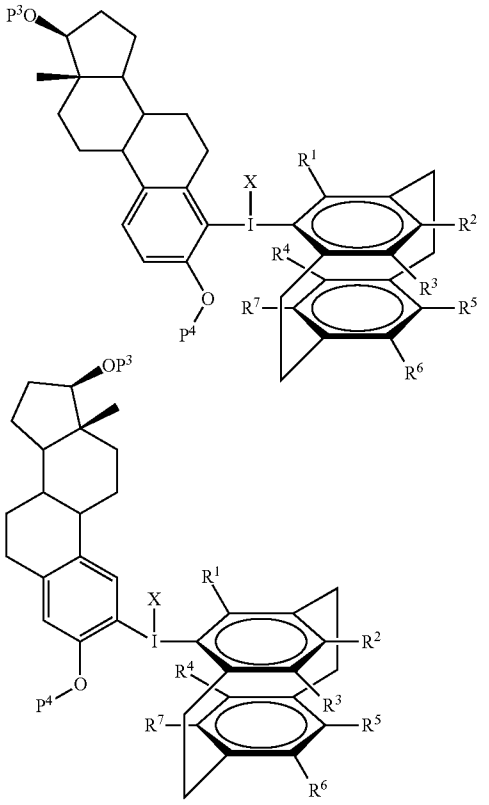


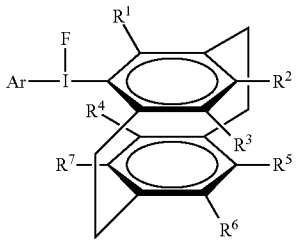
A compound of Formula (1) can also be selected from the group consisting of:



wherein:

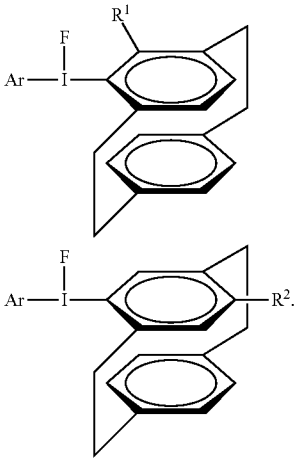
each of P^3 and P^4 are independently an alcohol protecting group.

Also provided herein is a compound of Formula (4):



(4)

wherein Ar, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 are as described above. For example, the compound of Formula (4) can be a compound of Formula (4A) or 4(B):

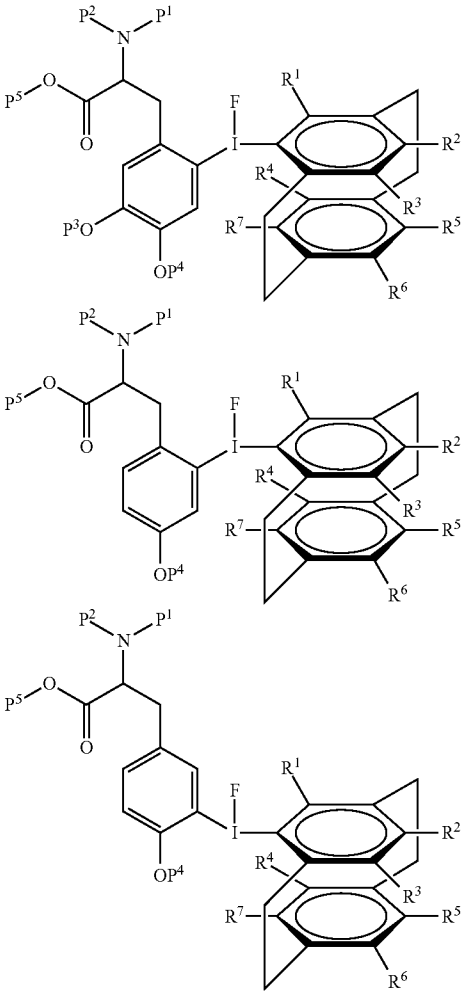


(4A)

(4B)

In some embodiments, F is ^{18}F.

The compound of Formula (4) can be selected from the group consisting of:



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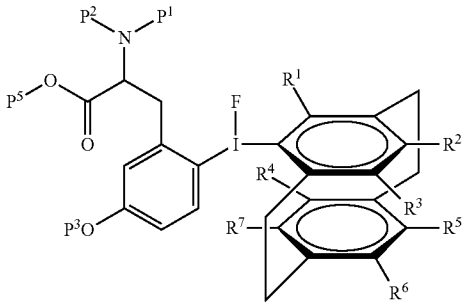
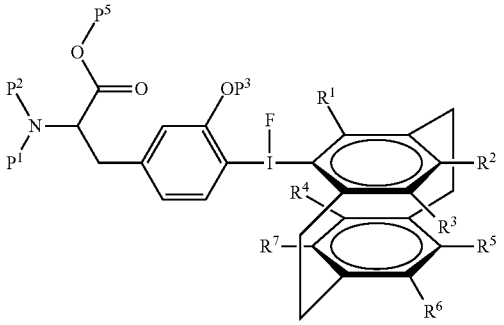
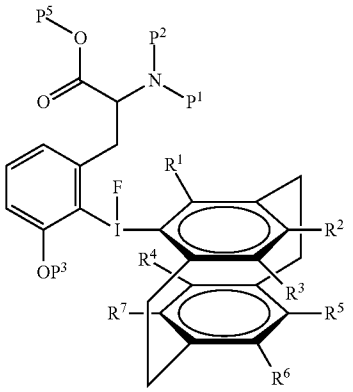






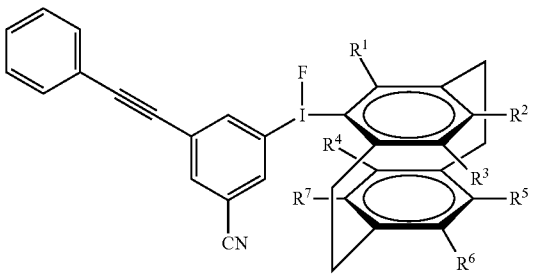
wherein:

each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

In some embodiments, the compound of Formula (4) is selected from the group consisting of:



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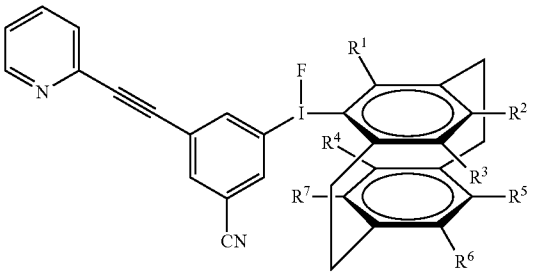
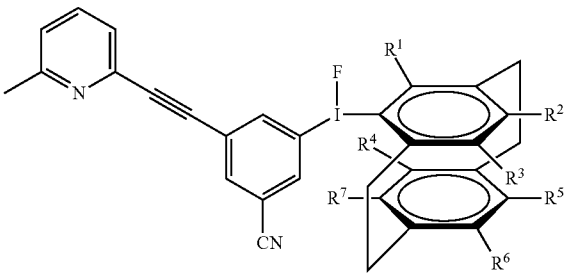
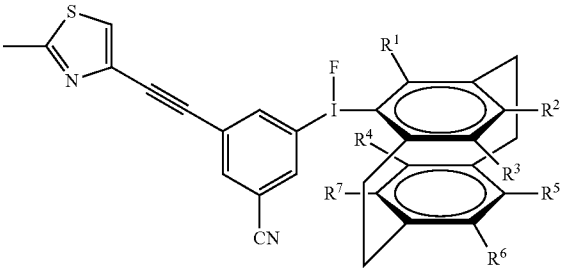
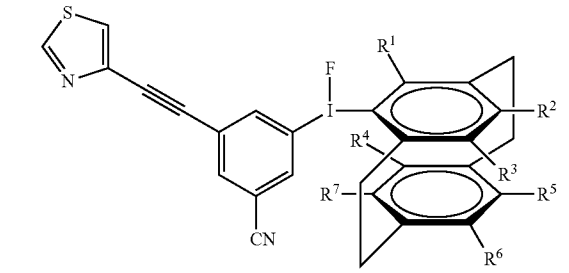
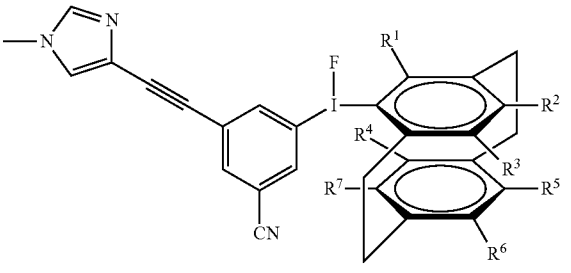
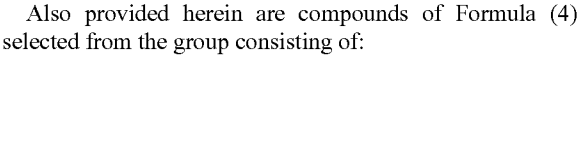




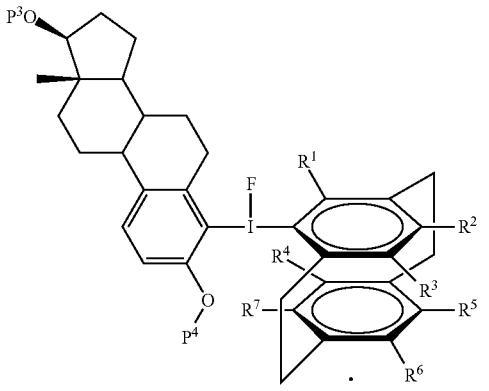


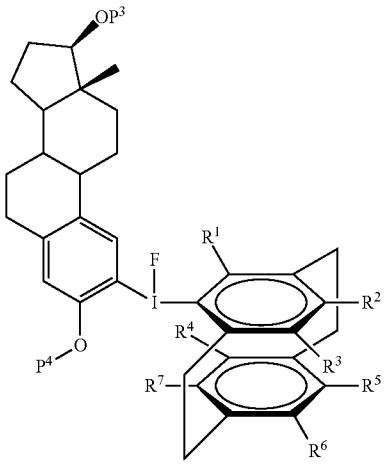






Also provided herein are compounds of Formula (4) selected from the group consisting of:





wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

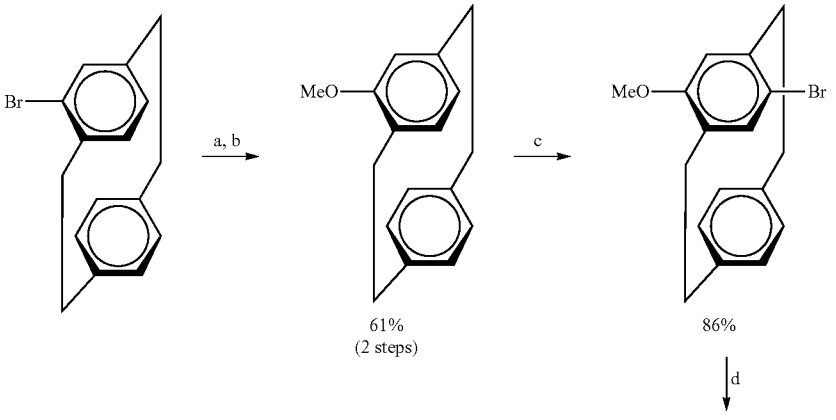
The iodonium cyclophane compounds described herein can be prepared from commercially available starting materials using various methods known to those of ordinary skill in the art. The method used for synthesizing the compounds will depend on the functionality present on the Ar moiety. Potentially reactive functional groups present on the Ar moiety can be masked using a protecting group prior to the synthesis of the iodonium cyclophane compound. The particular method employed for preparing the iodonium cyclophane compounds will be readily apparent to a person of ordinary skill in the art.

For compounds that bear sensitive functionality on the accepting group (Ar), organometallic reagents that feature more covalent (more stable) C-M bonds can be used. For example, organometallic compounds including tin, boron, and zinc. If there is no functional group incompatibility, more basic organometallic reagents (organolithium, Grignard, etc.) can be used to prepare the iodonium cyclophane salts.

In some embodiments, an unsymmetrical iodonium cyclophane salt can be prepared through the reaction of an arylzinc halide (e.g., arylzinc chloride). Arylzinc halide salts can be prepared by methods known by those of skill in the art. For example, 4-Bromo-[2.2]paracyclophane can be lithiated (e.g., using t-BuLi, Et_2O, −78° C.) and transmetalated with anhydrous zinc chloride to prepare an arylzinc chloride. This salt can then be reacted with an aryl iodonium salt (e.g., 2,5-dimethylphenyliodonium diacetate) at low temperature (e.g., −40° C.) to prepare a compound of Formula (I). Ion exchange or other method can be used to alter the nucleophile (e.g., X) as desired.

For example, a compound of Formula (1) can be made using the reaction shown in Scheme 1.

Scheme 1.



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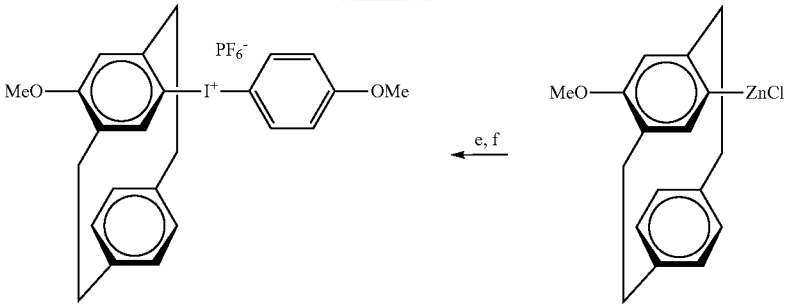


5
56%
(3 steps)

a. 1. t-BuLi, Et_2O, -78° C., 2. $B(OMe)_3$, 3. H_2O_2, NaOH, H_2O;
b. K_2CO_3, CH_3I, CH_3CN, 80° C.;
c. NBS, CH_2Cl_2;
d. 1. t-BuLi, Et_2O, -78° C., 2. $ZnCl_2$; and
e. 1. 4-$MeOC_6H_4I(OAc)_2$, CH_3CN, -40° C., f. $NaPF_6$, H_2O.

Additional examples are provided in the Examples section below.

Persons skilled in the art will be aware of variations of, and alternatives to, the processes described which allow the compounds defined herein to be obtained.

It will also be appreciated by persons skilled in the art that, within certain of the processes described, the order of the synthetic steps employed may be varied and will depend inter alia on factors such as the nature of other functional groups present in a particular substrate, the availability of key intermediates, and the protecting group strategy (if any) to be adopted. Clearly, such factors will also influence the choice of reagent for use in the synthetic steps.

The skilled person will appreciate that the iodonium cyclophane compounds described could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example US 2007/0092441, or using standard textbooks such as "Comprehensive Organic Transformations—A Guide to Functional Group Transformations", R C Larock, Wiley-VCH (1999 or later editions) and "Science of Synthesis", Volume 31a, 2007 (Houben-Weyl, Thieme)

Methods of Preparing Substituted Aryl and Heteroaryl Ring Systems

Provided herein are methods of preparing substituted aryl and heteroaryl ring systems using iodonium cyclophane compounds, salts, and intermediates. For example, iodonium cyclophane salts and iodonium cyclophane fluorides, as provided herein, can undergo decomposition to prepare an aryl fluoride.

For example, provided herein is a method of making a compound of Formula (2):

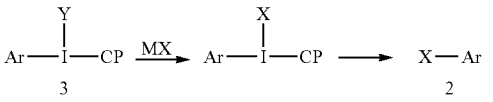
Ar—X

wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system; and

X is a moiety wherein the pKa of the acid H—X is less than 12. In some embodiments, a compound of Formula (2) can be prepared as shown in Scheme 2.

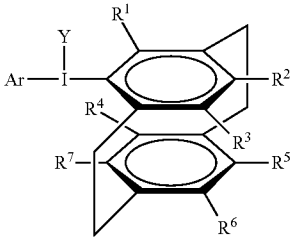
Scheme 2.



wherein CP is a cyclophane ligand as described herein.

In some embodiments, a compound of Formula (2) can be prepared by heating a solution having a compound MX, wherein M is a counter ion and X is as defined above, and a compound of Formula (3):

(3)



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system as described above;

Y is a leaving group;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_m$, $—SR^8$, $—SOR^8$, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$, $NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted

cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, and $(L)_p$-Z, or one or more of R^2 and R^3, R^4 and R^7, and R^5 and R^6 come together to form a fused cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring system;

each m, n, and p are independently an integer from 0 to 10;

each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

L is a linker; and

Z is a solid support.

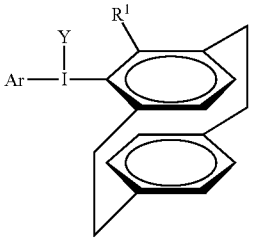
Substituted aryls and heteroaryls which are prepared using the methods described herein can have an X moiety which includes any moiety in which the pKa of H—X (i.e., the conjugate acid of X) is less than about 12. In some cases, X comprises a radioactive isotope (e.g., ^{18}F, ^{123}I, ^{131}I, ^{32}P, and ^{33}P). In some embodiments, X can be chosen from halide, aryl carboxylate, alkyl carboxylate, phosphate, phosphonate, phosphonite, azide, thiocyanate, cyanate, phenoxide, triflate, trifluoroethoxide, thiolates, and stabilized enolates. For example, X can be fluoride, chloride, bromide, iodide, trifluoroacetate, benzoate, and acetate. In some embodiments, X is fluoride. In some embodiments, X is a radioactive isotope of fluoride (e.g., ^{18}F).

Y can be any suitable leaving group. In some embodiments, Y is a weakly coordinating anion (i.e., an anion that coordinates only weakly with iodine). For example, Y can be the conjugate base of a strong acid, for example, any anion for which the pKa of the conjugate acid (H—Y) is less than about 1. In some embodiments, Y is chosen from triflate, mesylate, nonaflate, hexaflate, toluene sulfonate(tosylate), nitrophenyl sulfonate(nosylate), bromophenyl sulfonate(brosylate), perfluoroalkyl sulfonate (e.g., perfluoro C_{2-10} alkyl sulfonate), tetraphenylborate, hexafluorophosphate, trifluoroacetate, perfluoroalkylcarboxylate, tetrafluoroborate, perchlorate, hexafluorostibate, hexachlorostibate, chloride, bromide, and iodide. In some embodiments, a slightly more basic leaving group such as acetate or benzoate may be used.

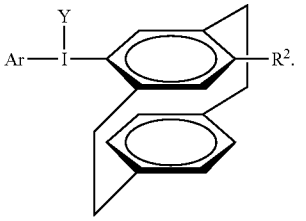
The counter ion M can be any suitable cation for the desired X. The choice of the source of X, and accordingly M, is readily within the knowledge of one of ordinary skill in the art. For example, M can be chosen from an alkali metal, alkaline earth metal and transition metal salts such as, for example, calcium, magnesium, potassium, sodium and zinc salts. Metal cations may also be complexed to cryptands or crown ethers to enhance their solubility and to labilize the X moiety. M can also include organic salts made from quaternized amines derived from, for example, N,N' dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. In some embodiments, M can be a lithium, sodium, potassium, or cesium with cryptands or crown ethers, a tetrasubstituted ammonium cation, or phosphonium cation. When X is fluoride, the choice of fluoride source is also readily within the knowledge of one of ordinary skill in the art. A variety of fluoride sources can be used in the preparation of the fluorinated aryl and heteroaryl compounds as provided herein, including but not limited to NaF, KF, CsF, tetrabutylammonium fluoride, and tetramethylammonium fluoride. In certain instances the choice of fluoride source will depend on the functionality present on the compound of Formula (3).

For the compounds of Formula (2) and (3), Ar, R^1, R^2, R^3, R^4, R^5, R^6, and R^7 can be as described above for the compounds of Formula (1) and (4). For example, a compound of Formula (3) can be a compound of Formula (3A) or a compound of Formula (3B)

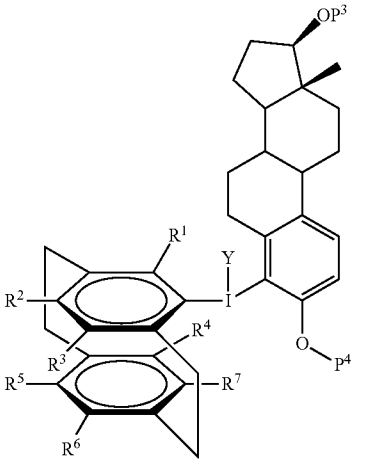
(3A)

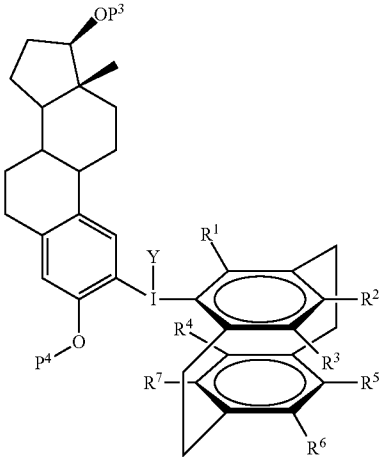


(3B)



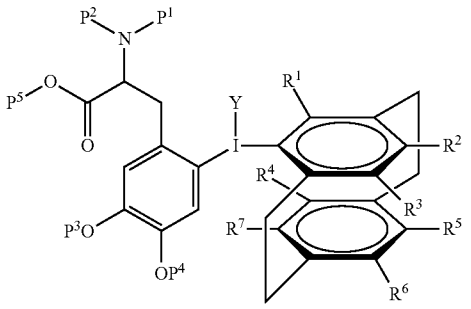
In some embodiments, the compound of Formula (3) is chosen from:





wherein each of P^3 and P^4 are independently an alcohol protecting group.

In some cases, the compound of Formula (3) is:

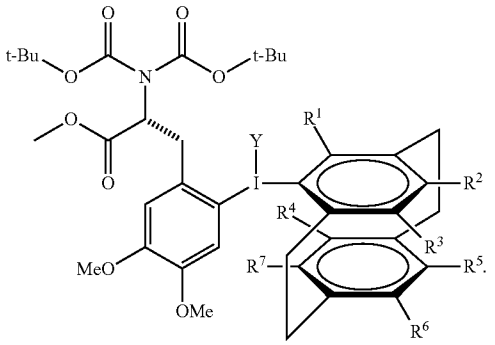


wherein:

each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

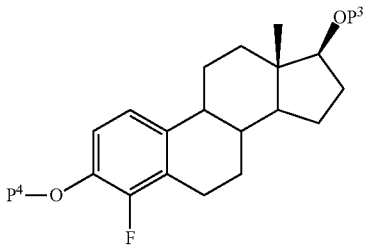
P^5 is a carboxylic acid protecting group. For example, the compound of Formula (3) is:



The methods described above can be useful in the preparation of fluorinated aryl and heteroaryl ring systems. In particular, the methods can be used to prepare radiolabeled fluorinated aryl and heteroaryl ring systems (e.g., PET radiotracers). Accordingly, provided herein is a method for making a compound of Formula (5):

wherein Ar is a substituted or unsubstituted aryl or heteroaryl ring system as described herein. The method can include heating a solution comprising a compound MF, wherein M is a counter ion, and a compound of Formula (3). In some embodiments, F is ^{18}F.

A compound according to Formula (2) or (5) can be chosen from:



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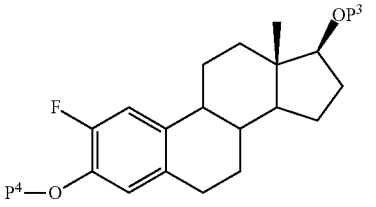
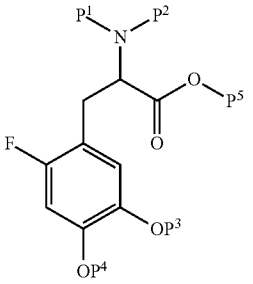


wherein each of P^3 and P^4 are independently an alcohol protecting group.

In some embodiments, a compound of Formula (2) or (5) is:

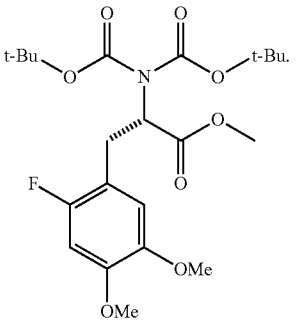


wherein:

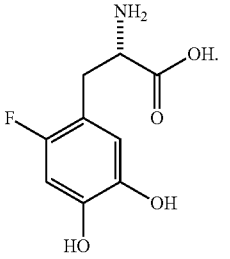
each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

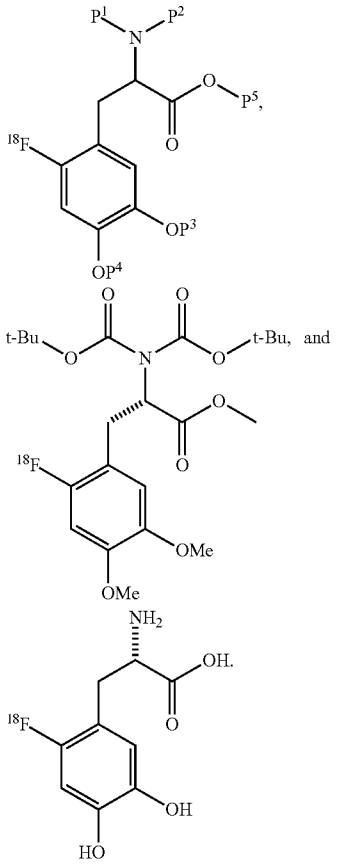
P^5 is a carboxylic acid protecting group. For example, the compound of Formula (2) or (5) can be:



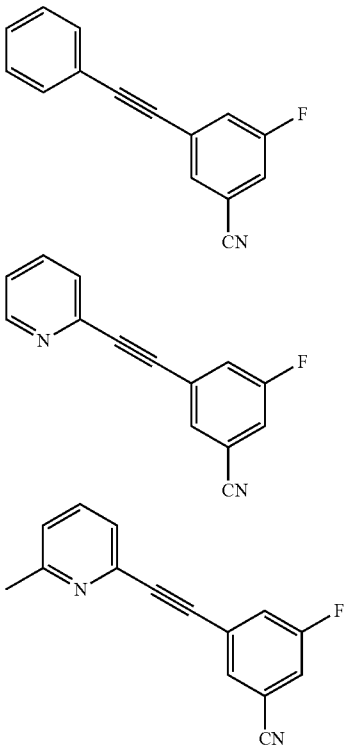
In some embodiments, a compound of Formula (2) or (5) is:



For example, the compound can be chosen from:



In some embodiments, a compound of Formula (2) or (5) can be



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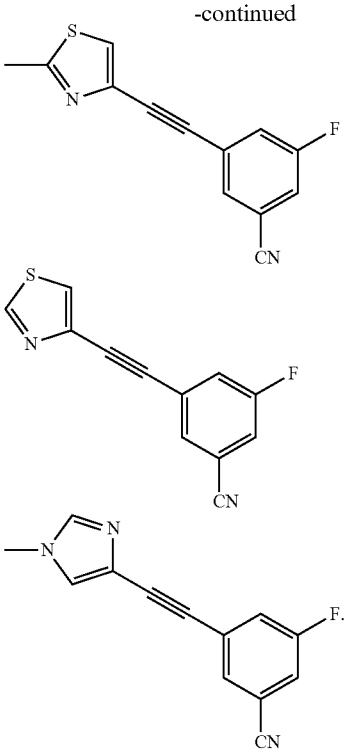


A nonpolar solvent can be any solvent having a dielectric constant of less than about 10. For example, a nonpolar solvent can be chosen from benzene, toluene, o-xylene, m-xylene, p-xylene, ethyl benzene, carbon tetrachloride, hexane, cyclohexane, fluorobenzene, chlorobenzene, nitrobenzene, and mixtures thereof. In some embodiments, the nonpolar solvent is selected from benzene, toluene, cyclohexane, and mixtures thereof In some embodiments the nonpolar solvent is a mixture, for example a mixture of cyclohexane and toluene.

A polar solvent is a solvent having a dielectric constant greater than about 10. In some embodiments, the polar solvent is a polar aprotic solvent, such as acetonitrile, acetone, dichloromethane, ethyl acetate, tetrahydrofuran, dimethylformamide, 1,2-difluorobenzene, benzotrifluoride, and mixtures thereof In some embodiments, the polar aprotic solvent is acetonitrile.

The methods described herein can further include filtering the solution to remove insoluble material prior to heating. In some embodiments, the insoluble material is a salt. In some cases, the solvent can be removed from the filtrate prior to heating. For example, the solvent can be removed and the filtrate can be dissolved in another solvent prior to heating. In some cases, the method can also include removing salt by chromatography (e.g., gel permeation chromatography). For example, if a polar solvent is used, it may be desirable to remove unwanted salts by chromatography prior to heating.

Heating can be accomplished by conventional means (e.g., heating bath, oven, heat gun, hot plate, Bunsen burner, heating mantle, and the like), by the use of a microwave, or by flash pyrolysis. Typically, the reaction mixture is heated at a temperature ranging from about 25° C. to about 250° C. (e.g., between about 80° C. to about 200° C., 100° C. to about 200° C., about 120° C. to about 170° C., about 120° C. to about 160° C., about 120° C. to about 150° C., and about 130° C. to about 150° C.). In some embodiments, the reaction mixture is heated to about 140° C.

Heating can occur for any time necessary to complete the reaction. For example, heating can occur for from about 1 second to about 25 minutes (e.g., from about 1 second to about 5 second; from about 1 second to about 10 seconds; from about 1 second to about 30 seconds; from about 1 second to about 1 minute; from about 1 second to about 2 minutes; from about 1 second to about 5 minutes; from about 1 second to about 8 minutes; from about 1 second to about 15 minutes; from about 1 second to about 20 minutes; from about 10 second to about 25 minutes; from about 30 seconds to about 25 minutes; from about 1 minute to about 25 minutes; from about 5 minutes to about 25 minutes; from about 10 minutes to about 25 minutes; from about 22 minutes to about 25 minutes; from about 5 to about 30 seconds; from about 30 seconds to about 2 minutes; from about 2 minutes to about 5 minutes; from about 5 minutes to about 10 minutes; from about 5 minutes to about 15 minutes; from about 3 minutes to about 8 minutes; from about 8 minutes to about 16 minutes; and from about 12 minutes to about 20 minutes). In some embodiments, heating can occur for from about 1 second to about 15 minutes.

In the methods described herein, a pressure tube or other reinforced closed system can be used in instances where the desired temperature is above the boiling point of the solvent utilized.

The reaction can be conducted in the presence of an inert gas such as nitrogen or argon. In some embodiments, steps are taken to remove oxygen and/or water from the reaction solvent and starting materials. This can be accomplished by a number of methods including distillation of solvents in the presence of agents that react with and/or sequester water and under an atmosphere of inert gas, and purging the reaction vessel with an inert gas.

The methods described herein can be used when MX (e.g., MF) is reacted in an amount ranging from about 1 picomole to about 10 millimoles (e.g., about 1 picomole to about 5 millimoles; about 1 picomole to about 1 millimole; about 1 picomole to about 500 micromoles; about 1 picomole to about 100 micromoles; about 1 picomole to about 50 micromoles; about 1 picomole to about 5 micromoles; about 1 picomole to about 1 micromole; about 1 picomole to about 500 nanomoles; about 1 picomole to about 100 nanomoles; about 1 picomole to about 50 nanomoles; about 1 picomole to about 5 nanomoles; about 1 picomole to about 1 nanomole; about 100 picomoles to about 10 millimoles; about 500 picomoles to about 10 millimoles; about 1 nanomole to about 10 millimoles; about 50 nanomoles to about 10 millimoles; about 100 nanomoles to about 10 millimoles; about 500 nanomoles to about 10 millimoles; about 1 micromole to about 10 millimoles; about 50 micromoles to about 10 millimoles; about 100 micromoles to about 10 millimoles; about 500 micromoles to about 10 millimoles and about 1 millimole to about 10 millimoles). In some embodiments, MX is reacted in the sample in an amount of less than about 10 millimoles. In many cases, the compound of Formula (3) is used in an excess when compared to the amount of MX present in the sample. In some embodiments, the reaction mixture having MX further contains additional compounds which may be present in an excess compared to MX. For example, the additional compounds may be present in more than one million fold excess compared to MX.

EXAMPLES

General Methods

Synthesis.

All materials were obtained from commercial sources and used as received unless otherwise noted. Zinc chloride melted under dynamic vacuum before use. Diethyl ether was distilled under reduced pressure from sodium/benzophenone. Tetrabutylammonium azide ($TBAN_3$), tetrabutylammonium thiocyanate (TBASCN), sodium phenoxide (NaOPh), sodium thiophenoxide (NaSPh), and sodium trifluoroethoxide ($NaOCH_2CF_3$) were dried at room temperature in a drying pistol (charged with P_20_5) under dynamic vacuum for one week. Acetonitrile and d_3-acetonitrile were heated at reflux over P_2O_5, distilled into flame-dried storage tubes, and transferred to an inert atmosphere glove box. Benzene and d_6-benzene were heated at reflux over CaH_2 overnight and distilled directly into flame-dried storage tubes under dry nitrogen. Tetrahydrofuran (THF) was dried over Na/benzophenone and distilled into a flame dried storage flask under dry nitrogen. All glassware, syringes, and NMR tubes were oven dried (140° C.) for more than 24 h before they were transferred into the glove box for use. All NMR experiments reported here were performed using Bruker spectrometers (400, 500, and 600 MHz) at the University of Nebraska-Lincoln. Yields from NMR scale reactions were determined by using the residual solvent peak as an internal standard. Additional product analyses were performed by GC-MS.

General Procedure for Reductive Elimination Reactions.

In a N_2 charged glove box, 0.025 mmol of an iodonium salt was dissolved in 0.3 mL of dry d_3-acetonitrile. The solution was combined with 0.3 mL d_3-acetonitrile solution of 1 equiv. of the appropriate salt ($TBAN_3$ (7.1 mg), TBASPh (8.8 mg), NaOPh (2.9 mg) $NaOCH_2CF_3$ (3.1 mg)). The mixture was transferred into a J-Young NMR tube, sealed, taken out of the glove box and an initial NMR spectrum was taken. The NMR tube was wrapped with aluminum foil and put into a 45° C. oil bath. (For acetate and thiocyanate, more vigorous conditions were required. The solutions containing TBAOAc (15 mg) and TBASCN (7.5 mg) were heated in an 80° C. oil bath.) The progress of the reaction was monitored by ^1H NMR until no I(III) species was left. Product analysis was performed by ^1H NMR and GC-MS.

Calculations.

All calculations were performed using the Gaussian suite of programs and visualization was performed with GaussView. Ground state geometries were identified after driving the C-C-I-H dihedral angle through a full range of motion. Structures were optimized and their energies calculated using DFT B3LYP/DGDZVP methods. Frequency calculations on minimized structures were performed to make the zero point energy and thermal corrections. Transition states were optimized at the same computational level.

Example 1

Computational study of [2,2]paracyclophan-4-yl iodonium salts

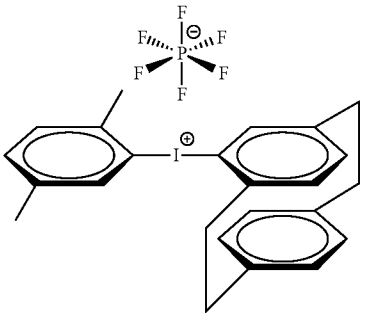
Azide transfer in diaryliodonium salts was investigated through a computational study as described above. Ground and transition state energies were calculated for a highly simplified model of azide substitution, loss of HI from the HIN3Ar complexes of p-xylene and [2.2]paracyclophane. For this study, diaryliodonium azides were used as they are known to undergo reductive elimination at or near room temperature (see J. J. Lubinkowski et al., *J. Org. Chem.* 1978, 43, 2432; and V. V. Grushin et al., *Izv. Akad. Nauk SSSR, Ser. Khim.* 1984, 2332), and because the small azide nucleophile has a relatively modest steric demand. The results of the computational study are show in FIG. **1**.

Inspection of FIG. **1** shows that movement from the ground state to the transition state geometries for azide substitution is

accompanied by ipso carbon rehybridization and deflection of the HI group out of the plane. For the xylyl derivative the C4-C1-I angle is 161.9°. However, in the [2.2]paracyclophan-4-yl transition state structure the significant steric demand of the second ring in the planar chiral ligand inhibits out of plane movement of the iodine atom (C4-C1-I angle is)167.2°. This structural difference is associated with an energetic penalty; the calculated free energy of activation for reductive elimination of HI from the p-xylene salt is 13.7 kcal/mol, while the barrier for the cyclophane derivative is 4.8 kcal/mol higher. These results indicate that an increase in steric demand above the plane of the aromatic ring destabilizes the reductive elimination transition state. For the [2.2]paracyclophan-4-yl iodonium salt, this effect is sufficiently large to provide stereoelectronic control of unidirectional reductive elimination (SECURE).

Example 2

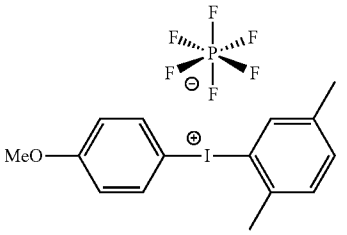
Preparation of ([2.2]paracyclophan-4-yl)(2',5'-dimethylphenyl)iodonium hexafluorophosphate (1)



In a 50 mL Schlenk tube under nitrogen, a stirred solution of 4-bromocyclophane (1 mmol, 282 mg) in 10 mL of anhydrous diethyl ether was cooled to −78° C. A solution of t-BuLi (1.7 M in pentane, 2.3 equiv.) was added dropwise and the resulting mixture was stirred at −78° C. for 20 minutes and then warmed to 0° C. and allowed to stir for an additional 20 min. The reaction mixture was cooled again to −78° C. before a solution of zinc chloride (200 mg, 1.5 mmol) in ether (10 mL) was added dropwise by cannula. After the addition, the reaction mixture was allowed to warm to room temperature over the course of one hour before the solvents were removed in vacuo. The remaining solid was dissolved in anhydrous CH_3CN and the solution was cooled to −40° C. and added dropwise to precooled (−40° C.) suspension of bis(acetyloxy)-(2,5-dimethylphenyl)-λ_3-iodane (350 mg, 1 mmol) in 10 mL of acetonitrile. The mixture was allowed to warm to room temperature over 30 minutes before the solvent was removed in vacuo. The resulting solid was washed with hexanes and then dissolved in aqueous acetonitrile. Addition of an aqueous $NaPF_6$ solution precipitated the product, which was extracted from the aqueous mixture with CH_2Cl_2. The organic layer was evaporated, dissolved in a minimal amount of CH_2Cl_2, precipitated with hexanes, filtered and dried in vacuo to yield 1 (105 mg, 18% yield).

Example 3

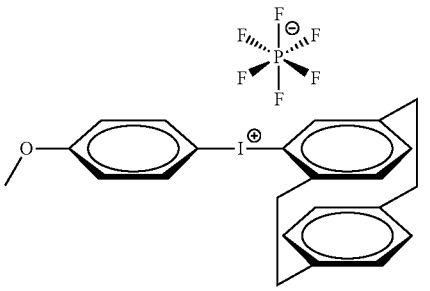
Preparation of (2,5-dimethylphenyl)(4'-methoxyphenyl)iodonium hexafluorophosphate (2)



In a N_2 charged glove box, 1-(diacetoxyiodo)-4-methoxybenzene (352 mg, 1 mmol) was dissolved in 1.5 mL of dry acetonitrile. The solution was combined with a solution of p-toluenesulfonic acid monohydrate (190 mg, 1 mmol) in 1.5 mL of dry acetonitrile. p-Xylene (117 mg, 1.1 mmol) was added and the mixture was allowed to stand at room temperature for 2 h. Water (10 mL) was added and the mixture was extracted (3×5 mL) with hexanes. The water layer was treated with $NaPF_6$ (502 mg, 3 mmol) and the white precipitate was extracted from the aqueous layer with CH_2Cl_2. Evaporation of the organic solvent followed by recrystallization from diethyl ether/dichloromethane gave 309 mg (65.2%) of (2,5-dimethylphenyl)-(4'-methoxyphenyl)iodonium hexafluorophosphate.

Example 4

Preparation of ([2.2]paracyclophan-4-yl)(4'-methoxyphenyl)iodonium hexafluorophosphate (3)

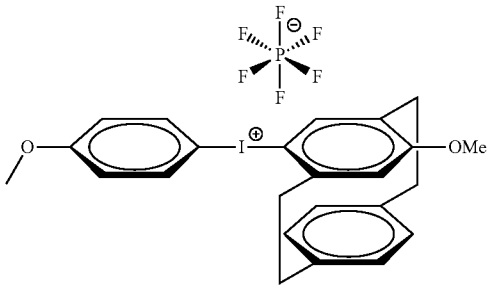


In a 50 mL Schlenk tube under nitrogen, a stirred solution of bromocyclophane (1 mmol, 282 mg) in 10 mL of anhydrous diethyl ether was cooled to −78° C. A solution of t-BuLi (1.7 M in pentane, 2.3 equiv.) was added dropwise and the resulting mixture was stirred at −78° C. for 20 minutes and then warmed to 0° C. and allowed to stir for an additional 20 min. The reaction mixture was cooled again to −78° C. before a solution of zinc chloride (200 mg, 1.5 mmol) in ether (10 mL) was added dropwise by cannula. After the addition, the reaction mixture was allowed to warm to room temperature over the course of one hour before the solvents were removed in vacuo. The remaining solid was dissolved in anhydrous CH_3CN and the solution was cooled to −40° C. and added dropwise to precooled (−40° C.) suspension of bis(acetyloxy)-(4-methoxyphenyl)-λ_3-iodane (352 mg, 1 mmol) in 10

mL of acetonitrile. The mixture was allowed to warm to room temperature over 30 minutes before the solvent was removed in vacuo. The resulting solid was washed with hexanes and then dissolved in aqueous acetonitrile. Addition of an aqueous $NaPF_6$ solution precipitated the product, which was extracted from the aqueous mixture with CH_2Cl_2. The organic layer was evaporated, dissolved in a minimal amount of CH_2Cl_2, precipitated with hexanes, filtered and dried in vacuo (225 mg, 38.4% yield).

Example 5

Preparation of (7-methoxy[2.2]paracyclophanyl)(4'-methoxyphenyl)iodonium hexafluorophosphate (4)



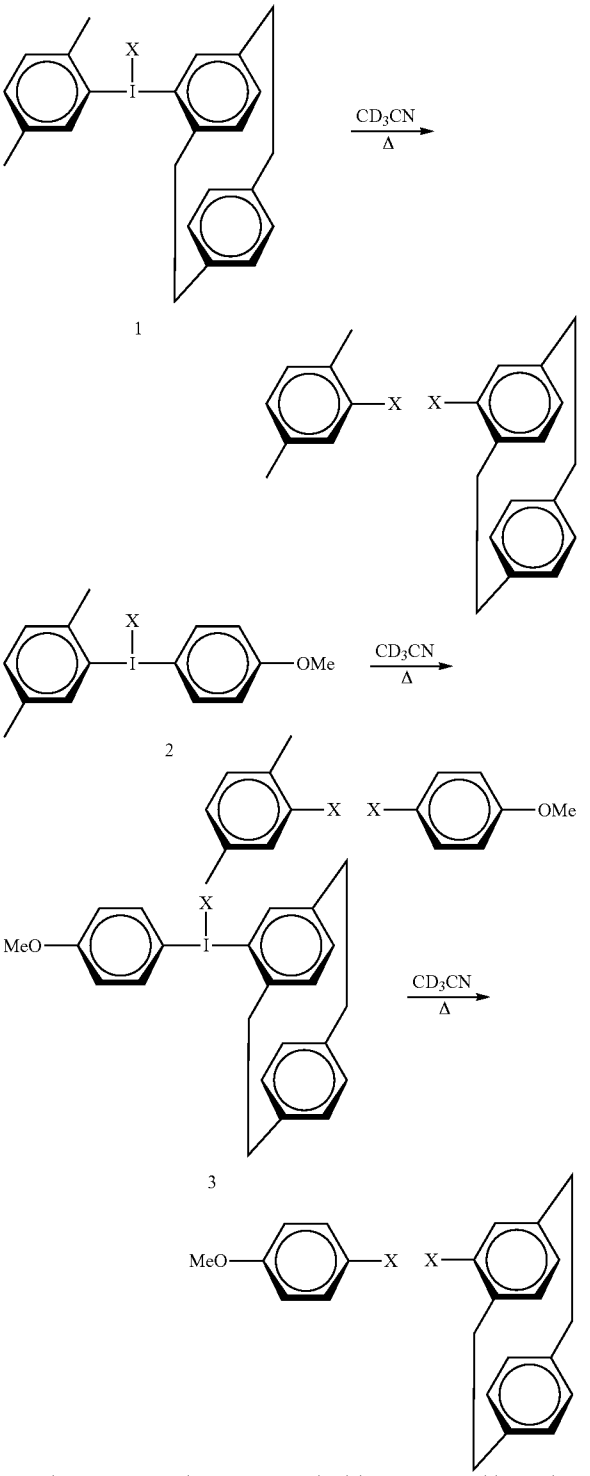
In a 100 mL Schlenk tube, 4-methoxy-7-bromo[2.2]paracyclophane (1.26 mmol, 400.6 mg) was dissolved in 25 mL of distilled ether and cooled to −78° C. To the cooled solution, 1.7M t-butyl lithium (3.16 mmol, 1.85 mL) was added dropwise and the stirred solution was held at −78° C. for 1 hour. A solution of anhydrous zinc chloride (1.51 mmol, 206.1 mg) in 10 mL of diethyl ether was added dropwise to the cooled solution. The mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residual solid (organozinc chloride reagent and lithium salts) was taken up in anhydrous acetonitrile and cooled to −40° C. before a solution of 4-methoxy(diacetoxyiodo)benzene (1.89 mmol, 665.5 mg) in acetonitrile (10 mL) was added in a dropwise fashion. After 1 hour at −40° C., the mixture was warmed to room temperature and the solvent was removed under reduced pressure. Deionized water and sodium hexafluorophosphate (410 mg) were added, followed by 50 mL of dichloromethane. The mixture was transferred to a separatory funnel and the organic phase was separated. The solvent was removed by rotary evaporation and the remaining solid was dissolved in 5 mL of dichloromethane and dripped into 150 mL hexanes. The precipitate was aged for one hour, collected by gravity filtration, and dried in vacuo to yield a colorless salt (55.6%, 431.7 mg).

Example 6

Reductive Elimination from Iodonium Salts

To compare the directing effects of the electronically similar p-xylyl and [2.2]paracylcophan-4-yl groups, a series of unsymmetrical iodonium salts were prepared by the methods described in Examples 2-4 (see Table 1) and arene functionalization by various nucleophiles (X) was investigated (see Scheme 3). The salts underwent reductive elimination using the general methods described above.

Scheme 3.



When compound 1 was treated with $TBAN_3$ and heated at 45° C. in CD_3CN (0.04 M), conversion of the diaryliodonium azide was complete within a few hours. The azidoxylene was formed exclusively in excellent yield, and no azidocyclophane was observed at the detection limit of ^1H NMR spectroscopy. This unidirectional elimination was also observed with thiocyanate, phenoxide, thiophenoxide, trifluoroethoxide, and acetate (Table 1). The observed selectivity (>99:1) corresponds to a difference in the free energies of activation ($DDG^{\ddagger}$) of at least 2.8 kcal/mol.

To provide context for the results obtained for compound 1, arene functionalization by various nucleophiles (X) in compound 2 was investigated. The regioselectivity observed during the reductive elimination of cyclophanyl-substituted diaryliodonium salts mirrors that of 4-methoxyphenyl derivatives (Table 1). The 4-methoxyphenyl moiety is one of the most effective, commonly employed directing group in diaryliodonium chemistry, perfect regioselectivity for arene functionalization, however, is not observed with this directing group. For the redox active thiophenoxide and phenoxide nucleophiles, some loss of regiocontrol was evident and functionalized anisoles were formed.

To test the relative directing group abilities of 4-methoxyphenyl and [2.2]paracyclophan-4-yl substituents, the unsymmetrical I(III) derivative of compound 3 were prepared from 4-methoxy(diacetoxyiodo)benzene (38% yield) and its thermal decomposition chemistry examined. More vigorous reaction conditions (80° C., CD_3CN) were necessary to promote speedy carbon-heteroatom bond formation with acetate and thiocyanate from 3 in comparison to 1 or 2. As can be seen from inspection of Table 1, the directing group ability of the [2.2]paracyclophane ligand is comparable or slightly superior to that of the 4-methoxyphenyl substituent on I(III).

TABLE 1

Yields of reductive elimination products from I(III) salts

X	1		2		3	
N_3	99<	0	99<	0	86	14
OAc	85	0	99<	0	68	31
OPh	87	0	96	4	51	40
OCH_2CF_3	82	0	80	0	19	39
SCN	99<	0	99<	0	81	18
SPh	98	0	95	5	43	52

As shown in Table 1, it appears that for oxygen or sulphur nucleophiles the directing group ability of the cyclophane ligand diminishes as nucleophile basicity and the driving force for functionalizing the more electron-poor ring increase. Such a trend is consistent with Hammond's postulate and a concerted, reductive elimination mechanism in which less steric strain is developed at the cyclophane ipso carbon atom as the reaction becomes more exergonic.

Example 7

Kinetics of Reductive Elimination

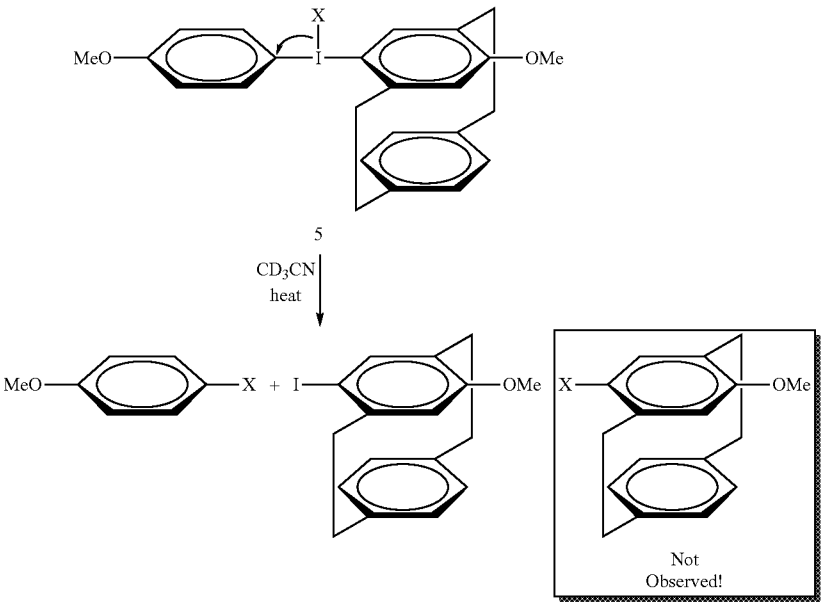
The kinetics of aryl azide formation from N_3 salts of 1, 2 and 3 were investigated to probe the relative steric and electronic contributions to the observed regioselectivity. The salts underwent reductive elimination using the general method described above. The observed rate constants for xylyl azide formation (CD_3CN, 45° C.) were 4.2×10^{-4} s^{-1}, 5.5×10^{-5} s^{-1}, and 3.3×10^{-6} s^{-1}, corresponding to free energies of activation of 21.7, 22.9, and 24.6 kcal/mol for the reactions of 1, 2 and 3, respectively. The fact that the rate constant for formation of azidoxylene is greater for 1 than 2 indicates that 4-iodo-[2.2]paracyclophane is a better leaving group than 4-iodoanisole. Since leaving group ability is correlated with the electron density on iodine in the aryl iodide being reductively eliminated, these kinetic data show experimentally that the [2.2]paracyclophane ligand is a more electron-poor aryl substituent than 4-methoxyphenyl and that steric destabilization of the transition state is responsible for the enhanced directing group ability of the [2.2]paracyclophane ligand.

Example 8

Reductive Elimination with Regiochemical Control

The reductive elimination of compound 4 with various nucleophiles (X) was studied. The salts underwent reductive elimination using the general method described above. This compound features an electron donating methoxy substituent para to the I(III) center.

Scheme 4.



X = N_3 96%
X = OAc 51%
X = OPh 84%
X = SCN 92%
X = SPh 82%

As shown in Scheme 4, only anisole substitution was observed after the thermal decomposition of the azide, acetate, phenoxide, thiocyanate, and thiophenoxide salts. However, a mixture of cyclophane- (30%) and anisole-substituted (60%) products was obtained from the reductive elimination of the 2,2,2-trifluoroethoxide salt of 4. The reason for the breakdown in regioselectivity was clear from the product analysis, which shows roughly equal amounts of 3- and 4-(2,2,2-trifluoroethoxy)anisole, as well as roughly equal amounts of the two CF_3CH_2O-substituted cyclophane regioisomers. This lack of selectivity and distribution of regioisomers is consistent with a change in mechanism to one involving benzyne intermediates. For this basic nucleophile, the strategy of raising the transition state energy for reductive elimination of the aryl iodide enables the benzyne reaction manifold to be competitive.

Example 9

Fluorination of (4-methoxyphenyl)-(5-methoxy-4-[2.2]paracyclophanyl)-iodonium hexafluorophosphate

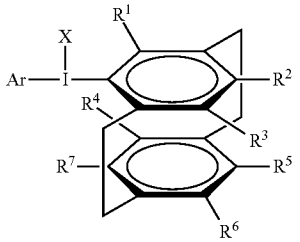
In a N_2 charged glove box, 12.3 mg of (4-methoxyphenyl)-4-[2.2]paracyclophanyliodonium hexafluorophosphate (0.02 mmol) was dissolved in 0.3 mL of dry acetonitrile, to which a solution of 1 mg anhydrous TMAF (1 equivalent) in 0.3 mL of dry acetonitrile was added dropwise. The solvent was evaporated, and the remainder was dissolved in 0.6 mL of d_6-benzene, passed through a 0.2 mm PTFE syringe filter, and transferred into a J-Young NMR tube. The tube was sealed, taken out of the box, and heated in a 140° C. oil bath for 15 minutes. Yields of fluorinated arenes were determined by ^1H and ^{19}F NMR spectroscopy and confirmed by GC-MS. 4-fluoroanisole was formed in 52% yield, 3-fluoroanisole in 24% yield, the rest of the fluoride ended up as unidentified inorganic species (singlet at −128.1 ppm and multiplets at −130.7 ppm in ^{19}F NMR).

For this salt, decomposition was also performed at 80° C., the reaction took 5 hours to finish and 4-fluoroanisole was formed in 66% yield, 3-fluoroanisole in 15% yield.

A number of embodiments of the invention have been described. Nevertheless, it will be understood that various modifications may be made without departing from the spirit and scope of the invention. Accordingly, other embodiments are within the scope of the following claims.

What is claimed is:

1. A compound of Formula (1):



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

X is either a moiety wherein the pKa of the acid H—X is less than 12 or a leaving group;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_m$, —SR^8, —SOR^8, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$, $NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

each m and n is independently an integer from 0 to 10; and

each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

2. The compound of claim **1**, wherein X comprises a radioactive isotope.

3. The compound of claim **1**, wherein X is selected from the group consisting of halide, aryl carboxylate, alkyl carboxylate, phosphate, phosphonate, phosphonite, azide, thiocyanate, cyanate, phenoxide, triflate, trifluoroethoxide, thiolates, and stabilized enolates.

4. The compound of claim **1**, wherein X is selected from the group consisting of: fluoride, chloride, bromide, iodide, triflate, trifluoroacetate, benzoate, acetate, phenoxide, trifluoroethoxide, cyanate, azide, thiocyanate, thiolates, phosphates, and stabilized enolates.

5. The compound of claim **4**, wherein X is fluoride.

6. The compound of claim **5**, wherein X is ^{18}F.

7. The compound of claim **1**, wherein X is selected from the group consisting of: triflate, mesylate, nonaflate, hexaflate, tosylate, nosylate, brosylate, perfluoroalkyl sulfonate, tetraphenylborate, hexafluorophosphate, trifluoroacetate, tetrafluoroborate, perchlorate, perfluoroalkylcarboxylate, chloride, bromide, and iodide.

8. The compound of claim **1**, wherein R^1 is selected from the group consisting of: —$(C_1$-$C_{10})$alkyl, —$(C_1$-$C_{10})$haloalkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, —O—$(C_1$-$C_{10})$alkyl, —C(O)—O—$(C_1$-$C_{10})$alkyl, aryl, and heteroaryl.

9. The compound of claim **8**, wherein R^1 is —O-$(C_1$-$C_{10})$alkyl.

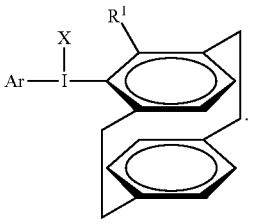
10. The compound of claim **9**, wherein R^1 is OCH_3.

11. The compound of claim **1**, wherein Ar is an electron rich aryl or heteroaryl ring system.

12. The compound of claim **11**, wherein Ar—H is more easily oxidized than benzene.

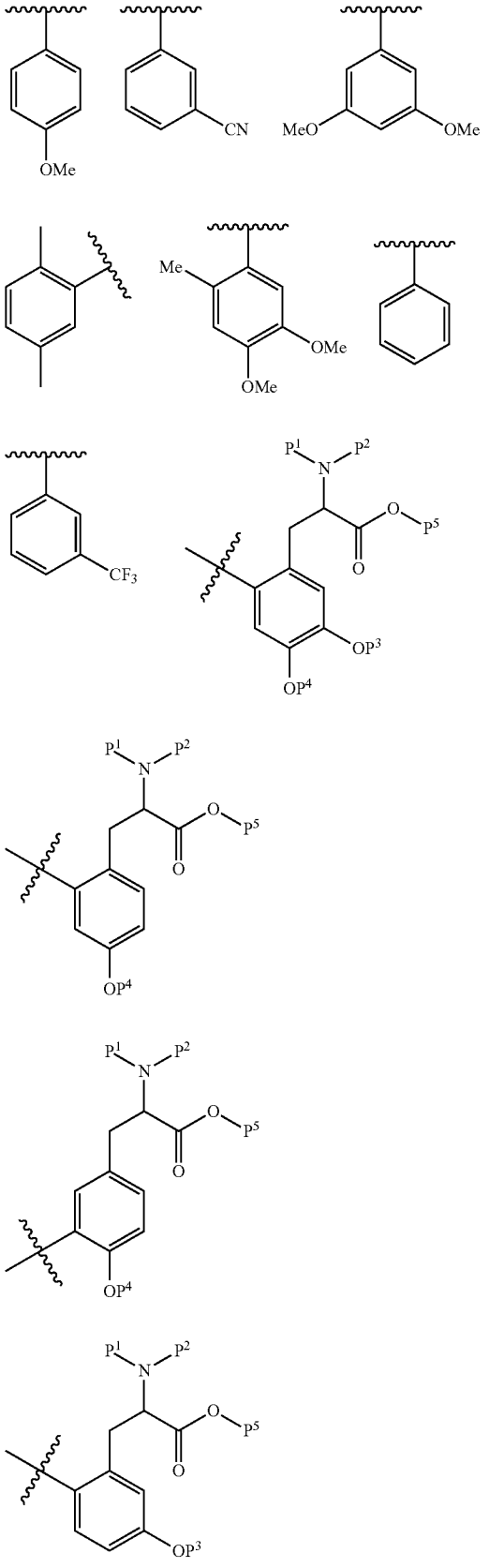
13. The compound of claim **1**, wherein Ar is chosen from a phenylalanine derivative, tyrosine derivative, tryptophan derivative, histidine derivative, and estradiol derivative.

14. The compound of claim **1**, wherein the compound of Formula (1) is a compound of Formula (1A):



15. The compound of claim **1**, wherein Ar is selected from the group consisting of:

-continued



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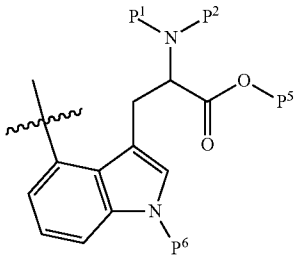

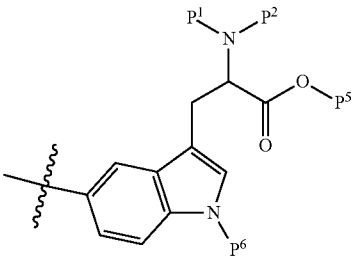

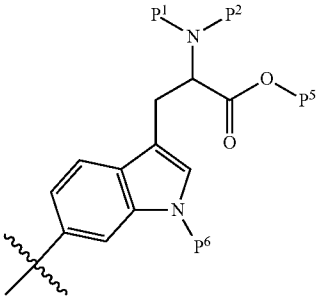

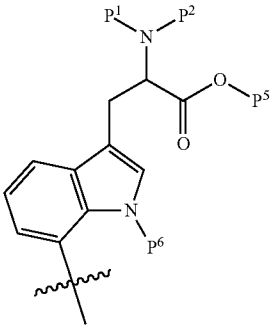

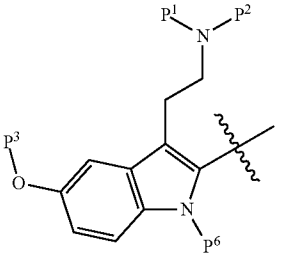

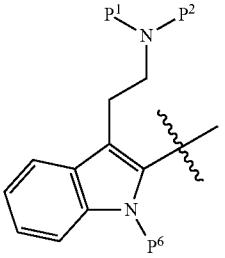

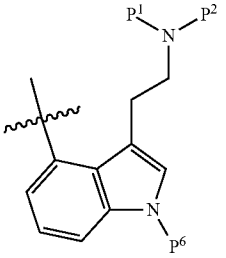

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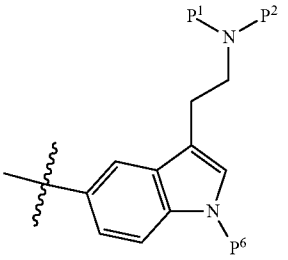

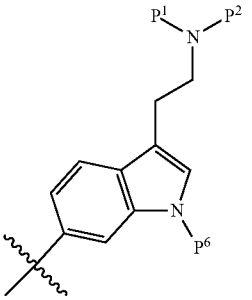

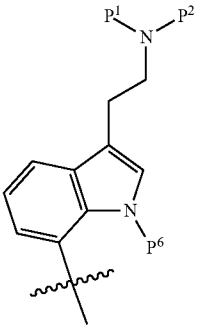

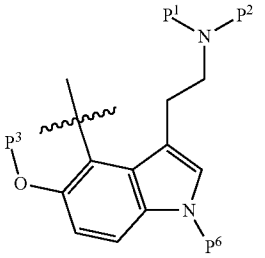

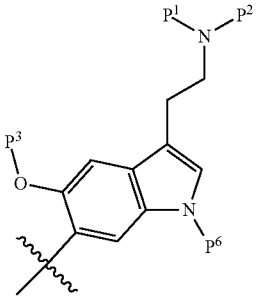

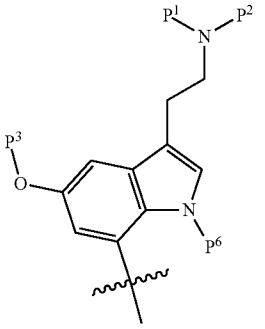

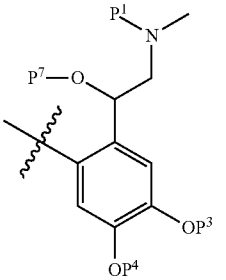

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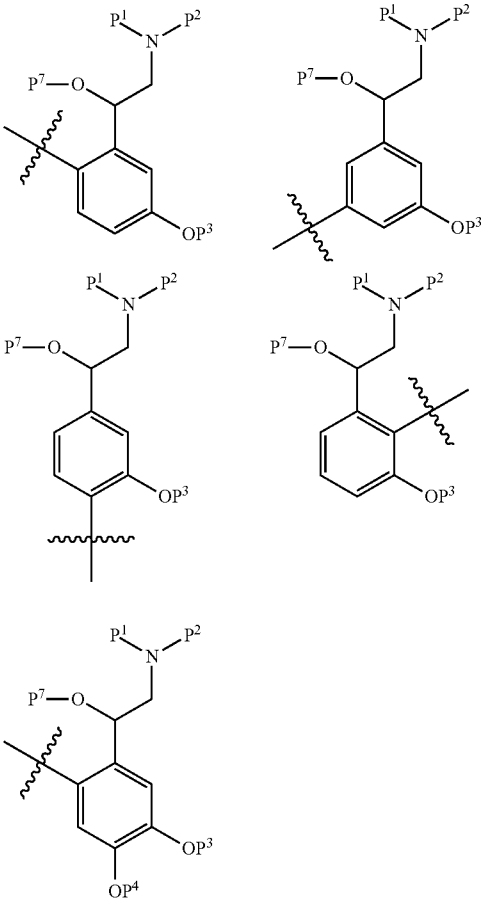

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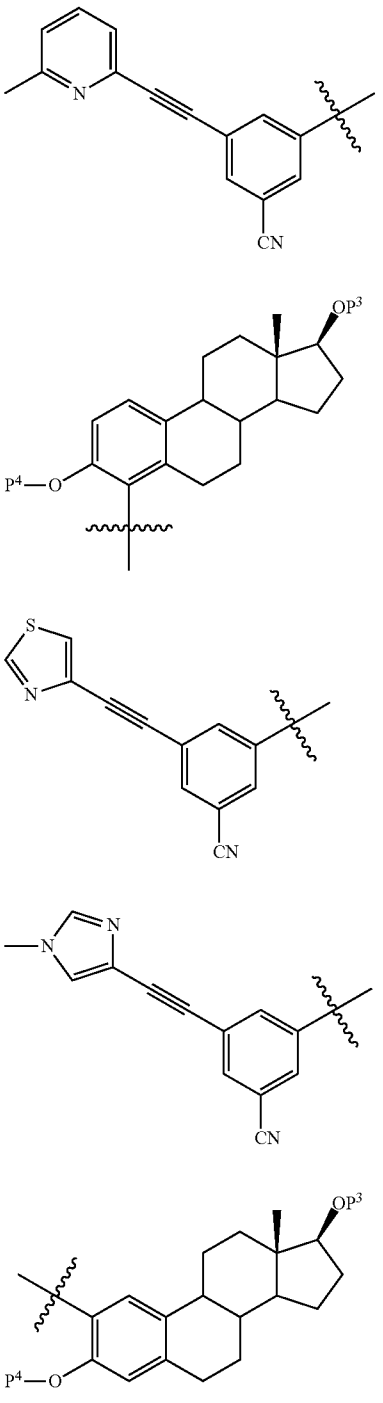


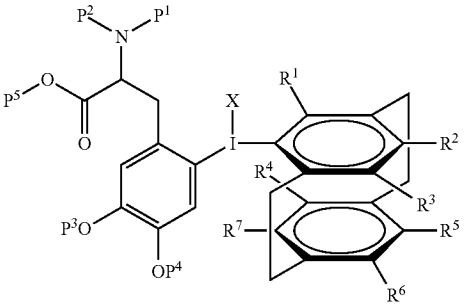
wherein:

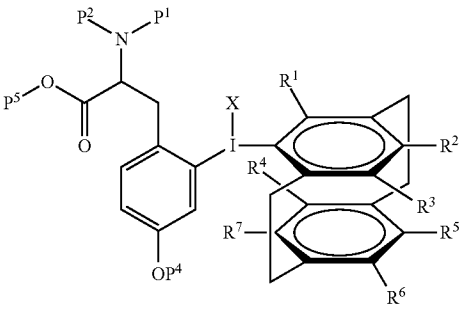
each of P^1, P^2 and P^6 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

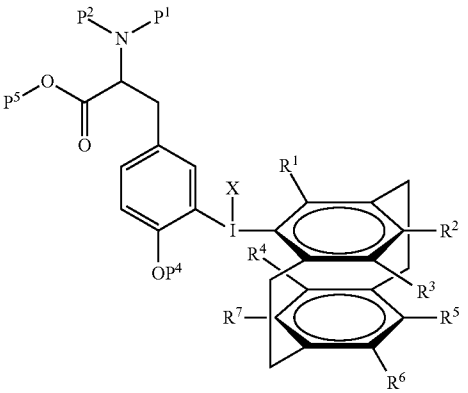
each of P^3, P^4, and P^7 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

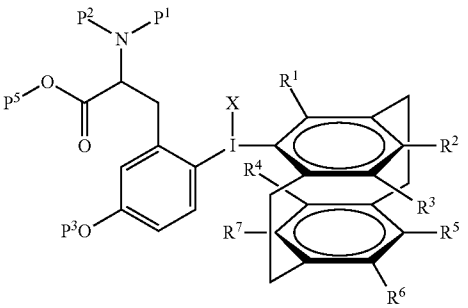
P^5 is a carboxylic acid protecting group.

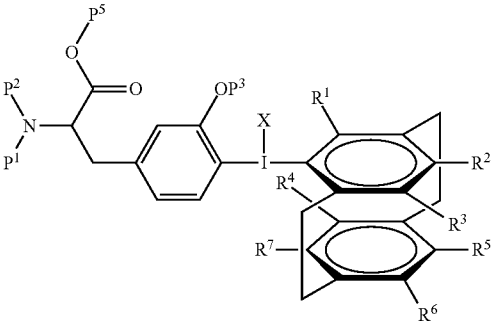
16. The compound of claim **1**, wherein the compound of Formula (1) is selected from the group consisting of:











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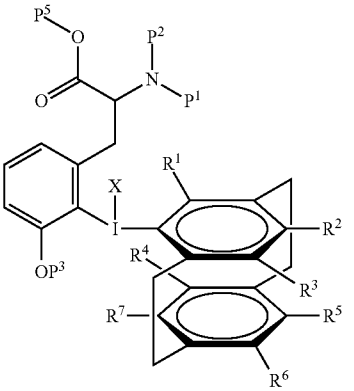


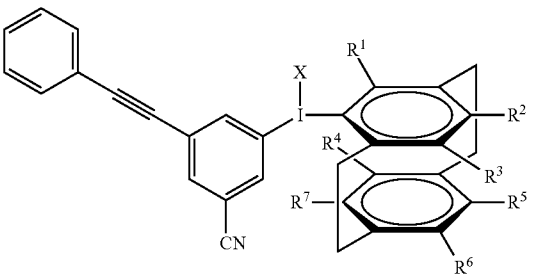
wherein:

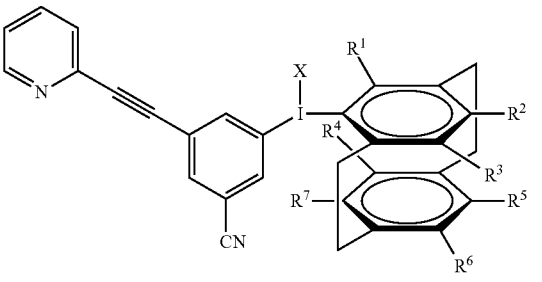
each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

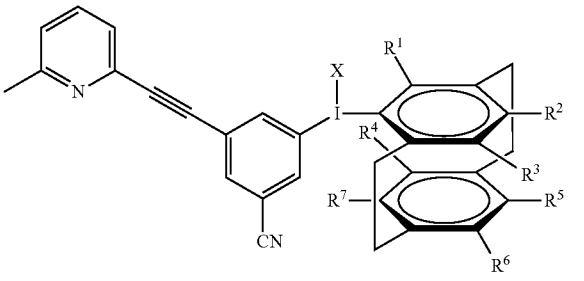
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

17. The compound of claim **1**, wherein the compound of Formula (1) is selected from the group consisting of:







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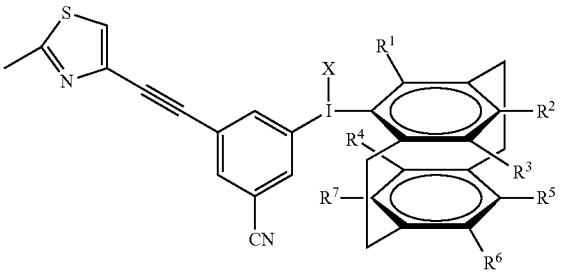
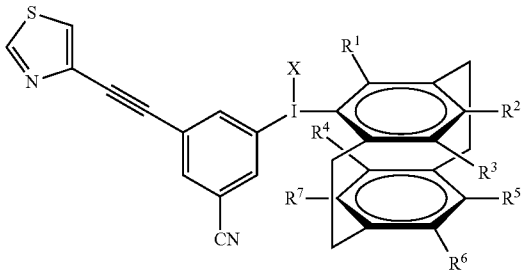
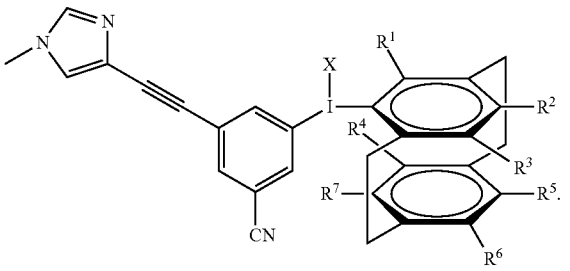
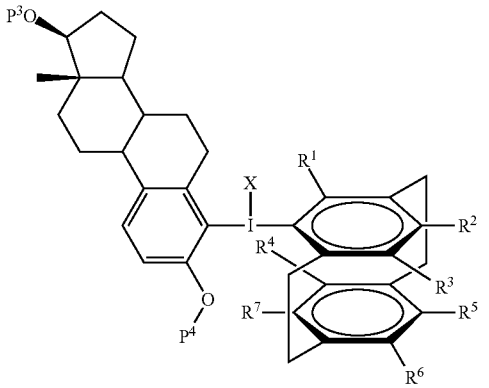






18. The compound of claim **1**, wherein the compound of Formula (1) is selected from the group consisting of:



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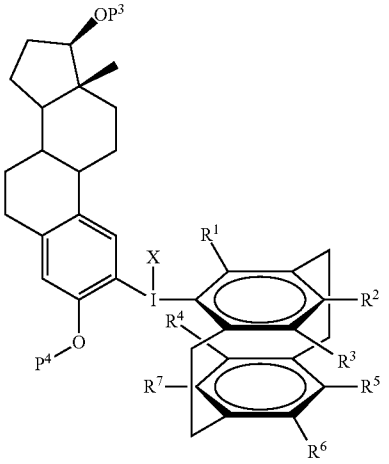


wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

19. The compound of claim **1**, wherein the Ar moiety is enantiomerically enriched.

20. The compound of claim **19**, wherein the Ar moiety is present in an enantiomeric excess of at least 75%.

21. The compound of claim **19**, wherein the Ar moiety is present in an enantiomeric excess of at least 95%.

22. The compound of claim **19**, wherein the Ar moiety is present in an enantiomeric excess of at least 98%.

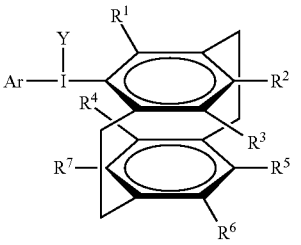
23. A method of making a compound of Formula (2):

wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system; and

X is a moiety wherein the pKa of the acid H—X is less than 12;

the method comprising heating a solution comprising a compound MX, wherein M is a counter ion, and a compound of Formula (3):



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

Y is a leaving group;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_m$, —SR^8, —SOR^8, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$, $NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or

unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

each m and n is independently an integer from 0 to 10; and

each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

24. The method of claim **23**, wherein M is selected from the group consisting of: potassium; sodium; cesium; complexes of lithium, sodium, potassium, or cesium with cryptands or crown ethers; tetrasubstituted ammonium cations; and phosphonium cations.

25. The method of claim **23**, wherein the solution further comprises a non-polar solvent.

26. The method of claim **25**, wherein the nonpolar solvent is selected from the group consisting of: benzene, toluene, o-xylene, m-xylene, p-xylene, ethyl benzene, carbon tetrachloride, hexane, cyclohexane, fluorobenzene, chlorobenzene, nitrobenzene, and mixtures thereof.

27. The method of claim **25**, wherein the method further comprises filtering the solution to remove insoluble material prior to heating.

28. The method of claim **27**, wherein the solvent is removed from the filtrate prior to heating.

29. The method of claim **23**, wherein the solution further comprises a polar solvent.

30. The method of claim **29**, wherein the polar solvent is chosen from: acetonitrile, acetone, dichloromethane, ethyl acetate, tetrahydrofuran, dimethylformamide, 1,2-difluorobenzene, benzotrifluoride and mixtures thereof.

31. The method of claim **29**, wherein the method further comprises filtering the solution to remove insoluble material prior to heating.

32. The method of claim **31**, wherein the solvent is removed from the filtrate prior to heating.

33. The method of claim **29**, wherein the method further comprises removing salt by chromatography.

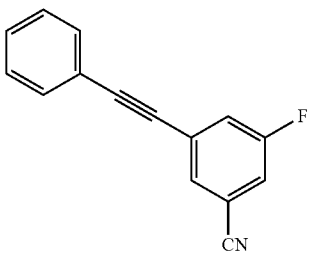
34. The method of claim **33**, wherein the chromatography is gel permeation chromatography.

35. The method of claim **23**, wherein the heating comprises heating at a temperature ranging from about 25° C. to about 250° C.

36. The method of claim **23**, wherein the heating occurs for from about 1 second to about 25 minutes.

37. The method of claim **36**, wherein the heating is accomplished by a flash pyrolysis method, a conventional heating method, or by a microwave method.

38. The method of claim **23**, wherein the compound of Formula (2) is chosen from:



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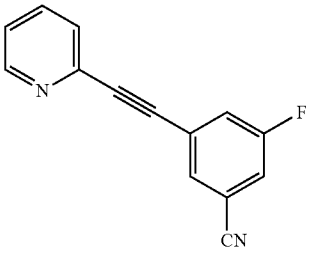
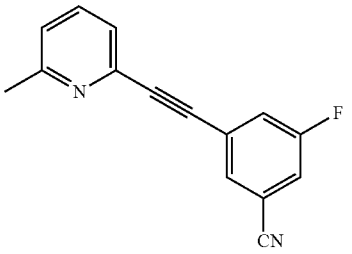
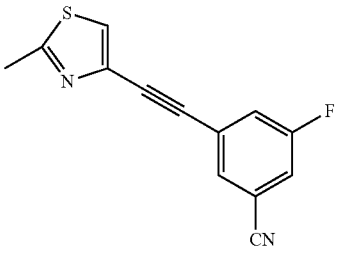
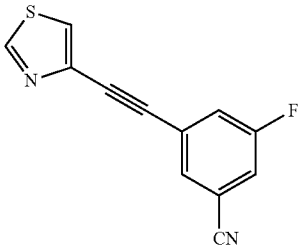
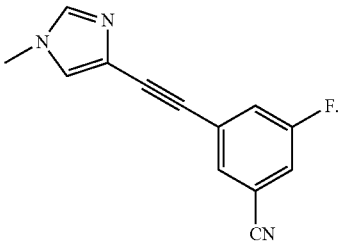


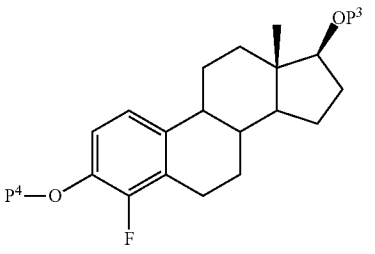








39. The method of claim **23**, wherein the compound of Formula (2) is chosen from:



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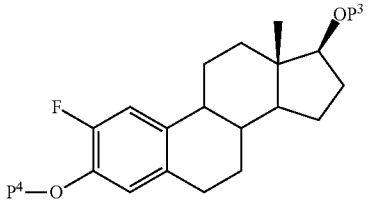
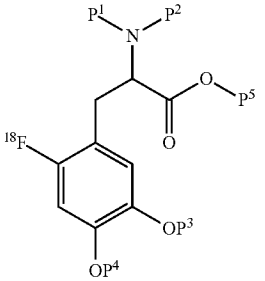


wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

40. The method of claim **23**, wherein the compound of Formula (2) is:



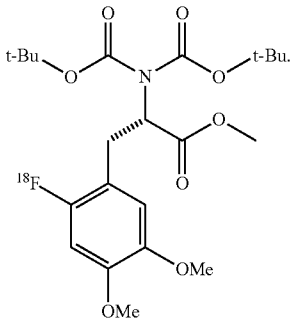
wherein:

each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

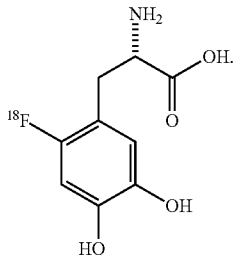
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

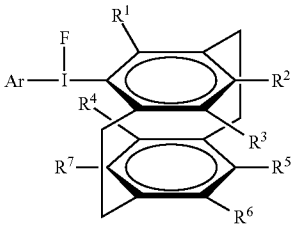
41. The method of claim **40**, wherein the compound of Formula (2) is:



42. The method of claim **23**, wherein the compound of Formula (2) is:



43. A compound of Formula (4):



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_{m,}{}_{SR}{}^{8}$, —$SOR^8$, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$, $NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

each m and n is independently an integer from 0 to 10; and

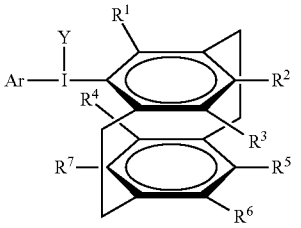
each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

44. A method of making a compound of Formula (5):

wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

the method comprising heating a solution comprising a compound MF, wherein M is a counter ion, and a compound of Formula (3):



wherein:

Ar is a substituted or unsubstituted aryl or heteroaryl ring system;

Y is a leaving group;

R^1 is hydrogen or a substituent having a Hammett σ_p value of less than zero; and

R^2, R^3, R^4, R^5, R^6, and R^7 are independently selected from the group consisting of: H, CF_3, OCF_3, CN, hydroxyl, amino, aminoalkyl, $(CH_2)_nN(CH_2)_m$, —SR^8, —SOR^8, halo, SO_2R^8, $(CH_2)_nOR^8$, $C(=O)NR^8R^9$, $SO_2NR^8R^9$,

$NR^8SO_2R^9$, $COOR^8$, $NR^8C(=O)R^9$, $NR^8C(=O)NR^9$, SO_2R^8, $(CH_2)_nC(=O)NR^8R^9$, $(CH_2)_nSO_2NR^8R^9$, $(CH_2)_nNR^8SO_2R^9$, $(CH_2)_nCOOR^8$, $(CH_2)_nNR^8C(=O)R^9$, $(CH_2)_nNR^8C(=O)NR^9$, alkoxy, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl;

each m and n is independently an integer from 0 to 10; and

each R^8 and R^9 are independently chosen from H, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.

45. The compound of claim **43**, wherein F is ^{18}F.

46. The compound of claim **43**, wherein R^1 is selected from the group consisting of: —$(C_1$-$C_{10})$alkyl, —$(C_1$-$C_{10})$halo alkyl, $(C_2$-$C_{10})$alkenyl, $(C_2$-$C_{10})$alkynyl, —O—$(C_1$-$C_{10})$ alkyl, —C(O)—O—$(C_1$-$C_{10})$alkyl, aryl, and heteroaryl.

47. The compound of claim **46**, wherein R^1 is —O—$(C_1$-$C_{10})$alkyl.

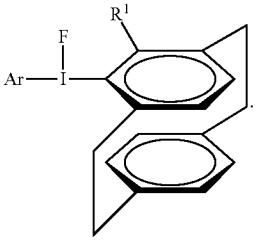
48. The compound of claim **47**, wherein R^1 is OCH_3.

49. The compound of claim **43**, wherein Ar is an electron rich aryl or heteroaryl ring system.

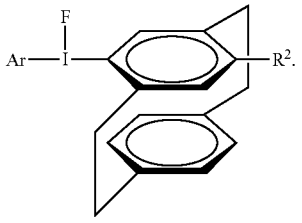
50. The compound of claim **49**, wherein Ar—H is more easily oxidized than benzene.

51. The compound of claim **43**, wherein Ar is chosen from a phenylalanine derivative, tyrosine derivative, tryptophan derivative, histidine derivative, and estradiol derivative.

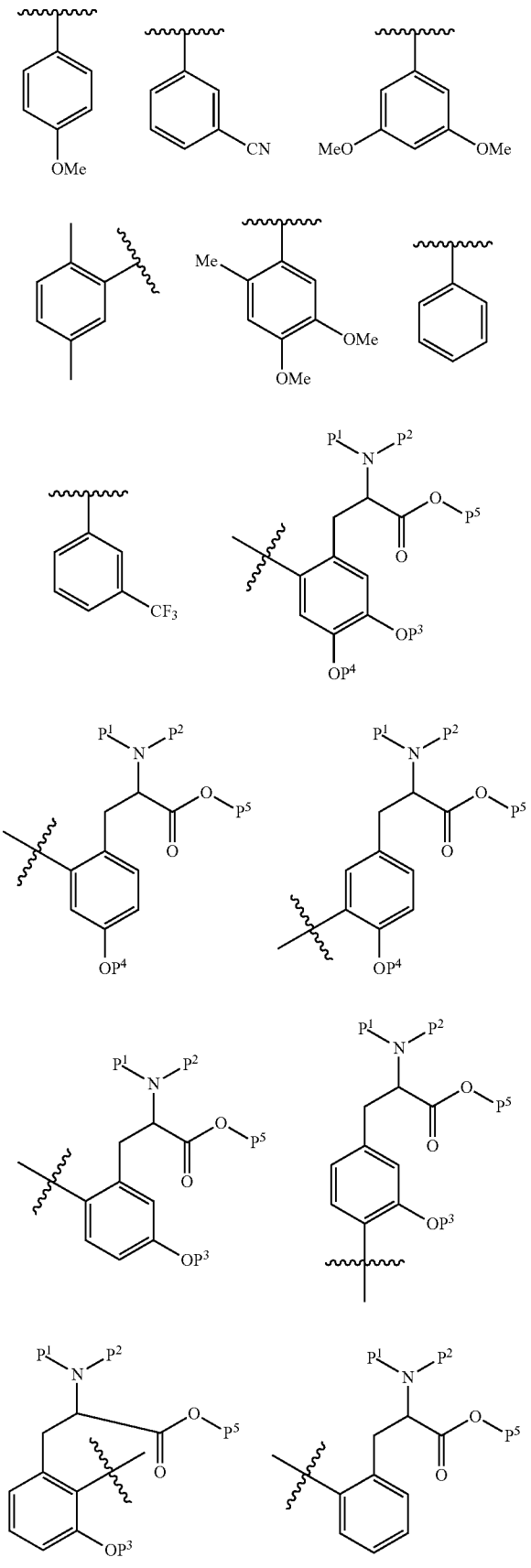
52. The compound of claim **43**, wherein the compound of Formula (4) is a compound of Formula (4A):



53. The compound of claim **43**, wherein the compound of Formula (4) is a compound of Formula (4B):



54. The compound of claim **43**, wherein Ar is selected from the group consisting of:



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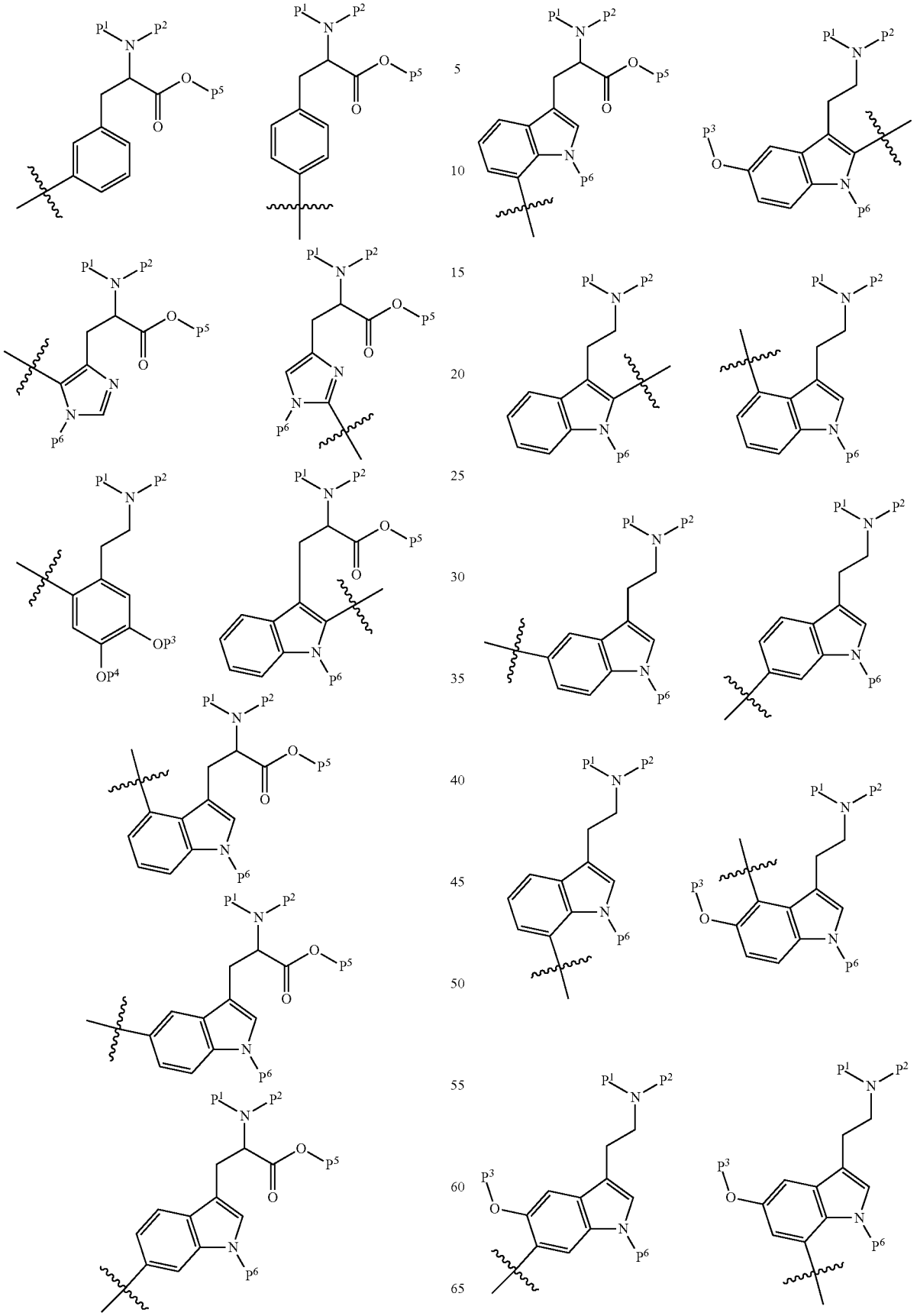

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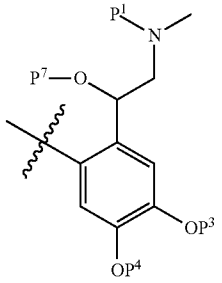

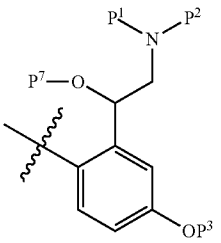

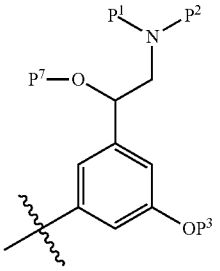

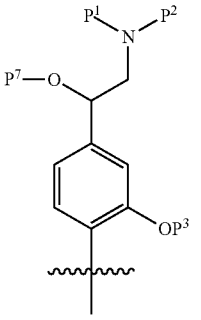

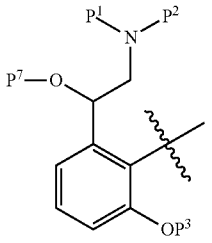

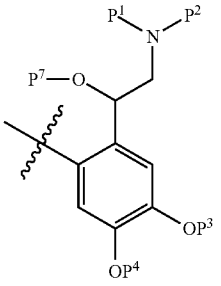

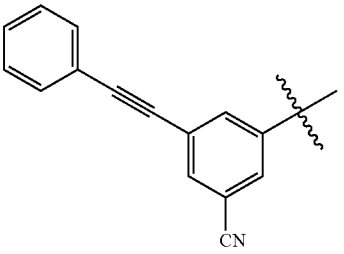

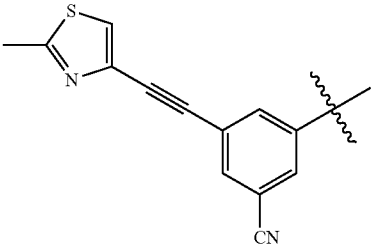

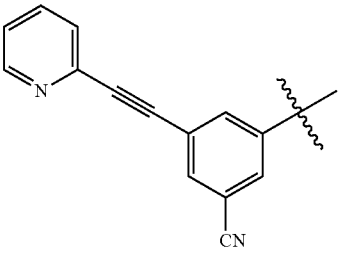

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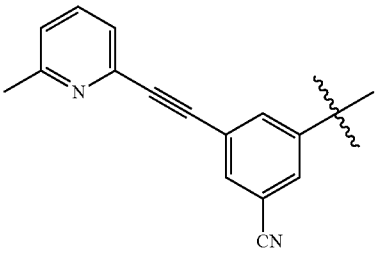
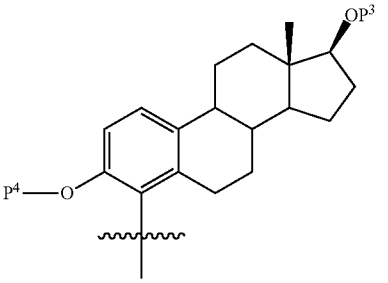
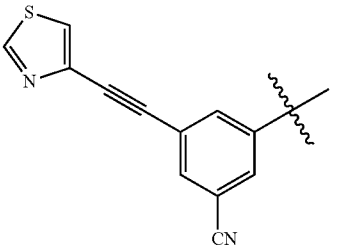
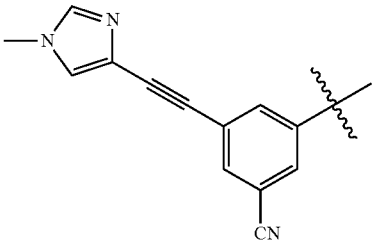
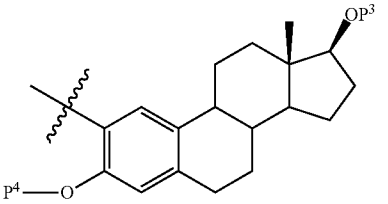










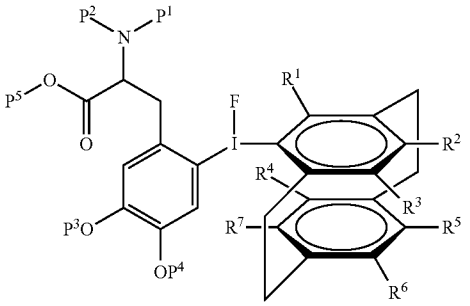
wherein:

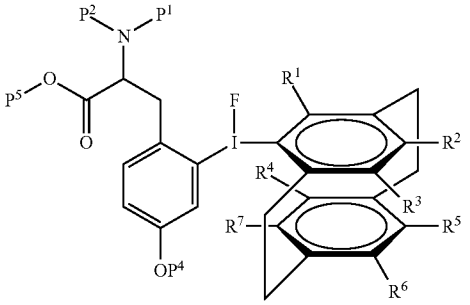
each of P^1, P^2 and P^6 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

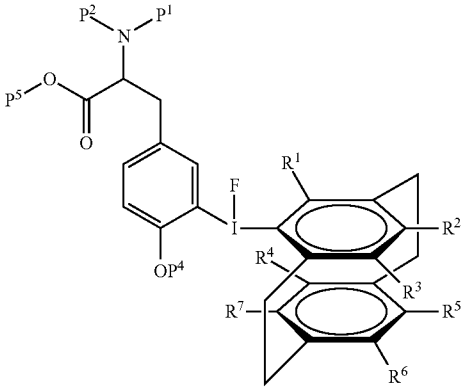
each of P^3, P^4, and P^7 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

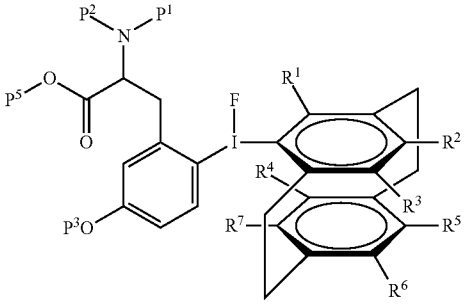
P^5 is a carboxylic acid protecting group.

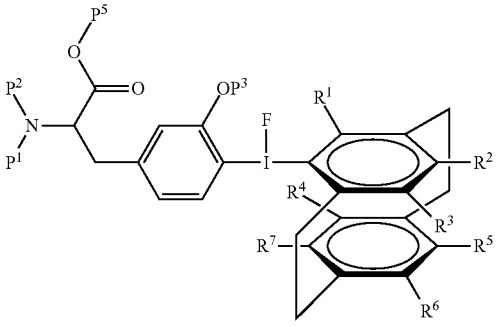
55. The compound of claim **43**, wherein the compound of Formula (4) is selected from the group consisting of:











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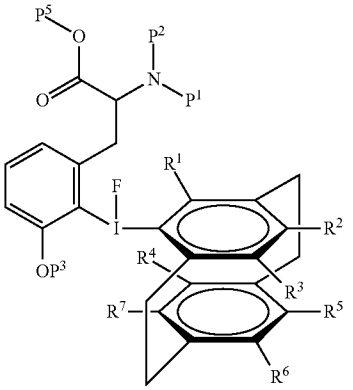


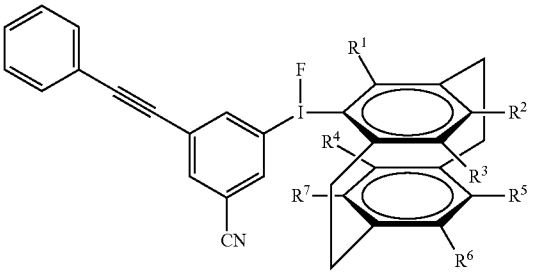
wherein:

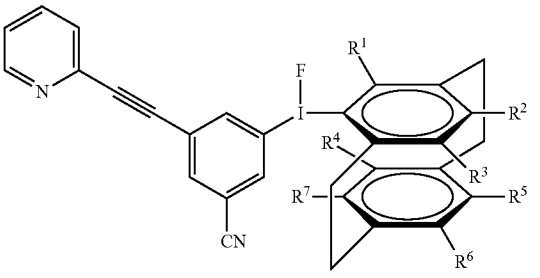
each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

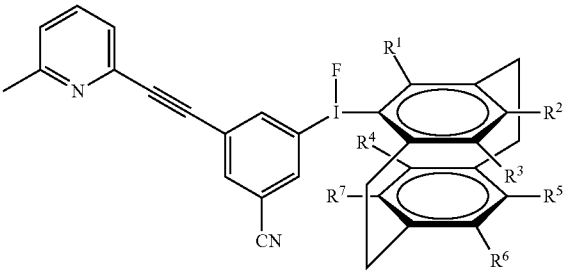
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

56. The compound of claim **43**, wherein the compound of Formula (4) is selected from the group consisting of:







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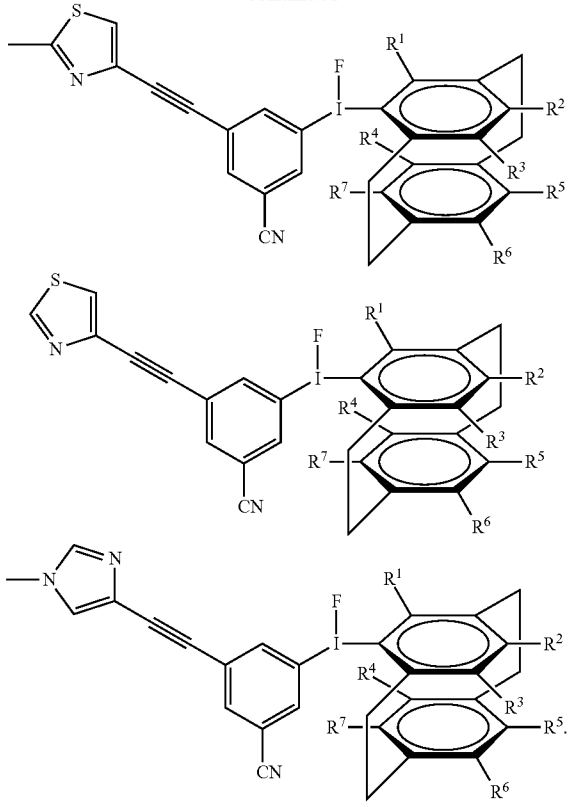
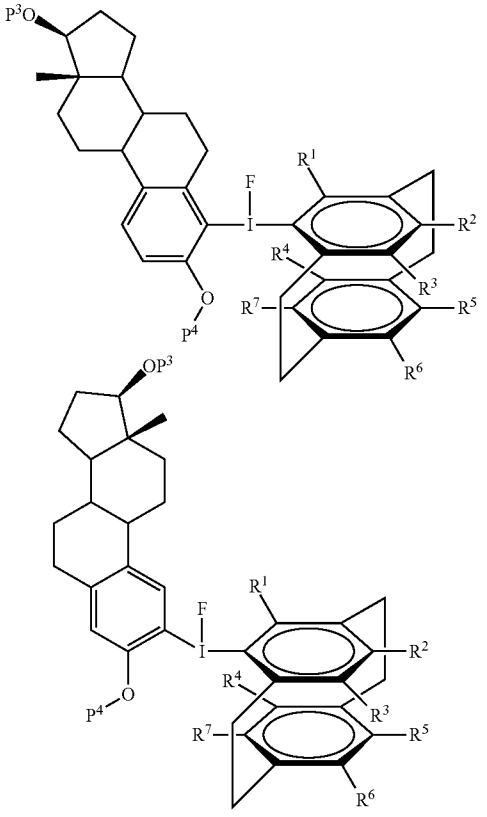


57. The compound of claim **43**, wherein the compound of Formula (4) is selected from the group consisting of:



wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

58. The compound of claim **43**, wherein the Ar moiety is enantiomerically enriched.

59. The compound of claim **58**, wherein the Ar moiety is present in an enantiomeric excess of at least 75%.

60. The compound of claim **58**, wherein the Ar moiety is present in an enantiomeric excess of at least 95%.

61. The compound of claim **58**, wherein the Ar moiety is present in an enantiomeric excess of at least 98%.

62. The method of claim **44**, wherein M is selected from the group consisting of: potassium; sodium; cesium; complexes of lithium, sodium, potassium, or cesium with cryptands or crown ethers; tetrasubstituted ammonium cations; and phosphonium cations.

63. The method of claim **44**, wherein the solution further comprises a non-polar solvent.

64. The method of claim **44**, wherein the nonpolar solvent is selected from the group consisting of: benzene, toluene, o-xylene, m-xylene, p-xylene, ethyl benzene, carbon tetrachloride, hexane, cyclohexane, fluorobenzene, chlorobenzene, nitrobenzene, and mixtures thereof.

65. The method of claim **44**, wherein the method further comprises filtering the solution to remove insoluble material prior to heating.

66. The method of claim **44**, wherein the solvent is removed from the filtrate prior to heating.

67. The method of claim **44**, wherein the solution further comprises a polar solvent.

68. The method of claim **67**, wherein the polar solvent is chosen from: acetonitrile, acetone, dichloromethane, ethyl acetate, tetrahydrofuran, dimethylformamide, 1,2-difluorobenzene, benzotrifluoride and mixtures thereof.

69. The method of claim **67**, wherein the method further comprises filtering the solution to remove insoluble material prior to heating.

70. The method of claim **69**, wherein the solvent is removed from the filtrate prior to heating.

71. The method of claim **67**, wherein the method further comprises removing salt by chromatography.

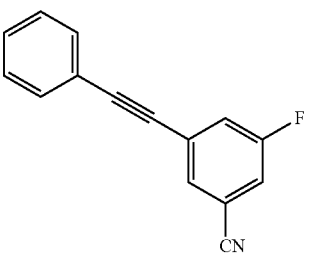
72. The method of claim **71**, wherein the chromatography is gel permeation chromatography.

73. The method of claim **44**, wherein the heating comprises heating at a temperature ranging from about 25° C. to about 250° C.

74. The method of claim **44**, wherein the heating occurs for from about 1 second to about 25 minutes.

75. The method of claim **73**, wherein the heating is accomplished by a flash pyrolysis method, a conventional heating method, or by a microwave method.

76. The method of claim **44**, wherein the compound of Formula (5) is chosen from:



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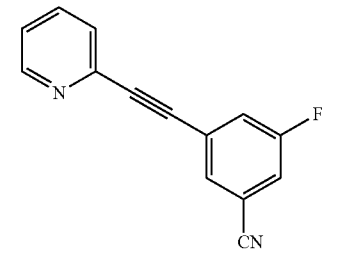
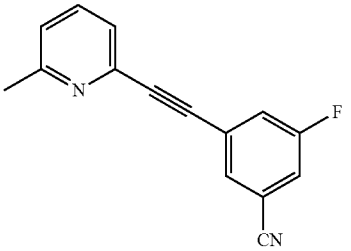
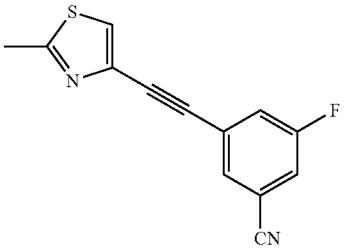
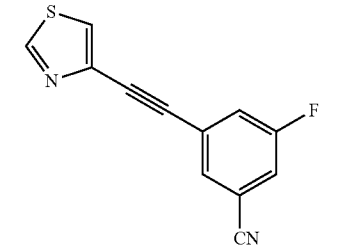
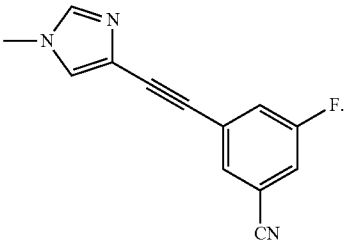


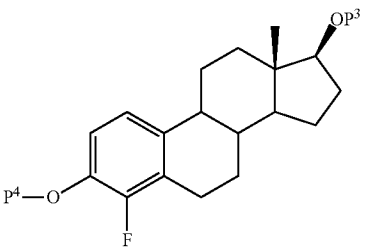








77. The method of claim **44**, wherein the compound of Formula (5) is chosen from:



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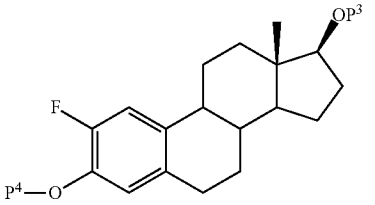
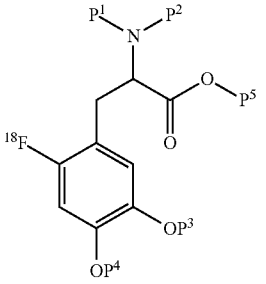


wherein:

each of P^3 and P^4 are independently an alcohol protecting group.

78. The method of claim **44**, wherein the compound of Formula (5) is:



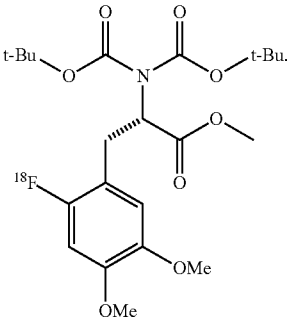
wherein:

each of P^1 and P^2 are independently a nitrogen protecting group, or P^1 and P^2 come together to form a single nitrogen protecting group;

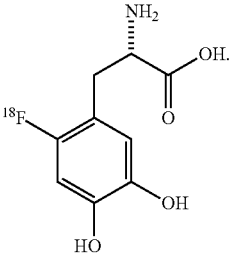
each of P^3, and P^4 are independently an alcohol protecting group, or P^3 and P^4 come together to form a single oxygen protecting group; and

P^5 is a carboxylic acid protecting group.

79. The method of claim **78**, wherein the compound of Formula (5) is:



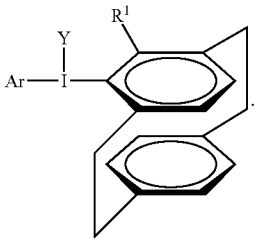
80. The method of claim **44**, wherein the compound of Formula (5) is:



81. The method of claim **44**, wherein F is ^{18}F.

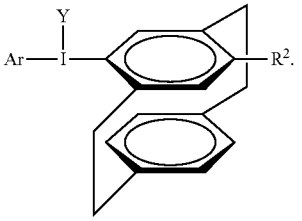
82. The method of claim **44**, wherein the compound of Formula (3) is a compound of Formula (3A):

(3A)



83. The method of claim **44**, wherein the compound of Formula (3) is a compound of Formula (3B):

(3B)



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