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(71) Applicant: **KALYRA PHARMACEUTICALS, INC.** [US/US]; 6181 Cornerstone Court, Ste. 106, San Diego, CA 92121 (US).

(72) Inventor: **BUNKER, Kevin, Duane**; 6181 Cornerstone Court, Ste. 106, San Diego, CA 92121 (US).

(74) Agent: **MILLER, Kimberly, J.**; Knobbe Martens Olson & Bear, LLP, 2040 Main Street, 14th Floor, Irvine, CA 92614 (US).

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(54) Title: BICYCLIC ALKYL COMPOUNDS AND SYNTHESIS

(57) Abstract: Disclosed herein are compounds of the general Formula (I), and methods of synthesizing a substituted bicyclo[1.1.1]pentane using a Group VII or Group IX transition metal compound.

BICYCLIC ALKYL COMPOUNDS AND SYNTHESIS

INCORPORATION BY REFERENCE TO ANY PRIORITY APPLICATIONS

[0001] Any and all applications for which a foreign or domestic priority claim is identified, for example, in the Application Data Sheet or Request as filed with the present application, are hereby incorporated by reference under 37 CFR 1.57, and Rules 4.18 and 20.6.

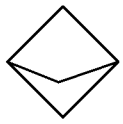
Field

[0002] The present disclosure relates to synthetic organic chemistry, and in particular to [1.1.1]-bicyclopentane-based compounds (propellane derivatives) and their synthesis.

Description

[0003] There is significant need for new categories of small organic molecules useful as reagents in synthetic organic chemistry. Although it has been estimated that there are 10^{60} possible small carbon-containing molecules, only a tiny fraction of those can be effectively and efficiently synthesized using known reactions and readily-available starting materials (or "building blocks"). New building blocks or more efficient methods of synthesizing known but expensive building blocks could expand the chemical space available for exploration, for example, in areas such as pharmaceuticals, agricultural chemistry, polymers, advanced materials, and many other areas of endeavor.

[0004] One structural motif that is highly under-represented in synthetic organic chemistry is bicyclo[1.1.1]pentane (BCP) having the structure:



BCP

[0005] This is largely due to the difficulty, high cost, and low yields of BCP and its derivatives using known synthetic schemes. Although BCP has been the subject of some experimentation as a structural motif in pharmaceuticals, polymers, liquid crystal displays, high energy density materials, nanoparticles or molecular rods, macrocycles, organometallic

complexes, and physical organic chemistry, compounds having a BCP structure have yet to be commercialized in those fields. In short, commercial use of BCPs has been hampered by availability and cost of reagents.

SUMMARY

[0006] Some embodiments disclosed herein relate to a method for preparing a substituted bicyclo[1.1.1]pentane compound that can include combining [1.1.1]propellane; a Group VII transition metal compound or a Group IX transition metal compound; a hydride source; and a reagent capable of contributing all or a part of a substituent group such that bicyclo[1.1.1]pentane is substituted with the substituent group.

[0007] Some embodiments described herein relate to using a method described herein to obtain a compound of Formula (I).

[0008] Some embodiments described herein relate to a compound of Formula (I).

DETAILED DESCRIPTION

[0009] Bicyclo[1.1.1]pentanes are remarkably stable, despite being highly ring-strained. The first example of an isolated bicyclo[1.1.1]pentane was reported by Wiberg in 1964 (Wiberg et al. *Tetrahedron Lett.* **1964,** 531-4). However, development of the bicyclo[1.1.1]pentane field was slow due to the difficult and low yielding chemistry. Some twenty years passed before a more productive route into BCPs was discovered by Wiberg (Wiberg et al. *J. Am. Chem. Soc.* **1982**, 104, 5239-40) and further developed by Sziemes (Semmler et al. *J. Am. Chem. Soc.* **1985**, 107, 6410-11) that utilized the highly ring-strained [1.1.1]propellane as a starting material.

[0010] Bicyclo[1.1.1]pentane has unique properties, including shape (sterics) and polarity (electronics) where the high ring-strain creates an electron withdrawing effect for substituents on the bridgehead carbons. For example, 1-bicyclo[1.1.1]pentyl amine is significantly less basic compared to tert-butylamine (pKa of the conjugate acid is 8.6 for 1-bicyclo[1.1.1]pentyl amine vs. 11.0 for $tBuNH_2$). Likewise, 1-carboxybicyclo[1.1.1]pentane is more acidic than pivalic acid (pKa of 4.09 for 1-carboxybicyclo[1.1.1]pentanes vs. 5.05 for pivalic acid). These and other properties suggest that BCPs may find significant application

as organic chemistry building blocks. Nevertheless, despite advances in synthesis of a few BCPs (see, e.g., Bunker et al., *Org. Lett.* **2011**, 13, 4746-4748), there is a need for additional BCP building blocks and for more cost-effective syntheses for known BCP-based compounds.

Abbreviations

[0011] As used herein, the following terminology is defined as indicated:

TERM	**DEFINITION**
THF	tetrahydrofuran
NMP	*N*-methyl-2-pyrrolidone
DMF	dimethylformamide
$Mn(dpm)_3$	tris(2,2,6,6-tetramethyl-3,5-heptanedionato) manganese (III)
DMSO	dimethylsulfoxide
MTBE	methyl(tert-butyl)ether

Definitions

[0012] Whenever a group is described as being "optionally substituted" that group may be unsubstituted or substituted with one or more of the indicated substituents. Likewise, when a group is described as being "unsubstituted or substituted" if substituted, the substituent(s) may be selected from one or more of the indicated substituents. If no substituents are indicated, it is meant that the indicated "optionally substituted" or "substituted" group may be substituted with one or more group(s) individually and independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl), (heterocyclyl)alkyl, hydroxy, alkoxy, acyl, cyano, halogen, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, sulfenyl, sulfinyl, sulfonyl, haloalkyl, haloalkoxy, an amino, a mono-substituted amino group and a di-substituted amino group.

[0013] As used herein, "C_a to C_b" in which "a" and "b" are integers refer to the number of carbon atoms in a group. The indicated group can contain from "a" to "b",

inclusive, carbon atoms. Thus, for example, a "C_1 to C_4 alkyl" group refers to all alkyl groups having from 1 to 4 carbons, that is, CH_3-, CH_3CH_2-, $CH_3CH_2CH_2$-, $(CH_3)_2CH$-, $CH_3CH_2CH_2CH_2$-, $CH_3CH_2CH(CH_3)$- and $(CH_3)_3C$-. If no "a" and "b" are designated, the broadest range described in these definitions is to be assumed.

[0014] As used herein, the term "alkyl" refers to a fully saturated aliphatic hydrocarbon group. The alkyl moiety may be branched or straight chain. Examples of branched alkyl groups include, but are not limited to, iso-propyl, sec-butyl, t-butyl and the like. Examples of straight chain alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and the like. The alkyl group may have 1 to 30 carbon atoms (whenever it appears herein, a numerical range such as "1 to 30" refers to each integer in the given range; *e.g.*, "1 to 30 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, *etc.*, up to and including 30 carbon atoms, although the present definition also covers the occurrence of the term "alkyl" where no numerical range is designated). The alkyl group may also be a medium size alkyl having 1 to 12 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 6 carbon atoms. An alkyl group may be substituted or unsubstituted.

[0015] The term "alkenyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon double bond(s) including, but not limited to, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl, and the like. An alkenyl group may be unsubstituted or substituted.

[0016] The term "alkynyl" used herein refers to a monovalent straight or branched chain radical of from two to twenty carbon atoms containing a carbon triple bond(s) including, but not limited to, 1-propynyl, 1-butynyl, 2-butynyl, and the like. An alkynyl group may be unsubstituted or substituted.

[0017] As used herein, "cycloalkyl" refers to a completely saturated (no double or triple bonds) mono- or multi- cyclic hydrocarbon ring system. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. Cycloalkyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are in no way limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

[0018] As used herein, "cycloalkenyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more double bonds in at least one ring; although, if there is more than one, the double bonds cannot form a fully delocalized pi-electron system throughout all the rings (otherwise the group would be "aryl," as defined herein). Cycloalkenyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro fashion. A cycloalkenyl group may be unsubstituted or substituted.

[0019] As used herein, "cycloalkynyl" refers to a mono- or multi- cyclic hydrocarbon ring system that contains one or more triple bonds in at least one ring. If there is more than one triple bond, the triple bonds cannot form a fully delocalized pi-electron system throughout all the rings. Cycloalkynyl groups can contain 3 to 10 atoms in the ring(s) or 3 to 8 atoms in the ring(s). When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro fashion. A cycloalkynyl group may be unsubstituted or substituted.

[0020] As used herein, "alkoxy" refers to the formula –OR wherein R is an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), (heteroaryl)alkyl or (heterocyclyl)alkyl. A non-limiting list of alkoxys are methoxy, ethoxy, n-propoxy, 1-methylethoxy (isopropoxy), n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, phenoxy and benzoxy. An alkoxy may be substituted or unsubstituted.

[0021] As used herein, "aryl" refers to a carbocyclic (all carbon) monocyclic or multicyclic aromatic ring system (including fused ring systems where two carbocyclic rings share a chemical bond) that has a fully delocalized pi-electron system throughout all the rings. The number of carbon atoms in an aryl group can vary. For example, the aryl group can be a C_6-C_{14} aryl group, a C_6-C_{10} aryl group, or a C_6 aryl group. Examples of aryl groups include, but are not limited to, benzene, naphthalene and azulene. An aryl group may be substituted or unsubstituted.

[0022] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system (a ring system with fully delocalized pi-electron system) that contain(s) one or more heteroatoms (for example, 1, 2 or 3 heteroatoms), that is, an element other than carbon, including but not limited to, nitrogen, oxygen and sulfur. The number of atoms in the ring(s)

of a heteroaryl group can vary. For example, the heteroaryl group can contain 4 to 14 atoms in the ring(s), 5 to 10 atoms in the ring(s) or 5 to 6 atoms in the ring(s). Furthermore, the term "heteroaryl" includes fused ring systems where two rings, such as at least one aryl ring and at least one heteroaryl ring, or at least two heteroaryl rings, share at least one chemical bond. Examples of heteroaryl rings include, but are not limited to, furan, furazan, thiophene, benzothiophene, phthalazine, pyrrole, oxazole, benzoxazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, thiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, benzothiazole, imidazole, benzimidazole, indole, indazole, pyrazole, benzopyrazole, isoxazole, benzoisoxazole, isothiazole, triazole, benzotriazole, thiadiazole, tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, purine, pteridine, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, and triazine. A heteroaryl group may be substituted or unsubstituted.

[0023] As used herein, "heterocyclyl" or "heteroalicyclyl" refers to three-, four-, five-, six-, seven-, eight-, nine-, ten-, up to 18-membered monocyclic, bicyclic, and tricyclic ring system wherein carbon atoms together with from 1 to 5 heteroatoms constitute said ring system. A heterocycle may optionally contain one or more unsaturated bonds situated in such a way, however, that a fully delocalized pi-electron system does not occur throughout all the rings. The heteroatom(s) is an element other than carbon including, but not limited to, oxygen, sulfur, and nitrogen. A heterocycle may further contain one or more carbonyl or thiocarbonyl functionalities, so as to make the definition include oxo-systems and thio-systems such as lactams, lactones, cyclic imides, cyclic thioimides and cyclic carbamates. When composed of two or more rings, the rings may be joined together in a fused or spiro fashion. Additionally, any nitrogens in a heteroalicyclic may be quaternized. Heterocyclyl or heteroalicyclic groups may be unsubstituted or substituted. Examples of such "heterocyclyl" or "heteroalicyclyl" groups include but are not limited to, 1,3-dioxin, 1,3-dioxane, 1,4-dioxane, 1,2-dioxolane, 1,3-dioxolane, 1,4-dioxolane, 1,3-oxathiane, 1,4-oxathiin, 1,3-oxathiolane, 1,3-dithiole, 1,3-dithiolane, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, trioxane, hexahydro-1,3,5-triazine, imidazoline, imidazolidine, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, morpholine, oxirane, piperidine N-Oxide, piperidine, piperazine, pyrrolidine, pyrrolidone,

pyrrolidione, 4-piperidone, pyrazoline, pyrazolidine, 2-oxopyrrolidine, tetrahydropyran, 4H-pyran, tetrahydrothiopyran, thiamorpholine, thiamorpholine sulfoxide, thiamorpholine sulfone, and their benzo-fused analogs (e.g., benzimidazolidinone, tetrahydroquinoline, 3,4-methylenedioxyphenyl).

[0024] As used herein, "aralkyl" and "aryl(alkyl)" refer to an aryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and aryl group of an aralkyl may be substituted or unsubstituted. Examples include but are not limited to benzyl, 2-phenyl(alkyl), 3-phenyl(alkyl), and naphthyl(alkyl).

[0025] As used herein, "heteroaralkyl" and "heteroaryl(alkyl)" refer to a heteroaryl group connected, as a substituent, via a lower alkylene group. The lower alkylene and heteroaryl group of heteroaralkyl may be substituted or unsubstituted. Examples include but are not limited to 2-thienyl(alkyl), 3-thienyl(alkyl), furyl(alkyl), thienyl(alkyl), pyrrolyl(alkyl), pyridyl(alkyl), isoxazolyl(alkyl), imidazolyl(alkyl), and their benzo-fused analogs.

[0026] A "heteroalicyclyl(alkyl)" and "heterocyclyl(alkyl)" refer to a heterocyclic or a heteroalicyclic group connected, as a substituent, via a lower alkylene group. The lower alkylene and heterocyclyl of a (heteroalicyclyl)alkyl may be substituted or unsubstituted. Examples include but are not limited tetrahydro-2H-pyran-4-yl(methyl), piperidin-4-yl(ethyl), piperidin-4-yl(propyl), tetrahydro-2H-thiopyran-4-yl(methyl), and 1,3-thiazinan-4-yl(methyl).

[0027] "Lower alkylene groups" are straight-chained -CH_2- tethering groups, forming bonds to connect molecular fragments via their terminal carbon atoms. Examples include but are not limited to methylene (-CH_2-), ethylene (-CH_2CH_2-), propylene (-$CH_2CH_2CH_2$-), and butylene (-$CH_2CH_2CH_2CH_2$-). A lower alkylene group can be substituted by replacing one or more hydrogen of the lower alkylene group and/or by substituting both hydrogens on the same carbon with a cycloalkyl group (e.g., ).

[0028] The term "carbonyl" used herein refers to C=O (i.e. carbon double bonded to oxygen).

[0029] As used herein, "acyl" refers to a hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), heteroaryl(alkyl) and heterocyclyl(alkyl) connected, as

substituents, via a carbonyl group. Examples include formyl, acetyl, propanoyl, benzoyl, and acryl. An acyl may be substituted or unsubstituted.

[0030] The term "amino" used herein refers -NH_2.

[0031] A "mono-substituted amino" group refers to a "-NHR" group in which R can be an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. A mono-substituted amino may be substituted or unsubstituted. Examples of mono-substituted amino groups include, but are not limited to, −NH(methyl), −NH(phenyl) and the like.

[0032] A "di-substituted amino" group refers to a "-NR_AR_B" group in which R_A and R_B can be independently an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl(alkyl), aryl(alkyl), heteroaryl(alkyl) or heterocyclyl(alkyl), as defined herein. A di-substituted amino may be substituted or unsubstituted. Examples of di-substituted amino groups include, but are not limited to, −N(methyl)$_2$, −N(phenyl)(methyl), −N(ethyl)(methyl) and the like.

[0033] The term "halogen atom" or "halogen" as used herein, means any one of the radio-stable atoms of column 7 of the Periodic Table of the Elements, such as, fluorine, chlorine, bromine and iodine.

[0034] As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkyl, di-haloalkyl and tri-haloalkyl). Such groups include but are not limited to, chloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl and 1-chloro-2-fluoromethyl, 2-fluoroisobutyl. A haloalkyl may be substituted or unsubstituted.

[0035] As used herein, "hydroxyalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxy group. Exemplary hydroxyalkyl groups include but are not limited to, 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, and 2,2-dihydroxyethyl. A hydroxyalkyl may be substituted or unsubstituted.

[0036] As used herein, "alkoxyalkyl" refers to an alkoxy group connected, as a substituent, via a lower alkylene group. Examples include alkyl-O-(CH_2)n- ,wherein n is an integer in the range of 1 to 6.

[0037] As used herein, "acylalkyl" refers to an acyl connected, as a substituent, via a lower alkylene group. Examples include aryl-C(=O)-(CH_2)n- and heteroaryl-C(=O)-(CH_2)n-, where n is an integer in the range of 1 to 6. An acylalkyl may be substituted or unsubstituted.

[0038] As used herein, "aminoalkyl" refers to an optionally substituted amino group connected, as a substituent, via a lower alkylene group. Examples include H_2N-(CH_2)n-, $(CH_3)_2N$-(CH_2)n- and (CH_3)(phenyl)N-(CH_2)n-,wherein n is an integer in the range of 1 to 6.

[0039] As used herein, "haloalkoxy" refers to an –O-alkyl group in which one or more of the hydrogen atoms are replaced by a halogen (e.g., mono-haloalkoxy, di- haloalkoxy and tri- haloalkoxy). Such groups include but are not limited to, chloromethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy, 1-chloro-2-fluoromethoxy and 2-fluoroisobutoxy. A haloalkoxy may be substituted or unsubstituted.

[0040] A "sulfonyl" group refers to an "SO_2R" group in which R can be hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl, heteroaryl, heterocyclyl, aryl(alkyl), (heteroaryl)alkyl or (heterocyclyl)alkyl. A sulfenyl may be substituted or unsubstituted.

[0041] Where the numbers of substituents is not specified (e.g. haloalkyl), there may be one or more substituents present. For example "haloalkyl" may include one or more of the same or different halogens. As another example, "C_1-C_3 alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three atoms.

[0042] As used herein, a radical indicates species with a single, unpaired electron such that the species containing the radical can be covalently bonded to another species. Hence, in this context, a radical is not necessarily a free radical. Rather, a radical indicates a specific portion of a larger molecule. The term "radical" can be used interchangeably with the term "group."

[0043] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched,

racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof.

[0044] It is to be understood that where compounds disclosed herein have unfilled valencies, then the valencies are to be filled with hydrogens or isotopes thereof, e.g., hydrogen-1 (protium) and hydrogen-2 (deuterium).

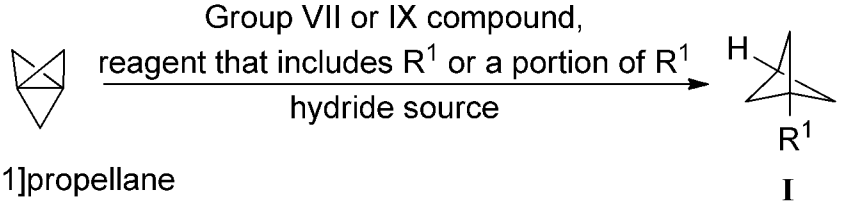
[0045] Where a range of values is provided, it is understood that the upper and lower limit, and each intervening value between the upper and lower limit of the range is encompassed within the embodiments.

Methods

[0046] Some embodiments disclosed herein relate to a method for preparing a substituted bicyclo[1.1.1]pentane compound that can include combining [1.1.1]propellane; a Group VII transition metal compound or a Group IX transition metal compound; a hydride source; and a reagent capable of contributing all or a part of a substituent group such that bicyclo[1.1.1]pentane is substituted with the substituent group.

[0047] A general synthetic route for preparing a substituted bicyclo[1.1.1]pentane compound is shown in Schemes 1 and 2, and described herein. The route shown and described herein is illustrative only and is not intended, nor is to be construed, to limit the scope of the claims in any manner whatsoever. Those skilled in the art will be able to recognize modifications of the disclosed syntheses and to devise alternate routes based on the disclosures herein; all such modifications and alternate routes are within the scope of the claims.

Scheme 1



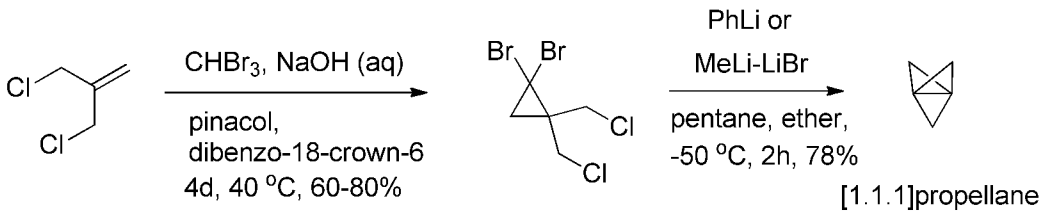
[1.1.1]propellane

I

[0048] As shown in Scheme 1, the hydride source contributes the shown hydrogen and the reagent contributes R^1 or a portion of R^1 to the substituted bicyclo[1.1.1]pentane compound. As provided herein, various Group VII compounds, Group IX compounds, reagents that include R^1 or a portion of R^1 and hydride sources can be used to form a substituted bicyclo[1.1.1]pentane compound.

[0049] [1.1.1]Propellane can be prepared via various methods. Suitable methods are described by Shtarev et al., *J. Am. Chem. Soc.* **2001**, *123*, 3484-3492 and Lynch et al., *Org. Synth.* **1998**, *75*, 98-105, which are hereby incorporated by reference in their entireties. One example of a suitable method is shown in Scheme 2.

Scheme 2



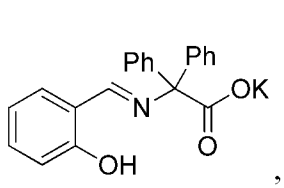
Metal-compounds

[0050] Those skilled in the art understand that Group VII includes the following elements: cobalt, rhodium, iridium and meitnerium; and Group IX includes manganese, technetium, rhenium and bohrium. In some embodiments, the Group VII transition metal compound can be a cobalt-based transition metal compound. The oxidation state of the transition metal compound can vary. For example, in some embodiments, the oxidation state of cobalt can be Co(II), such that the Group VII transition metal compound is a Co(II)-based transition metal compound. In other embodiments, the oxidation state of cobalt can be Co(III), such that the Group VII transition metal compound is a Co(III)-based transition metal compound.

[0051] In some embodiments, the Group IX transition metal compound can be a manganese-based compound. As with cobalt, the oxidation state of the manganese of the manganese-based transition metal compound can vary. In some embodiments, the oxidation state of manganese can be Mn(II), such that the Group IX transition metal compound is a

Mn(II)-based transition metal compound. In other embodiments, the oxidation state of manganese can be Mn(III), such that the Group IX transition metal compound is a Mn(III)-based transition metal compound. The Group VII and Group IX transition metal compound can be a salt, a solvate (including mono- and per-solvates) or a hydrate (including mono- and per-hydrates).

[0052] In some embodiments, the Group VII transition metal compound can include one or more ligands attached and/or coordinated to the Group VII metal, such that the Group VII transition metal compound is a Group VII transition metal complex. In some embodiments, the Group IX transition metal compound can include one or more ligands attached and/or coordinated to the Group IX metal, such that the Group IX transition metal compound is a Group IX transition metal complex. As used herein, the term "ligand" is used herein in its ordinary sense as understood by those skilled in the art, and refers to a group bound to a central atom in a chelate or a coordination compound. Examples of suitable ligands include Schiff-based ligands (such as salen-type ligands), 2-(3,5-di-*tert*-butyl-2-hydroxybenzylideneamino)-2,2-diphenylacetate, salicylaldehyde together with 2-aminoisobutyric acid and salicylaldehyde together with alanine. Additional examples of suitable ligands are provided below:



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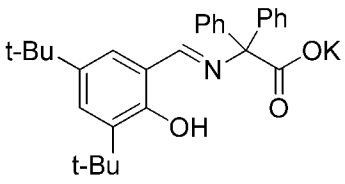

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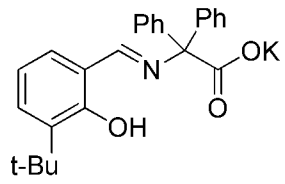

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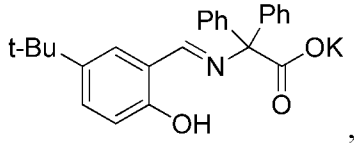

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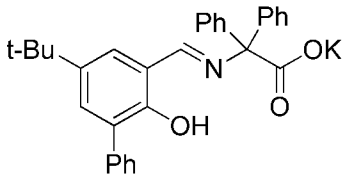

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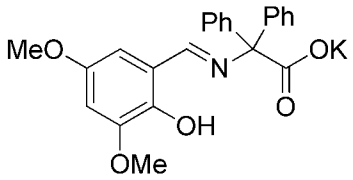

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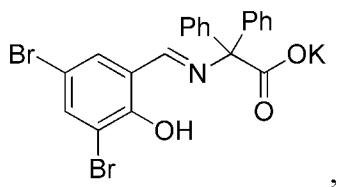

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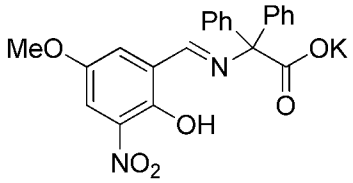

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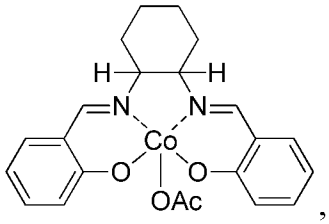
[0053] In some embodiments, more than one ligand can be present in the Group VII transition metal complex. In some embodiments, more than one ligand may be present in

the Group IX transition metal complex. In some embodiments, the Group VII transition metal complex can be a cobalt-based transition metal complex. In some embodiments, the Group IX transition metal complex can be a manganese-based transition metal complex.

[0054] The amount of the Group VII transition metal compound or the Group IX transition metal compound used in a method described herein can vary. In some embodiments, the Group VII transition metal compound or the Group IX transition metal compound can be present in a stoichiometric amount. In other embodiments, the Group VII transition metal compound or the Group IX transition metal compound can be present in a catalytic amount. In still other embodiments, the Group VII transition metal compound or the Group IX transition metal compound can be present in an excess amount. Examples of suitable Group VII and Group IX transition metal compounds include the following: tris(2,2,6,6-tetramethyl-3,5-heptanedionato) manganese(III) [$Mn(dpm)_3$], (acetato-κO)[[rel-(1R,2R)-2,2'-[1,2-cyclohexanediylbis[(nitrilo-κN)methylidyne]]bis[4,6-bis(1,1-dimethylethyl)phenolato-κO]](2-)]cobalt(III), and [N,N'-(1,1,2,2-tetramethylethylene)bis(3,5-di-tert-butylsalicylideneiminato)]cobalt(II). Additional examples include, but are not limited to, cobalt(II) nitrate, cobalt(II) acetate, cobalt(II) chloride, cobalt(II) tetrafluoroborate, bis(2,4-pentanedionato)cobalt ($Co(acac)_2$, bis(2,2,6,6-tetramethyl-3,5-heptanedionato) cobalt(II), bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedio-nato)cobalt(II) ($Co(modp)_2$), manganese(II) acetate, and the like.

[0055] Further examples of transition metal compounds include the following:



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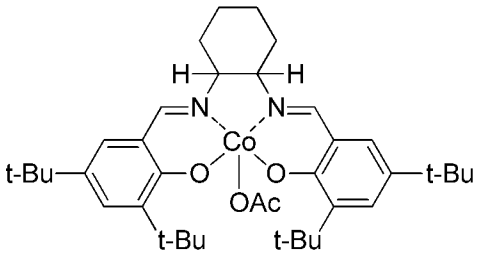

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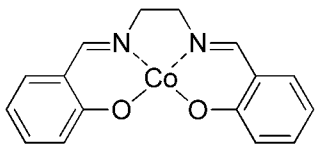

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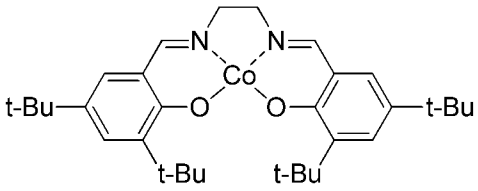

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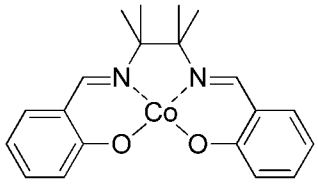

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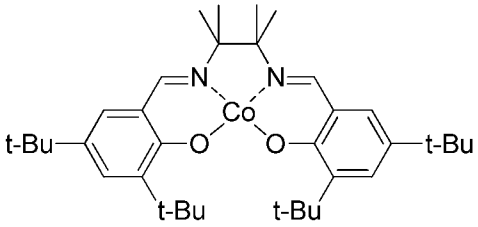
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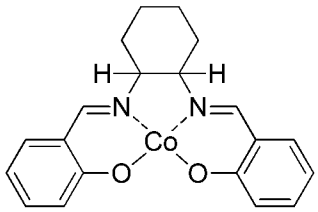
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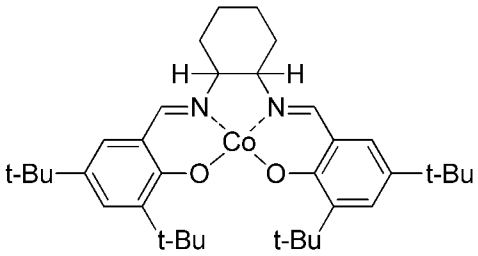
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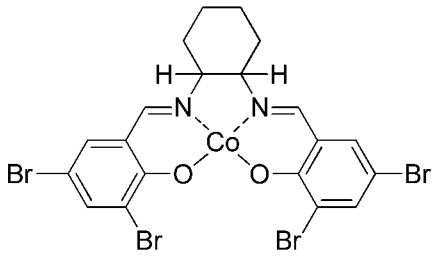
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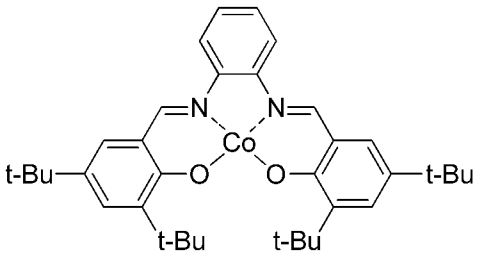
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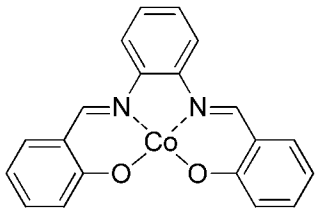
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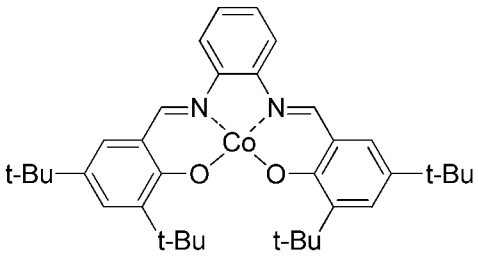
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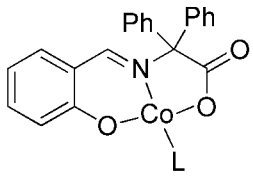
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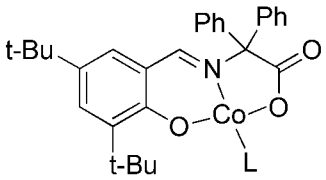
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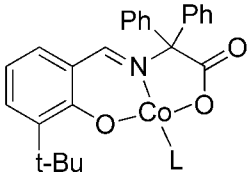
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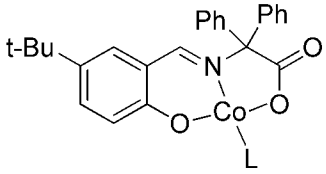
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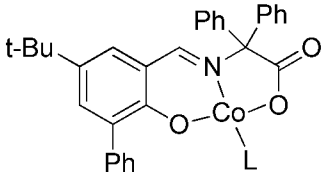
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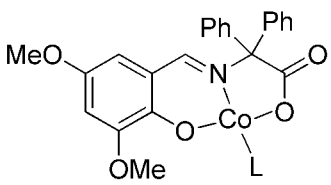
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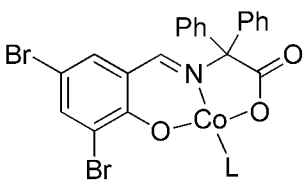
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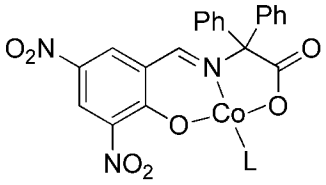
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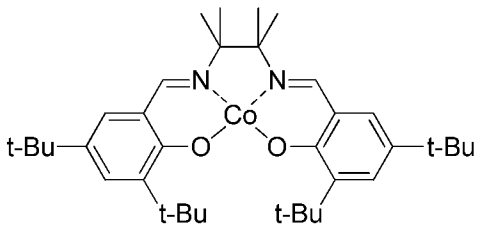
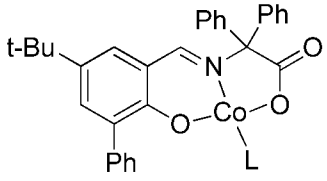
wherein L can be a coordinating solvent (for example, water, methanol, ethanol, THF, acetone, and the like). In some embodiments, the Group VII transition metal compound can

be  . In other embodiments, the Group VII transition metal compound can be  .

[0056] The Group VII and Group IX transition metal compounds are commercially available and/or can be prepared using methods known to those skilled in the art. Examples are provided in the following: Gaspar et al., *Angew. Chem., Int. Ed.* **2007**, 46, 4519-4522; Gaspar et al., *Angew. Chem., Int. Ed.* **2008**, 47, 5758-5760; Schaus et al., *J. Am. Chem. Soc.*, **2002**, *124*, 1307–1315; European Patent Publication EP1323725, published July 2, 2003; Waser et al., *J. Am. Chem. Soc.* **2006**, *128*, 11693-11712; and Gaspar et al., *Am. Chem. Soc.* **2009**, 131, 13214-13215, which are hereby incorporated by reference in their entireties.

Reagents

[0057] Various reagents can be used to contribute all or a part of a substituent group to the bicyclo[1.1.1]pentane compound. In some embodiments, the reagent can function as an electrophile and can trap a nucleophile. In other embodiments, the reagent can function as a radical trap of a carbon radical species to provide the substituted BCP.

[0058] In some embodiments, the reagent capable of contributing all or a part of a substituent group can have the structure LG^1-R^1, wherein R^1 attaches to a carbon of [1.1.1]propellane and LG^1 is a leaving group.

[0059] As used herein, "leaving group" refers to any atom or moiety that is capable of being displaced by another atom or moiety in a chemical reaction. More specifically, in some embodiments, "leaving group" refers to the atom or moiety that is displaced in a nucleophilic substitution reaction. In some embodiments, "leaving groups" are any atoms or moieties that are conjugate bases of strong acids. Examples of suitable leaving

groups include, but are not limited to, tosylates, mesylates, sulfonyls, and halogens (e.g., I, Br, and Cl). Non-limiting characteristics and examples of leaving groups can be found, for example in *Organic Chemistry*, 2nd ed., Francis Carey (1992), pages 328-331; *Introduction to Organic Chemistry*, 2nd ed., Andrew Streitwieser and Clayton Heathcock (1981), pages 169-171; and *Organic Chemistry*, 5th ed., John McMurry (2000), pages 398 and 408; all of which are incorporated herein by reference for the limited purpose of disclosing characteristics and examples of leaving groups.

[0060] In some embodiments, LG^1 can be an optionally substituted sulfonyl, an optionally substituted phosphonate, an alkali metal or a transition metal. Various of optionally substituted sulfonyls and optionally substituted phosphonate are suitable. In some embodiments, the optionally substituted sulfonyl can be an optionally substituted tosyl. In some embodiments, the optionally substituted phosphonate can be an optionally substituted di(alkyl)cyanophosphonate (for example, di(ethyl)cyanophosphonate).

[0061] A non-limiting list of examples of the reagents having the structure LG^1-R^1 include tosyl azide, sulfonyl azide, lithium azide, sodium azide, potassium azide, cesium azide, zinc azide, tosyl cyanide, tosyl chloride, potassium thiocyanate, potassium cyanate, sodium nitrite, (E)-(phenylsulfonyl)methanal O-benzyl oxime, (E)-N-(benzyloxy)-1-(phenylsulfonyl)methanimidoyl cyanide, diethyl phosphorocyanidate, *tert*-butylisocyanate, and an optionally substituted sulfonyl oxime.

[0062] In other embodiments, the reagent capable of contributing all or a part of a substituent group can have the structure R^{1A}-R^{1B}, wherein R^{1B} attaches to a carbon of [1.1.1]propellane and undergoes a further transformation to form R^1, and R^{1A} forms a byproduct. An example of R^{1A}-R^{1B} is molecular oxygen. One oxygen atom of molecular oxygen attached to a carbon of [1.1.1]propellane and the other oxygen forms an oxide byproduct (e.g., silanoxy byproduct). A further example of a reagent capable of contributing all or a part of a substituent group having the structure R^{1A}-R^{1B} is an optionally substituted oxaziridine.

[0063] In still other embodiments, the reagent capable of contributing all or a part of a substituent group can have the structure R^1. For these reagents, all the atoms of the

reagent can add to a carbon of [1.1.1]propellane to form the substituted BCP. An example of this type of reagent is 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).

[0064] In yet still other embodiments, the reagent capable of contributing all or a part of a substituent group can have the structure of an optionally substituted R^1-C_{2-10} alkenyl. In some embodiments, R^1-C_{2-10} alkenyl can be unsubstituted. In other embodiments, R^1-C_{2-10} alkenyl can be substituted. In some embodiments, the reagent capable of contributing all or a part of a substituent group can have the structure of an optionally substituted R^1-C_{2-6} alkenyl

Hydride Sources

[0065] Various reagents can be used to donate a hydrogen to [1.1.1]propellane. As used herein, "hydride source" is a reagent capable of donating a H^- or H-radical (H•). Suitable hydride sources can transfer a hydride to [1.1.1]propellane or the metal center of the Group VII or IX transition metal compound to give a metal-hydride complex.

[0066] In some embodiments, the hydride source can be a metal-based hydride source. Examples include, but are not limited to, alkali metal-based hydrides, and alkali metal-based borohydrides (such as, sodium borohydride, sodium cyanoborohydride, lithium borohydride and sodium triacetoxyborohydride). In other embodiments, the hydride source can be a non-metal-based hydride source. Examples of non-metal-based hydride sources include, but are not limited to, silanes (for example, phenylsilane and methyldiphenylsilane), 1,1,3,3-tetramethyldisiloxane (TMDSO) and an optionally substituted borane (such as, BH_3, BH_3-complex, 9-Borabicyclo[3.3.1]nonane (9-BBN), and isopinocampheylborane).

[0067] Hydride source reagents can be obtained from commercial vendors and/or prepared utilizing methods known to those skilled in the art. The deuterated equivalents can also be obtained from commercial vendors and/or prepared using commercially available reagents, for example, as described in Keinan et al., *J. Org. Chem.*, **1987**, *52*, 2576–2580 and Harvey et al., *J. Am. Chem. Soc.*, **1957**, *79*, 1437–1439. which are hereby incorporated by reference in their entireties. In some embodiments, a method provided herein can include adding a first portion of a hydride source and a second portion of a hydride source.

[0068] The amounts of [1.1.1]propellane, the Group VII or Group IX transition metal compound, the hydride source and the reagent capable of contributing all or a part of a

substituent group can vary. In some embodiments, one or more of the [1.1.1]propellane, the Group VII or Group IX transition metal compound, the hydride source and the reagent capable of contributing all or a part of a substituent group can be in excess to another one or more of the aforementioned compounds. In some embodiments, the reagent capable of contributing all or a part of a substituent group can be in excess of [1.1.1]propellane and/or the hydride source. In other embodiments, the hydride source can be in excess of [1.1.1]propellane and/or the reagent capable of contributing all or a part of a substituent group. In still other embodiments, [1.1.1]propellane can be in excess of the hydride source and/or the reagent capable of contributing all or a part of a substituent group. The amount in excess can vary. For example, the amount in excess can be about 1.2 times or more, about 1.5 times or more, about 2 times or more, about 3 times or more, or about 4 times or more. In other embodiments, one or more of [1.1.1]propellane, the Group VII or Group IX transition metal compound, the hydride source and the reagent capable of contributing all or a part of a substituent group can be in approximately equal molar amounts to another one or more of the aforementioned compounds.

[0069] The order in which each of [1.1.1]propellane, the Group VII or Group IX transition metal compound, the hydride source and the reagent capable of contributing all or a part of a substituent group are combined can also vary. For example, the Group VII or Group IX transition metal compound can be combined with the reagent capable of contributing all or a part of a substituent group, followed by the addition of [1.1.1]propellane and the hydride source. Alternatively, [1.1.1]propellane can be added before the reagent capable of contributing all or a part of a substituent group.

Additional Compounds

[0070] In some embodiments, a method described herein can include one or more additional compounds. For example, a method described herein can also include an additional compound that can act as an initiator. An initiator can generate a reactive radical species to facilitate the reaction.

[0071] In some embodiments, a method described herein can also include a compound that can act as a trapping compound. As an example, a trapping compound can

combine with a byproduct of one of the compounds formed in a method described herein and can reduce the number of side reaction(s) and/or the amount of side products formed during the reaction. In other embodiments, the trapping compound can be a radical trapping compound. An example of a radical trapping compound is butylated hydroxytoluene (BHT).

[0072] In some embodiments, a method described herein can also include an additional compound that can act as an additive. As used herein, an "additive" facilitates the regeneration of a reactive compound. For example, an additive can regenerate the reactive transition metal compound. Suitable additional compounds that can be used in a methods descried herein include, for example, *tert*-butyl hydroperoxide, benzoyl peroxide, di-*tert*-butyl peroxide, 2,2′-azobis(2-methylpropionitrile) (AIBN), methylmorpholine oxide, potassium hexacyanoferrate(III), oxygen, sodium periodate, silver bromoate, silver chloroformate, ceric ammonium nitrate, hydrogen peroxide, sodium hypochlorite, Oxone®, 3-chloroperbenzoic acid, and the like.

[0073] One or more additional compounds can be included in a method provided herein at various points. Likewise, various amounts of one or more additional compounds can be included in a method provided herein. The timing and amounts of additional compounds to include in a methods provided herein is within the knowledge of those skilled in the art.

Solvents

[0074] A variety of solvents can be utilized in the methods described herein. In some embodiments, the solvent can be an alcohol-based solvent. In some embodiments, a co-solvent can be used in a method described herein. Suitable solvents and co-solvents include, but are not limited to, ethanol, methanol, isopropanol, H_2O, THF, Et_2O, NMP, DMF, DMSO, MTBE, CH_3CN, CH_2Cl_2, toluene, or dioxane, and mixtures thereof. In some embodiments, the solvent can be H_2O. In other embodiments, the solvent can be THF. In some embodiments, the solvent and co-solvent combination can be H_2O and THF. In some embodiments, the solvent can be isopropanol. In some embodiments, the solvent can be a solvent system of methanol and Et_2O.

Time and Temperature

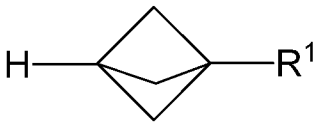
[0075] The methods provided herein can be conducted at various temperatures. Further, the temperature can be lowered and/or raised during the method. In some embodiments, the temperature can be in the range of about -5 °C to about 30 °C. In some embodiments, the temperature can be room temperature (about 25 °C). In other embodiments, the temperature can be about 0 °C. In some embodiments, the temperature can be greater 30 °C. In other embodiments, the temperature can be less than 0 °C.

[0076] The time can also vary for a method described herein. For example, the time of a method provided herein can be in the range of about 30 minutes to about 3 hours. In some embodiments, the time can be in the range of about 10 hours to about 24 hours.

[0077] As provided herein, the R^1 that is first attached to the BCP can undergo further transformations to form other R^1 groups. For example, an R^1 group can be reduced using methods known to those skilled in the art to form other R^1 groups. Examples of further transformations include reduction, oxidation, addition, elimination, condensation, coupling, metathesis, rearrangements, cyclizations, aromatization, annulations, fragmentations, substitutions, transfers, homologations, and multicomponent reactions. As a specific example, an azide can be reduced using methods known to those skilled in the art to form an amino group. Further examples of suitable transformations are provided in Richard C. Larock *Comprehensive Organic Transformations: A Guide to Functional Group Preparations* (2nd Ed., Wiley, John & Sons, Inc., Nov. 1999); and Jerry March, (*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (6th Ed., Wiley, John & Sons, Inc., Jan. 2007).

Compounds

[0078] Some embodiments disclosed herein relate to a compound of Formula (I):



(I)

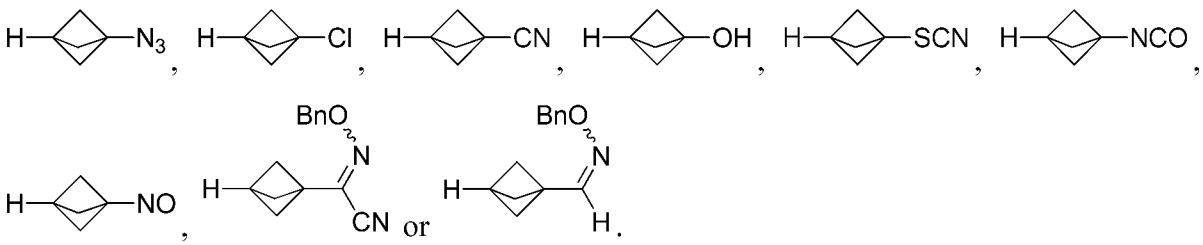
wherein: R^1 can be N_3, CF_3, F, Cl, Br, I, CN, OH, SCN, NCO, NO, -C(=NOR^2)(CN), or -CH(=NOR^2), and R^2 can be (C_1 to C_{10}) alkoxy, substituted or unsubstituted (C_1 to C_{30}) alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or

unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocycle, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl(alkyl), substituted or unsubstituted alkyl(aryl), or substituted or unsubstituted heteroaryl(alkyl).

[0079] One or more methods described herein can be used to obtain a compound of Formula (I). For example, in some embodiments, R^1 can be N_3, SCN, -C(=NOR^2)(CN) or -CH(=NOR^2). In other embodiments, R^1 can be CF_3, F, Cl, Br, I, CN, OH or NCO. In some embodiments, R^1 can be N_3. In other embodiments, R^1 can be CF_3. In still other embodiments, R^1 can be F. In yet still other embodiments, R^1 can be Cl. In some embodiments, R^1 can be Br. In other embodiments, R^1 can be I. In still other embodiments, R^1 can be CN. In still other embodiments, R^1 can be OH. In yet still other embodiments, R^1 can be SCN. In some embodiments, R^1 can be NCO. In other embodiments, R^1 can be NO. In still other embodiments, R^1 can be -C(=NOR^2)(CN). In yet still other embodiments, R^1 can be -CH(=NOR^2).

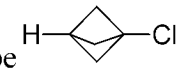
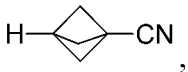
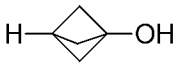
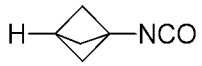
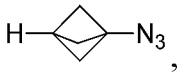
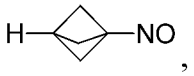
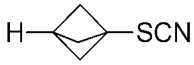
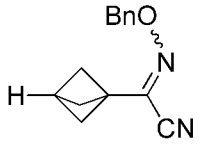
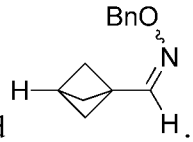
[0080] As provided herein, R^2 can be a variety of groups. For example, R^2 can be (C_1 to C_{10}) alkoxy, substituted or unsubstituted (C_1 to C_{30}) alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl(alkyl), substituted or unsubstituted alkyl(aryl), or substituted or unsubstituted heteroaryl(alkyl). In some embodiments, R^2 can be an optionally substituted benzyl. In some embodiments, OR^2 can be carbimidoyl cyanide, carbaldehyde oxime, (benzyloxy) carbimidoyl cyanide or carbaldehyde O-benzyl oxime.

[0081] A non-limiting list of compounds of Formula (I) include the following:

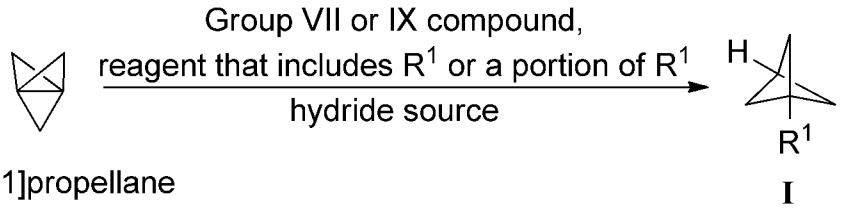


[0082] In some embodiments, R^1 cannot be N_3. In other embodiments, R^1 cannot be CF_3. In still other embodiments, R^1 cannot be F. In yet still other embodiments, R^1 cannot

be Cl. In some embodiments, R^1 cannot be Br. In other embodiments, R^1 cannot be I. In still other embodiments, R^1 cannot be CN. In still other embodiments, R^1 cannot be OH. In yet still other embodiments, R^1 cannot be SCN. In some embodiments, R^1 cannot be NCO. In other embodiments, R^1 cannot be NO. In still other embodiments, R^1 cannot be -C(=NOR^2)(CN). In yet still other embodiments, R^1 cannot be -CH(=NOR^2).

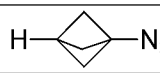
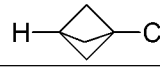
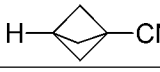
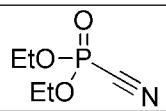
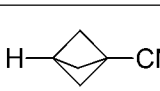
[0083] In some embodiments, a compound of Formula (I) cannot be  ,  ,  and  . In other embodiments, a compound of Formula (I) cannot be  ,  ,  ,  and  .

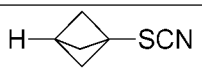
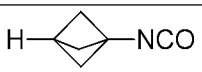
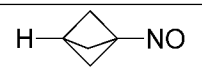
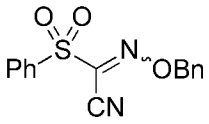
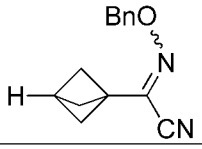
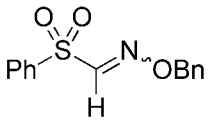
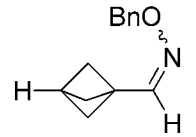
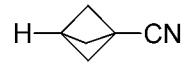
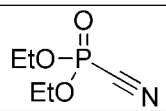
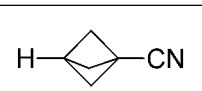
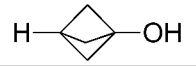
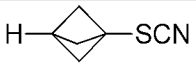
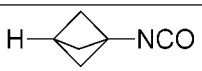
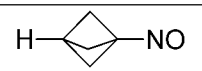
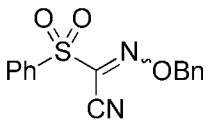
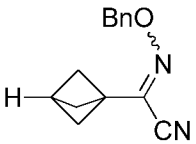
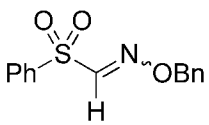
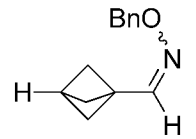
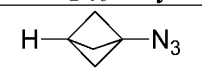
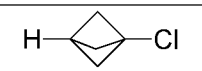
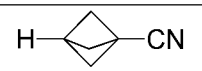
[0084] Additional details for preparing substituted bicyclo[1.1.1]pentane compounds are provided in Table 1.

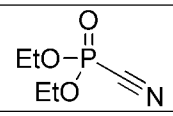
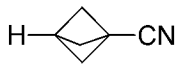
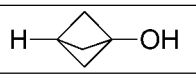
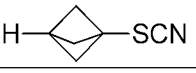
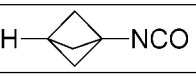
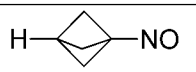
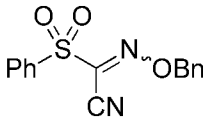
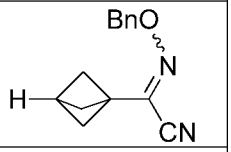
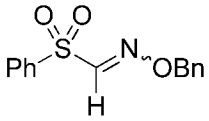
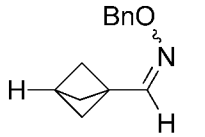


[1.1.1]propellane **I**

Table 1

Reagent for R^1	Group VII or IX compound	Hydride Source	Product
TsN_3	$Mn(dpm)_3$	$PhSiH_3$	
TsCl	$Mn(dpm)_3$	$PhSiH_3$	
TsCN	$Mn(dpm)_3$	$PhSiH_3$	
	$Mn(dpm)_3$	$PhSiH_3$	
O_2	$Mn(dpm)_3$	$PhSiH_3$	

Reagent for R^1	Group VII or IX compound	Hydride Source	Product
KSCN	$Mn(dpm)_3$	$PhSiH_3$	
KOCN	$Mn(dpm)_3$	$PhSiH_3$	
$NaNO_2$	$Mn(dpm)_3$	$PhSiH_3$	
	$Mn(dpm)_3$	$PhSiH_3$	
	$Mn(dpm)_3$	$PhSiH_3$	
R^1-C_{2-10} alkenyl*	$Mn(dpm)_3$	$PhSiH_3$	R^1-C_{2-10} alkyl*
TsN_3	Co(t-butyl-salen)	$PhSiH_3$	
TsCl	Co(t-butyl-salen)	$PhSiH_3$	
TsCN	Co(t-butyl-salen)	$PhSiH_3$	
	Co(t-butyl-salen)	$PhSiH_3$	
O_2	Co(t-butyl-salen)	$PhSiH_3$	
KSCN	Co(t-butyl-salen)	$PhSiH_3$	
KOCN	Co(t-butyl-salen)	$PhSiH_3$	
$NaNO_2$	Co(t-butyl-salen)	$PhSiH_3$	
	Co(t-butyl-salen)	$PhSiH_3$	
	Co(t-butyl-salen)	$PhSiH_3$	
R^1-C_{2-10} alkenyl*	Co(t-butyl-salen)	$PhSiH_3$	R^1-C_{2-10} alkyl*
TsN_3	Co(sal-diphenyl)	$PhSiH_3$	
TsCl	Co(sal-diphenyl)	$PhSiH_3$	
TsCN	Co(sal-diphenyl)	$PhSiH_3$	

Reagent for R^1	Group VII or IX compound	Hydride Source	Product
	Co(sal-diphenyl)	$PhSiH_3$	
O_2	Co(sal-diphenyl)	$PhSiH_3$	
KSCN	Co(sal-diphenyl)	$PhSiH_3$	
KOCN	Co(sal-diphenyl)	$PhSiH_3$	
$NaNO_2$	Co(sal-diphenyl)	$PhSiH_3$	
	Co(sal-diphenyl)	$PhSiH_3$	
	Co(sal-diphenyl)	$PhSiH_3$	
R^1-C_{2-10} alkenyl*	Co(sal-diphenyl)	$PhSiH_3$	R^1-C_{2-10} alkyl*

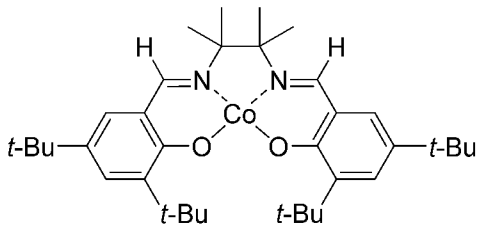
* indicates that the alkenyl and alkyl can be optionally substituted

[0085] It should be noted that one skilled in the art would know how to modify the procedures set forth in the illustrative schemes and examples to arrive at the desired products.

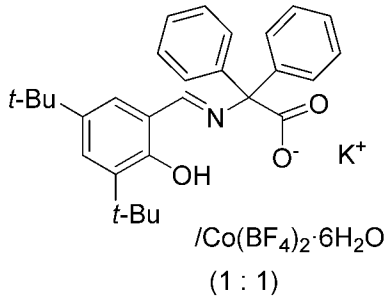
EXAMPLES

EXAMPLE 1: General Procedure

[0086] A solution of catalyst **A** or **B** (2-5 mol %) was dissolved in either a 3:1 or 2:1 mixture of anhydrous MeOH and anhydrous Et_2O containing 1 ppm BHT (10 mM final concentration) and stirred under N_2 for 2 mins. Propellane (1 eq.) and the appropriate trapping agent (1.2 – 1.5 eq.) were added followed by $PhSiH_3$ (1.0 eq.). After stirring overnight at RT (room temperature), the mixture was concentrated to afford the desired compound that was either further purified by flash chromatography on silica gel or used without further purification.

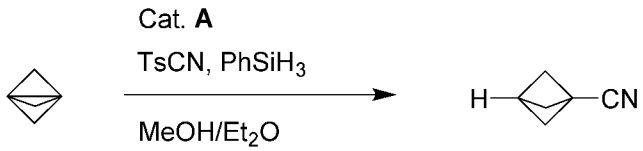


Catalyst A
Co(t-butyl-salen)



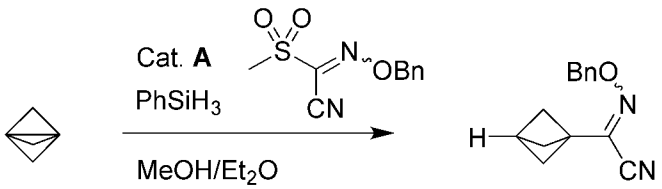
Catalyst B
Co(sal-diphenyl)

EXAMPLE 2: bicyclo[1.1.1]pentane-1-carbonitrile:



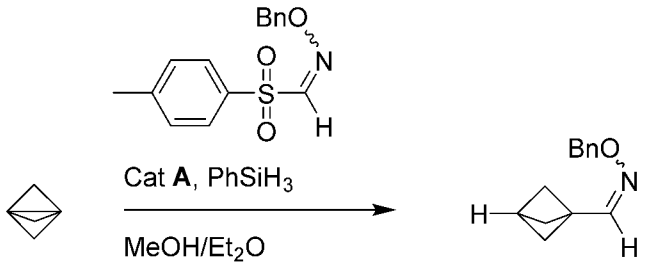
[0087] Bicyclo[1.1.1]pentane-1-carbonitrile was prepared according to the general procedure of Example 1 using tosyl cyanide, catalyst A and phenylsilane in MeOH/Et_2O. ^1H NMR (400 MHz, MeOH-*d*4) δ 2.40 (s, 1 H), 2.31 (s, 6 H).

EXAMPLE 3: N-(benzyloxy)bicyclo[1.1.1]pentane-1-carbimidoyl cyanide:



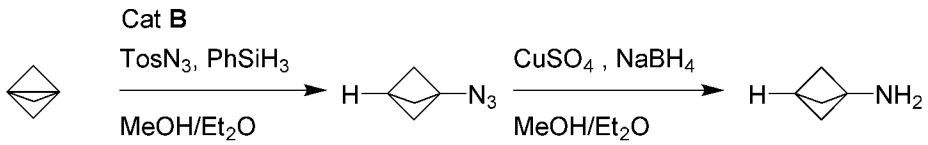
[0088] N-(benzyloxy)bicyclo[1.1.1]pentane-1-carbimidoyl cyanide was prepared according to the general procedure of Example 1 using N-(benzyloxy)-1-(methylsulfonyl)methanimidoyl cyanide, catalyst A and phenylsilane in MeOH/Et_2O. The product was isolated as a mixture of isomers (E and Z). Major isomer: ^1H NMR (400 MHz, MeOH-d4) δ 7.37 – 7.33 (m, 5H), 5.24 (s, 2H, 2.53 (s, 1H), 2.07 (s, 6H). Minor isomer: ^1H NMR (400 MHz, MeOH-d4) δ 7.37 – 7.33 (m, 5H), 5.22 (s, 1H), 2.51 (s, 1H), 2.19 (s, 6H).

EXAMPLE 4: bicyclo[1.1.1]pentane-1-carbaldehyde O-benzyl oxime:



[0089] N-(benzyloxy)bicyclo[1.1.1]pentane-1-carbimidoyl cyanide was prepared according to the general procedure of Example 1 using tosylmethanal O-benzyl oxime, catalyst A and phenylsilane in MeOH/Et_2O. LC/MS (APCI) *m/z* 202.1 [$C_{13}H_{15}NO + H^+$].

EXAMPLE 5: 1-azidobicyclo[1.1.1]pentane and 1-aminobicyclo[1.1.1]pentane:

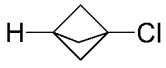


[0090] 1-azidobicyclo[1.1.1]pentane was prepared according to the general procedure of Example 1 using tosyl azide, catalyst B and phenysilane in MeOH/Et_2O.

[0091] To the crude azide from the previous step in MeOH/Et_2O was added a suspension of $CuSO_4$ (0.1 eq.), $NaBH_4$ (1 eq.) in MeOH at 0 °C. $NaBH_4$ (4 eq.) was added portionwise over 1 h. The mixture was stirred overnight, and then acidified with 4N HCl in dioxane. The mixture was then concentration to dryness followed by trituration with Et_2O to afford 1-aminobicyclo[1.1.1]pentane. LC/MS (APCI) *m/z* 84.1 $[C_5H_9N+H]^+$.

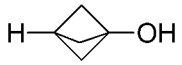
[0092] Those skilled in the art understand that 1-aminobicyclo[1.1.1]pentane is formed from 1-azidobicyclo[1.1.1]pentane using the conditions described herein. (See Goh, Y. L., et al., *Organic Letters* **2014,** *16(7)*, 1884-1887). Therefore, obtaining 1-aminobicyclo[1.1.1]pentane from the conditions described herein is evidence of the formation of 1-azidobicyclo[1.1.1]pentane from BCP using tosyl azide, catalyst B and phenysilane in MeOH/Et_2O.

EXAMPLE 6: 1-chlorobicyclo[1.1.1]pentane:



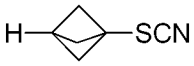
[0093] Under a nitrogen atmosphere, $Mn(dpm)_3$ (0.02 mmol) is dissolved in *iso*-propanol (5 mL) at room temperature and then cooled to 0 °C. Phenylsilane (1 mmol) and tosyl chloride (1.5 mmol; addition reagent) dissolved in dichloromethane (5 mL) are added, followed by the addition of [1.1.1]propellane solution (1 mmol, ~0.2-0.5 M ether/pentane solution). The resulting mixture is stirred at 0 °C for 21 h. The reaction is quenched by adding water and brine. The mixture is stirred 5 min and then extracted with ethyl acetate. The combined organic layers are dried ($MgSO_4$), filtered and the volatiles removed under reduced pressure. The crude residue is then used in the next step, otherwise it is subjected to flash chromatography to give 1-chlorobicyclo[1.1.1]pentane.

EXAMPLE 7: bicyclo[1.1.1]pentan-1-ol:



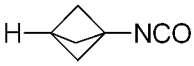
[0094] The general procedure of Example 6 is repeated using oxygen as an addition reagent, and to produce bicyclo[1.1.1]pentan-1-ol. Alternatively, the general procedure of Example 1 is followed using the appropriate reagents.

EXAMPLE 8: 1-thiocyanatobicyclo[1.1.1]pentane:



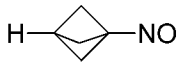
[0095] The general procedure of Example 6 is repeated using potassium thiocyanate as an addition reagent, producing 1-thiocyanatobicyclo[1.1.1]pentane. Alternatively, the general procedure of Example 1 is followed using the appropriate reagents.

EXAMPLE 9: 1-isocyanatobicyclo[1.1.1]pentane:



[0096] The general procedure of Example 6 is repeated using potassium cyanate as addition reagent, to produce 1-isocyanatobicyclo[1.1.1]pentane. Alternatively, the general procedure of Example 1 is followed using the appropriate reagents.

EXAMPLE 10: 1-nitrosobicyclo[1.1.1]pentane:



[0097] The general procedure of Example 6 is repeated using sodium nitrite as an addition reagent, to produce 1-nitrosobicyclo[1.1.1]pentane. Alternatively, the general procedure of Example 1 is followed using the appropriate reagents.

[0098] Although the foregoing has been described in some detail by way of illustrations and examples for purposes of clarity and understanding, it will be understood by those of skill in the art that numerous and various modifications can be made without departing from the spirit of the present disclosure. Therefore, it should be clearly understood that the forms disclosed herein are illustrative only and are not intended to limit the scope of the present disclosure, but rather to also cover all modification and alternatives coming with the true scope and spirit of the invention.

WHAT IS CLAIMED IS:

1. A method for making a compound of Formula (I) comprising:

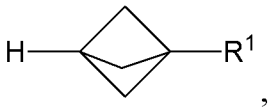
combining [1.1.1]propellane;

a Group VII transition metal compound or a Group IX transition metal compound;

a hydride source; and

a reagent capable of contributing all or a part of a substituent group such that bicyclo[1.1.1]pentane is substituted with the substituent group;

wherein the compound of Formula (I) has the structure:



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wherein:

R^1 is N_3, F, Cl, Br, I, CN, OH, SCN, NCO, NO, -C(=NOR^2)(CN) or -CH(=NOR^2); and

R^2 is (C_1 to C_{10}) alkoxy, substituted or unsubstituted (C_1 to C_{30}) alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocycle, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl(alkyl), substituted or unsubstituted alkyl(aryl), or substituted or unsubstituted heteroaryl(alkyl).

2. The method of Claim 1, wherein method uses a Group VII transition metal compound.

3. The method of Claim 2, wherein the Group VII transition metal compound is a cobalt-based transition metal compound.

4. The method of Claim 3, wherein the cobalt compound is a Co(II) compound.

5. The method of Claim 3, wherein the cobalt compound is a Co(III) compound.

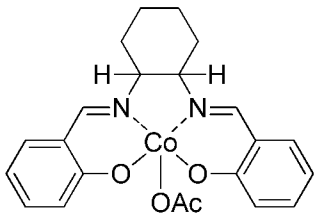
6. The method of Claim 1, wherein method uses a Group IX transition metal compound.

7. The method of Claim 6, wherein the Group IX transition metal compound is a manganese-based transition metal compound.

8. The method of Claim 7, wherein the manganese compound is a Mn(II) compound.

9. The method of Claim 7, wherein the manganese compound is a Mn(III) compound.

10. The method of Claim 1, wherein the transition metal compound is selected from the group consisting of:



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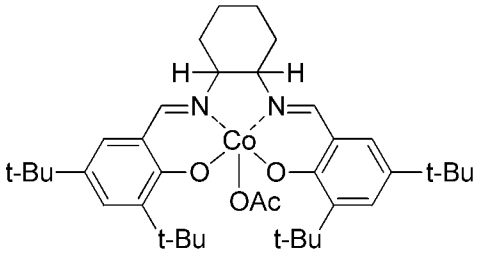

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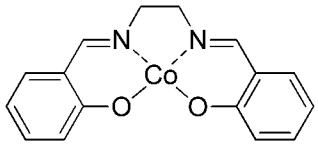

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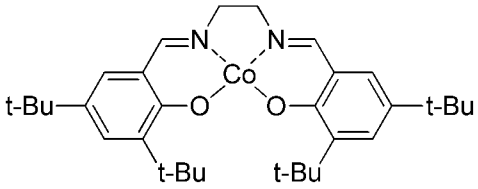

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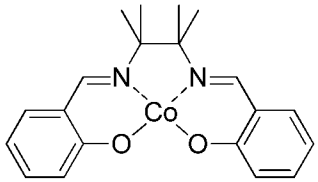

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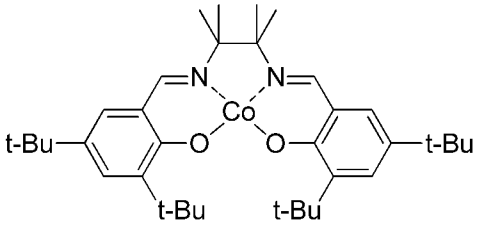

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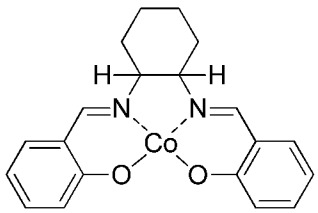

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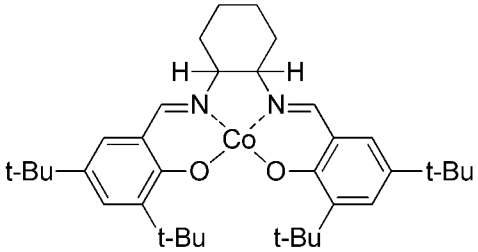

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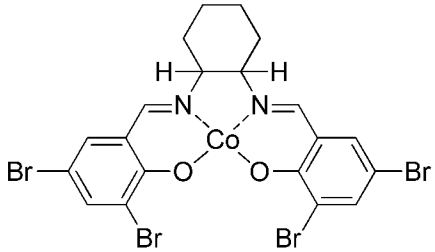

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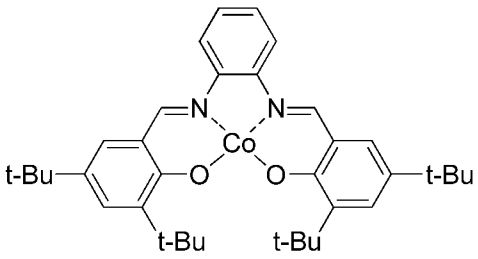

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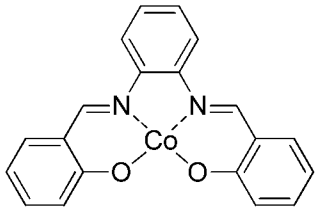

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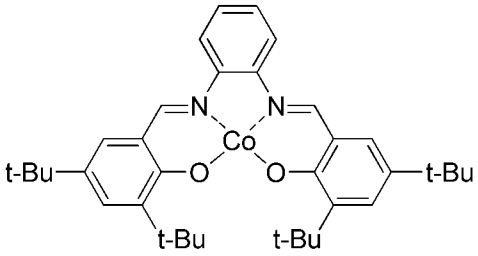

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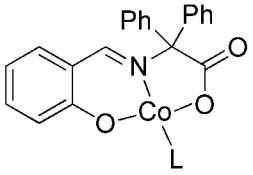

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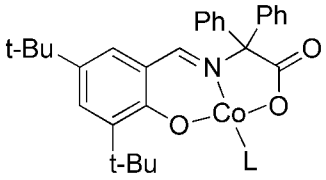

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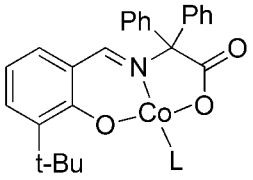

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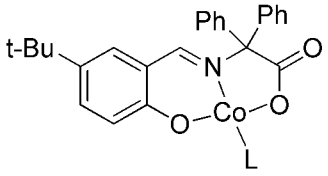

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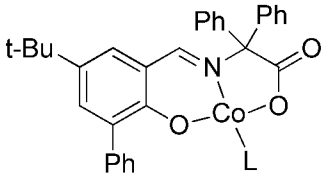

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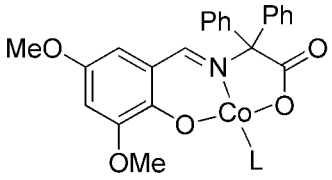

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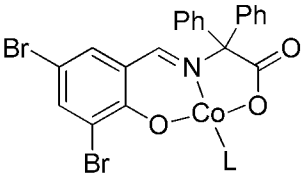

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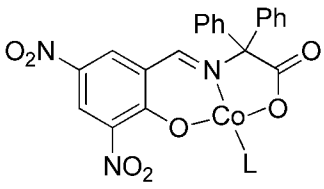


and $Mn(dmp)_3$,

wherein L is a coordinating solvent.

11. The method of Claim 10, wherein the transition metal compound is $Mn(dmp)_3$.

12. The method of any one of Claims 1-11, wherein the hydride source is a metal-based hydride source.

13. The method of Claim 12, wherein the metal-based hydride source is an alkali metal-based hydride source.

14. The method of Claim 13, wherein the alkali metal-based hydride source is $NaBH_4$.

15. The method of any one of Claims 1-11, wherein the hydride source is a non-metal-based hydride source.

16. The method of Claim 15, wherein the non-metal-based hydride source is a silane.

17. The method of Claim 16, wherein the silane is $PhSiH_3$.

18. The method of any one of Claims 1-17, wherein the reagent capable of contributing all or a part of a substituent group has the structure LG^1-R^1, wherein R^1 attaches to a carbon of [1.1.1]propellane and LG^1 is a leaving group.

19. The method of Claim 18, wherein the LG^1 is an optionally substituted sulfonyl, an optionally substituted phosphonate, an alkali metal or a transition metal.

20. The method of Claim 19, wherein the optionally substituted sulfonyl is an optionally substituted tosyl.

21. The method of Claim 18, wherein the reagent is selected from the group consisting of: tosyl azide, sulfonyl azide, lithium azide, sodium azide, potassium azide, cesium azide, zinc azide, tosyl cyanide, tosyl chloride, potassium thiocyanate, potassium cyanate, sodium nitrite, (E)-(phenylsulfonyl)methanal O-benzyl oxime, (E)-N-(benzyloxy)-1-(phenylsulfonyl)methanimidoyl cyanide, diethyl phosphorocyanidate, *tert*-butylisocyanate and an optionally substituted sulfonyl oxime.

22. The method of any one of Claims 1-17, wherein the reagent capable of contributing all or a part of a substituent group has the structure R^{1A}-R^{1B}, wherein R^{1B} attaches to a carbon of [1.1.1]propellane and undergoes a further transformation to form R^1, and R^{1A} forms a byproduct.

23. The method of Claim 22, wherein the reagent is molecular oxygen or an optionally substituted oxaziridine.

24. The method of any one of Claims 1-17, wherein the reagent capable of contributing all or a part of a substituent group has the structure R^1.

25. The method of Claim 24, wherein the reagent is 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).

26. The method of any one of Claims 1-17, wherein the reagent capable of contributing all or a part of a substituent group has the structure of an optionally substituted R^1-$C_{2\text{-}10}$ alkenyl.

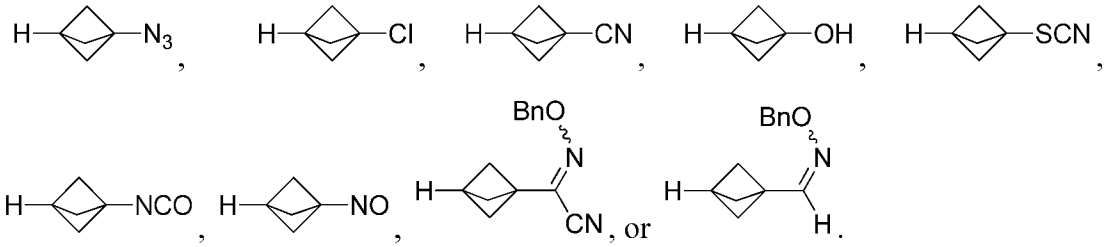
27. The method of any one of Claims 1-26, wherein R^1 is N_3, SCN, -$C(=NOR^2)(CN)$ or -$CH(=NOR^2)$.

28. The method of any one of Claims 1-26, wherein R^1 is CF_3, F, Cl, Br, I, CN, OH or NCO.

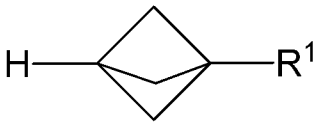
29. The method of any one of Claims 1-28, wherein OR^2 is carbimidoyl cyanide, carbaldehyde oxime, (benzyloxy) carbimidoyl cyanide or carbaldehyde O-benzyl oxime.

30. The method of any one of Claims 1-28, wherein R^2 is benzyl.

31. The method of any one of Claims 1-30, wherein the compound of Formula (I) is:



32. A compound having the structure of Formula (I):



(I)

wherein:

R^1 is N_3, CF_3, F, Cl, Br, I, CN, OH, SCN, NCO, NO, -C(=NOR^2)(CN), or -CH(=NOR^2), and

R^2 is (C_1 to C_{10}) alkoxy, substituted or unsubstituted (C_1 to C_{30}) alkyl, substituted or unsubstituted aryl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted cycloalkynyl, substituted or unsubstituted heterocycle, substituted or unsubstituted heteroaryl, substituted or unsubstituted aryl(alkyl), substituted or unsubstituted alkyl(aryl), or substituted or unsubstituted heteroaryl(alkyl).

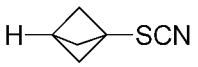
33. The compound of Claim 32, wherein R^1 is N_3, SCN, -C(=NOR^2)(CN) or -CH(=NOR^2).

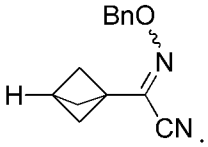
34. The compound of Claim 32, wherein R^1 is CF_3, F, Cl, Br, I, CN, OH or NCO.

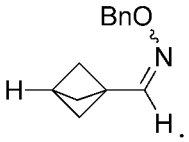
35. The compound of any one of Claims 32-34, wherein OR^2 is carbimidoyl cyanide, carbaldehyde oxime, (benzyloxy) carbimidoyl cyanide, or carbaldehyde O-benzyl oxime.

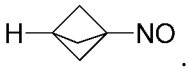
36. The compound of any one of Claims 32-34, wherein R^2 is benzyl.

37. The compound of Claim 32, having the structure  .

38. The compound of Claim 32, having the structure  .

39. The compound of Claim 32, having the structure  .

40. The compound of Claim 32, having the structure  .

41. The compound of Claim 32, having the structure  .

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/69517

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07C 211/41 (2015.01)
CPC - C07C 255/47
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C07C 211/41, 39 (2015.01)
CPC - C07C 255/47, 2102/38, 2103/08, 233/10; USPC - 514/511

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, INPADOC Data) ProQuest; Google; Google Scholar; SureChem; PubMed; PubChem; [1.1.1]propellane; bicyclo[1.1.1]pentane; manganese; cobalt; silane; phenylsilane; hydride; borohydride

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEVIN, MD et al. 'Bicyclo[1.1.1]pentanes, [1.1.1]Propellanes, and Tricyclo[2.1.0.0]pentanes'. 2000, Chem. Rev.; vol. 100; pages 169-234; Chart 3; page 172.	32-34, 37-38
Y	BUNKER, KD et al. 'Scalable Synthesis of 1-Bicyclo[1.1.1]pentylamine via a Hydrohydrazination Reaction'. 2011; Organic Letters; vol. 13, no.17; pages 4746-4748; scheme 3; column 2, second paragraph of page 4747; column 2, second paragraph of page 4748.	1-11, 12/1-11, 13/12/1-11, 14/13/12/1-11, 15/1-11, 16/15/1-11, 17/16/15/1-11, 32-34, 35/32-34, 36/32-34, 37-41
Y	WASER, J et al. 'Hydrazines and Azides via the Metal-Catalyzed Hydrohydrazination and *Hydroazidation of Olefins*'. 2006; J. Am. Chem. Soc.; 126; pagesd 11693-11712; Table 2; page 11695-11696; equations 7 and 8; Table 7; column 2, second paragraph of page 11701 to column 2, last paragraph of page 11702.	1-11, 12/1-11, 13/12/1-11, 14/13/12/1-11, 15/1-11, 16/15/1-11, 17/16/15/1-11, 32-34, 35/32-34, 36/32-34, 37-41
Y	GASPAR, B et al. ABSTRACT-'Cobalt Catalyzed Functionalization of Unactivated Alkenes: Regioselective Reductive C-C Bond Forming Reactions'. 2009; J. Am. Chem. Soc.; 131; pages 13214-13215; abstract.	35/32-34, 36/32-34, 39, 40
A	US 5,404,550 A1 (MICHL, J et al.) 11 April 1995; abstract; column 3, lines 1-60.	1-17

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2015 (11.02.2015)	24 MAR 2015
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US14/69517

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 18-31
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.