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(54) Title: PROCESS FOR PREPARING BRANCHED SKIPPED DIENES

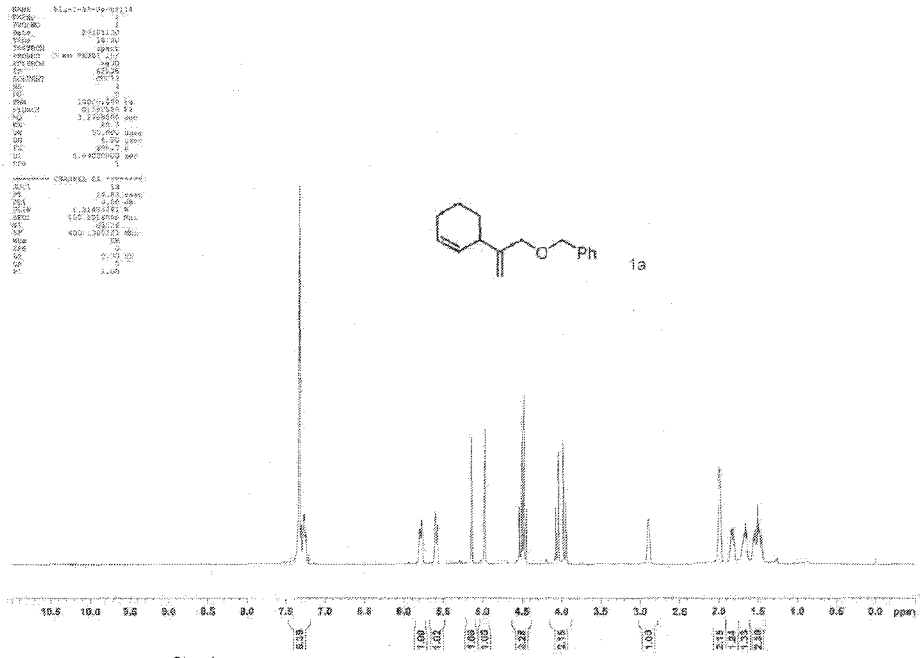

FIG. 1

(57) Abstract: The present invention is a process for preparing skipped dienes from simple endocyclic dienes and simple olefins by a transition metal catalyst.

[Continued on next page]

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PROCESS FOR PREPARING BRANCHED SKIPPED DIENES

TECHNICAL FIELD

[0001] The present application is directed to organic synthesis chemistry, in particular to a process for preparing branched skipped dienes from simple endocyclic dienes and simple alkenes, and to derivatives prepared via said process.

BACKGROUND

[0002] Synthesis of new skipped dienes, particularly skipped dienes featured with an unsymmetrical 1,1'-disubstituted alkenes, 1,2-disubstituted alkenes and tri-substituted alkenes is one of the most important aspects in organic synthesis chemistry, since skipped dienes have found broad applications due to their unique properties and applications such as chemical reactivity, polymer preparation and drug synthesis, etc.

[0003] The existing preparation methods for skipped dienes featured with an unsymmetrical 1,1'-disubstituted alkenes, 1,2-disubstituted alkenes and tri-substituted alkenes may generally rely on expensive starting materials. Most of the methods are stoichiometric in nature or suffered from very significant waste disposal problems on large scale (e.g. phosphine oxide, arylsulfonate, titanium/aluminum salt, silyl ether and halides) or high substrate preparation cost and availability.

[0004] There are only very limited availability and choices of 1,1'-disubstituted alkenes and skipped dienes on the market, mainly constrained by the availability of natural products, petroleum cracking and selective dehydrogenation of several alkanes. According to the scifinder, there are only around twenty 1,1'-disubstituted alkenes available in stock and in which rarely have a skipped diene structure (a very low amount comparing to aromatic alkenes and alpha-alkenes). Yet, both endocyclic dienes and simple alkenes are commonly observed structural motifs in bulk natural products and resources, and can be obtained easily.

[0005] Former advances are limited to those with acyclic dienes as one of the

starting materials. Those gave acyclic products that involved a diene isomerization step, and it results a mixture of regioisomers. Simple endocyclic dienes and simple olefins are incompatible substrates and unproductive. Side reactions such as olefin isomerization/oligomerization, self-dimerization, hydrogenative dimerization, etc. prevailed over the desired reactivity.

[0006] Since the simple olefins isomerization and oligomerization are kinetically more accessible than endocyclic olefins starting materials, and also conjugated olefins are thermodynamically more stable than the skipped dienes products, a skilled person in the art will not envisage the application or modifications of the closest prior art and traditional protocols to arrive the subject of matter by using a transition metal hydride or equivalent. Thus, a selective skipped dienes preparation process from those two starting materials by a transition metal hydride catalyst is unobvious over the prior art.

SUMMARY

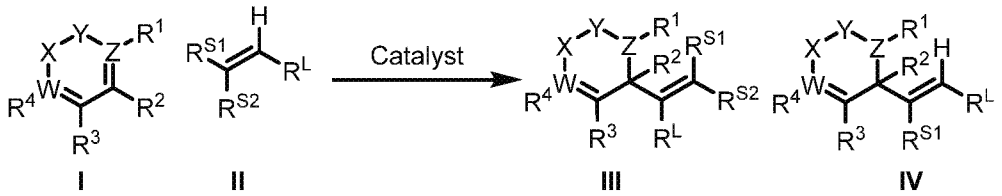
[0007] The invention aimed to change the typically observed reactivity pattern of simple endocyclic diene and simple olefin towards transition metal complex, and to control the selectivity of a carbon-carbon bond forming reaction between the pairs, strongly favoring the production of skipped diene with higher substituted alkene versus starting materials.

[0008] The invention also aimed to provide a cost effective and environmentally friendly way to fulfill the increasing demand of both skipped dienes, 1,1'-disubstituted alkenes, 1,2-disubstituted alkenes and tri-substituted alkenes, which are of limited availability and choices on the market or only available in high cost.

[0009] The invention also aimed to convert relatively unreactive alkenes into a more reactive one. Make this technology available also help to provide related products by combining with conventional olefins and by skipped dienes functionalization methodology.

[0010] In one aspect, the present application is directed to a process for preparing compounds of formula (III) and (IV) with a compound of formula (I) and a compound of

formula (II) in the presence of a transition metal catalyst or a precursor thereof,



I II III IV

wherein,

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y are linkers that connects the diene to form a n-member ring, and n is an integer, and they are each independently selected from the group consisting of Group 13-16 elements, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and the substituents are optionally linked together and

W, Z are each independently selected from the group consisting of substituted Group 13-15 elements, and

R^{S1}, R^{S2} and R^L are not all equal to H, and thereafter are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y, R^1, R^2, R^3, R^4, R^{S1}, R^{S2} and R^L are each independently selected from the above and optionally linked together.

BRIEF DESCRIPTION OF FIGURES

[0011] FIG. 1 show ^{1}H NMR spectrum of compound 1a;

[0012] FIG. 2 show ^{1}H NMR spectrum of compound 2a;

[0013] FIG. 3 show ^{1}H NMR spectrum of compound 3a;

[0014] FIG. 4 show ^{1}H NMR spectrum of compound 4a; and

[0015] FIG. 5 show ^{1}H NMR spectrum of compound 5a.

DETAILED DESCRIPTION

Definitions

[0016] In the following description, certain specific details are included to facilitate a thorough understanding of various disclosed embodiments. One skilled in the relevant art, however, will recognize that embodiments may be practiced without one or more of these specific details, or with other methods, components, materials, etc.

[0017] Unless the context requires otherwise, throughout the specification and claims which follow, the word "comprise" and variations thereof, such as "comprises" and "comprising", are to be construed in an open, inclusive sense, which is as "including, but not limited to".

[0018] Reference throughout this specification to "one embodiment", or "an embodiment", or "in another embodiment", or "some embodiments", or "in some embodiments" means that a particular referent feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearance of the phrases "in one embodiment", or "in an embodiment", or "in another embodiment", or "in some embodiments" in various places throughout this specification are not necessarily all referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

[0019] It should be noted that, as used in this specification and the appended claims, the singular forms "a", "an", and "the" include plural referents unless the content clearly dictates otherwise. In the present application, the use of "or" means "and/or" unless stated otherwise.

[0020] Certain chemical groups named herein are preceded by a shorthand notation indicating the total number of carbon atoms that are to be found in the indicated chemical group. For example, C_7-C_{12} alkyl describes an alkyl group, as defined below, having a total of 7 to 12 carbon atoms, and C_4-C_{12} cycloalkylalkyl describes a cycloalkylalkyl

group, as defined below, having a total of 4 to 12 carbon atoms. The total number of carbons in the shorthand notation does not include carbons that may exist in substituents of the group described.

[0021] As used herein, "C_m to C_n" or "$C_{m\ to\ n}$" in which "m" and "n" are integers refers to the number of carbon atoms in an alkyl, alkenyl or alkynyl group or the number of carbon atoms in the ring of a cycloalkyl or cycloalkenyl group. That is, the alkyl, alkenyl, alkynyl, ring of the cycloalkyl or ring of the cycloalkenyl can contain from "m" to "n", 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 "m" and "n" are designated with regard to an alkyl, alkenyl, alkynyl, cycloalkyl or cycloalkenyl group, the broadest range described in these definitions is to be assumed.

[0022] Accordingly, as used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated:

[0023] The term "alkyl" as used herein alone or as part of a group means any unbranched or branched, substituted or unsubstituted, saturated hydrocarbon group. The alkyl moiety may be branched or straight chain. The alkyl group may have 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that the alkyl group may consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 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 10 carbon atoms. The alkyl group could also be a lower alkyl having 1 to 5 carbon atoms. The alkyl group may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl" indicates that there are one to four carbon atoms in the alkyl chain, i.e., the alkyl chain is selected from the group consisting of methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[0024] The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is(are) one or more group(s) individually and independently

selected from substituted or unsubstituted cycloalkyl, substituted or unsubstituted cycloalkenyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted or unsubstituted heteroaryloxy, heterocyclyl, heterocyclyloxy, heteroalicyclyl, hydroxy, substituted or unsubstituted alkoxy, substituted or unsubstituted aryloxy, acyl, thiol, substituted or unsubstituted thioalkoxy, alkylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, acylalkyl, acylamino, acyloxy, aminoacyl, aminoacyloxy, oxyacylamino, keto, thioketo, *O*-carbamyl, *N*-carbamyl, *O*-thiocarbamyl, *N*-thiocarbamyl, *C*-amido, *N*-amido, *S*-sulfonamido, *N*-sulfonamido, *C*-carboxy, *O*-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and substituted or unsubstituted amino, including mono- and di-substituted amino groups, and the protected derivatives thereof, hydroxyamino, alkoxyamino, nitro, -SO-alkyl, -SO-substituted alkyl, -SO-aryl, -SO-heteroaryl, $-SO_2$-alkyl, $-SO_2$-substituted alkyl, $-SO_2$-aryl and $-SO_2$-heteroaryl.

[0025] Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, pentyl, hexyl, and the like. Wherever a substituent is described as being "optionally substituted", that substituent may be substituted with one or more of the above substituents.

[0026] The term "alkenyl" as used herein alone or as part of a group refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one double bond, having from two to twelve carbon atoms, preferably two to eight carbon atoms and which is attached to the rest of the molecule by a single bond, *e.g.*, ethenyl, propenyl, butenyl, pentenyl, penta-1,4-dienyl, and the like.

[0027] The term "alkynyl" as used herein alone or as part of a group refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing at least one triple bond, having from two to twelve carbon atoms, preferably two to eight carbon atoms and which is attached to the rest of the molecule by a single bond, *e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like.

[0028] The term "alkylene" or "alkylene chain" as used herein alone or as part of a group refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, *e.g.*, methylene, ethylene,

propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

[0029] The term "alkenylene" or "alkenylene chain" as used herein alone or as part of a group refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one double bond and having from two to twelve carbon atoms, *e.g.*, ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

[0030] The term "alkynylene" or "alkynylene chain" as used herein alone or as part of a group refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one triple bond and having from two to twelve carbon atoms, *e.g.*, propynylene, *n*-butynylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain.

[0031] The term "cycloalkyl" as used herein alone or as part of a group refers to a completely saturated (no double 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-connected fashion. Cycloalkyl groups of the present application may range from C_3 to C_{10}. In other embodiments, it may range from C_3 to C_6. A cycloalkyl group may be unsubstituted or substituted. Typical cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like. If substituted, the substituent(s) may be an alkyl or selected from those indicated above with regard to substitution of an alkyl group unless otherwise indicated.

[0032] The term "cycloalkenyl" as used herein alone or as part of a group refers to a cycloalkyl group that contains one or more double bonds in the ring although, if there is more than one, they cannot form a fully delocalized pi-electron system in the ring (otherwise the group would be "aryl", as defined herein). When composed of two or more rings, the rings may be connected together in a fused, bridged or spiro-connected fashion. A cycloalkenyl group of the present application may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated.

[0033] The term "cycloalkynyl" as used herein alone or as part of a group refers to a cycloalkyl group that contains one or more triple bonds in the ring. When composed of two or more rings, the rings may be joined together in a fused, bridged or spiro-connected fashion. A cycloalkynyl group of the present application may be unsubstituted or substituted. When substituted, the substituent(s) may be an alkyl or selected from the groups disclosed above with regard to alkyl group substitution unless otherwise indicated.

[0034] The term "carbonyl" as used herein alone or as part of a group refers to the group -(C=O).

[0035] The term "alkoxy" as used herein alone or as part of a group refers to any unbranched, or branched, substituted or unsubstituted, saturated or unsaturated ether, with C_1-C_6 unbranched, saturated, unsubstituted ethers being preferred, with methoxy and ethoxy being preferred.

[0036] The term "alkylamino" as used herein alone or as part of a group refers to the group -NH-alkyl.

[0037] The term "dialkylamino" herein alone or as part of a group refers to the group -N(alkyl)$_2$, where the alkyl groups may be the same or different.

[0038] The term "alkylcarbonyl" as used herein alone or as part of a group refers to an alkyl group bonded through a carbonyl group.

[0039] The term "alkoxycarbonyl" as used herein alone or as part of a group refers to an alkoxy group bonded through a carbonyl group.

[0040] The term "alkylaminocarbonyl" as used herein alone or as part of a group refers to an alkylamino group bonded through a carbonyl group.

[0041] The term "dialkylaminocarbonyl" as used herein alone or as part of a group refers to a dialkylamino group bonded through a carbonyl group.

[0042] The term "cycloalkoxy" as used herein alone or as part of a group refers to a cycloalkyl group, as defined above, covalently bonded to the parent molecule through an -O- linkage.

[0043] The term "halo" or "halogen" as used herein alone or as part of a group refers to bromo, chloro, fluoro or iodo.

[0044] The term "haloalkyl" as used herein alone or as part of a group refers to an alkyl radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethyl, difluoromethyl, trichloromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, 3-bromo-2-fluoropropyl, 1-bromomethyl-2-bromoethyl, and the like. The alkyl part of the haloalkyl radical may be optionally substituted as defined above for an alkyl group.

[0045] The term "trihaloalkyl" as used herein alone or as part of a group refers to an alkyl radical, as defined above, which is substituted by three halo radicals, as defined above, *e.g.*, trifluoromethyl. The alkyl part of the trihaloalkyl radical may be optionally substituted as defined above for an alkyl group.

[0046] The term "haloalkoxy" as used herein alone or as part of a group refers to an alkoxy radical, as defined above, that is substituted by one or more halo radicals, as defined above, *e.g.*, trifluoromethoxy, difluoromethoxy, trichloromethoxy, 2,2,2-trifluoroethoxy, 1-fluoromethyl-2-fluoroethoxy, 3-bromo-2-fluoropropoxy, 1-bromomethyl-2-bromoethoxy, and the like. The alkoxy part of the haloalkoxy radical may be optionally substituted as defined above for an alkoxy group.

[0047] The term "trihaloalkoxy" as used herein alone or as part of a group refers to an alkoxy group, as defined above, which is substituted by three halo radicals, as defined above. The alkoxy part of the trihaloalkoxy group may be optionally substituted as defined above for an alkoxy group.

[0048] The term "heterocyclyl" as used herein alone or as part of a group is

intended to mean three-, four-, five-, six-, seven-, and eight- or more membered rings wherein carbon atoms together with from 1 to 3 heteroatoms constitute the ring. A heterocyclyl can optionally contain one or more unsaturated bonds situated in such a way, however, that an aromatic *pi*-electron system does not arise. The heteroatoms are independently selected from oxygen, sulfur, and nitrogen.

[0049] A heterocyclyl can 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, cyclic carbamates, and the like.

[0050] Heterocyclyl rings can optionally be fused ring systems containing two or more rings wherein at least one atom is shared between two or more rings to form bicyclic or tricyclic structures. In some embodiments, such fused ring systems are formed by a bridging moiety between two atoms of a heterocyclyl.

[0051] Heterocyclyl rings can optionally also be fused to aryl rings, such that the definition includes bicyclic structures. Typically such fused heterocyclyl groups share one bond with an optionally substituted benzene ring. Examples of benzo-fused heterocyclyl groups include, but are not limited to, benzimidazolidinone, tetrahydroquinoline, and methylenedioxybenzene ring structures.

[0052] Some examples of "heterocyclyls" include, but are not limited to, tetrahydrothiopyran, 4*H*-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2*H*-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, 1,3-oxathiolane, and an azabicyclo system such as azabicyclo[3.2.1]octyl (tropane). Binding to the heterocycle can be at the position of a heteroatom or via a carbon atom of the heterocycle, or, for benzo-fused derivatives, via a carbon of the benzenoid ring.

[0053] The term "aromatic" as used herein refers to an aromatic group which has at

least one ring having a conjugated *pi* electron system and includes both carbocyclic aryl (*e.g.*, phenyl) and heterocyclic aryl groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups.

[0054] The term "carbocyclic" as used herein, refers to a compound which contains one or more covalently closed ring structures, and that the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from heterocyclic rings in which the ring backbone contains at least one atom which is different from carbon. The term "heteroaromatic" as used herein, refers to an aromatic group which contains at least one heterocyclic ring.

[0055] The term "aryl" as used herein alone or as part of a group is intended to mean a carbocyclic aromatic ring or ring system. Moreover, the term "aryl" includes fused ring systems wherein at least two aryl rings, or at least one aryl and at least one C_{3-8}-cycloalkyl share at least one chemical bond. Some examples of "aryl" rings include optionally substituted phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl.

[0056] The term "aryl" relates to aromatic, including, for example, benzenoid groups, connected via one of the ring-forming carbon atoms, and optionally carrying one or more substituents selected from heterocyclyl, heteroaryl, halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-aminoalkyl, C_{1-6}-alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, or trifluoromethyl. The aryl group can be substituted at the para and/or meta positions. In other embodiments, the aryl group can be substituted at the ortho position. Representative examples of aryl groups include, but are not limited to, phenyl, 3-halophenyl, 4-halophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, dimethylphenyl, naphthyl, hydroxynaphthyl, hydroxymethylphenyl, trifluoromethylphenyl, alkoxyphenyl, 4-morpholin-4-ylphenyl, 4-pyrrolidin-1-ylphenyl, 4-pyrazolylphenyl, 4-triazolylphenyl, and 4-(2-oxopyrrolidin-1-yl)phenyl.

[0057] The term "arylalkyl" or "aralkyl" as used herein alone or as part of a group which are used synonymously and interchangeably refers to an aryl group covalently bonded to an alkyl group, as defined herein. A "phenylalkyl" is a species of an aralkyl group, and refers to a phenyl ring covalently bonded to an alkyl group as defined herein. Examples of phenylalkyl groups include, but are not limited to, benzyl, 2-phenylethyl, 1-phenylpropyl, 4-phenylhexyl, 3-phenylamyl and 3-phenyl-2-methylpropyl. Presently preferred phenylalkyl groups are those wherein the phenyl group is covalently bonded to one of the presently preferred alkyl groups. A phenyl alkyl group of the present application may be unsubstituted or substituted. Examples of substituted phenylalkyl groups include, but are not limited to, 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxyphenyl)hexyl, 2-(5-cyano-3-methoxyphenyl)pentyl, 3-(2,6-dimethylphenyl)propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)-3-(aminomethyl)pentyl and 5-phenyl-3-oxo-pent-1-yl.

[0058] The term "heteroaryl" as used herein alone or as part of a group is intended to mean a heterocyclic aromatic group where one or more carbon atoms in an aromatic ring have been replaced with one or more heteroatoms selected from the group comprising nitrogen, sulfur, and oxygen.

[0059] Furthermore, in the present context, the term "heteroaryl" comprises fused ring systems wherein at least one aryl ring and at least one heteroaryl ring, at least two heteroaryl rings, at least one heteroaryl ring and at least one heterocyclyl ring, or at least one heteroaryl ring and at least one cycloalkyl ring share at least one chemical bond.

[0060] The term "heteroaryl" is understood to relate to aromatic, C_{3-8} cyclic groups further containing one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom with up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. Heteroaryl groups can carry one or more substituents, selected from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_{1-6}-alkoxy, C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-aminoalkyl, C_{1-6}-alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, or trifluoromethyl. In some

embodiments, heteroaryl groups can be five- and six-membered aromatic heterocyclic systems carrying 0, 1, or 2 substituents, which can be the same as or different from one another, selected from the list above.

[0061] Representative examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine, purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, pteridine, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, *O*-C_{1-6}-alkyl, C_{1-6}-alkyl, hydroxy-C_{1-6}-alkyl, and amino-C_{1-6}-alkyl.

[0062] The term "phenyl" as used herein alone or as part of a group refers to a six-membered aryl group. A phenyl group may be unsubstituted or substituted. When substituted the substituent(s) is(are) one or more, preferably one or two, group(s) independently selected from the group consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, alkyl, alkoxy, acyl, acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, -NRR', carboxamide, protected carboxamide, *N*-alkylcarboxamide, protected *N*-alkylcarboxamide, *N,N*-dialkylcarboxamide, trifluoromethyl, *N*-alkylsulfonylamino, *N*-(phenylsulfonyl)amino and phenyl (resulting in the formation of a biphenyl group).

[0063] Examples of substituted phenyl groups include, but are not limited to, 2-, 3- or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2-, 3- or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof, 2-, 3- or 4-nitrophenyl; 2-, 3- or 4-cyanophenyl, 2-, 3- or 4-methylphenyl, 2,4-dimethylphenyl, 2-, 3- or 4-(iso-propyl)phenyl, 2-, 3- or 4-ethylphenyl, 2-, 3- or 4-(*n*-propyl)phenyl, 2,6-dimethoxyphenyl, 2-, 3- or 4-methoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 2-, 3- or 4-(isopropoxy)phenyl, 2-, 3- or 4-(*t*-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl, 2-, 3- or 4-trifluoromethylphenyl, 2-, 3- or 4-carboxyphenyl

or 2,4-di(protected carboxy)phenyl, 2-, 3-, or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl, 2-, 3- or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl, and 2-, 3- or 4-(*N*-(methylsulfonylamino))phenyl.

[0064] The term "phenylalkoxy" as used herein alone or as part of a group refers to a "phenylalkyl-O-" group with "phenyl" and "alkyl" as defined herein. A phenylalkoxy group of the present application may be substituted or unsubstituted on the phenyl ring, in the alkyl group or both. Examples of phenylalkoxy groups include, but are not limited to, 2-(4-hydroxyphenyl)ethoxy, 4-(4-methoxyphenyl)butoxy, (2*R*)-3-phenyl-2-amino-propoxy, (2*S*)-3-phenyl-2-amino-propoxy, 2-indanoxy, 6-phenyl-1-hexanoxy, cinnamyloxy, 2-phenyl-1-propoxy and 2,2-dimethyl-3-phenyl-1-propoxy.

[0065] The term "mercapto" as used herein refers to a group of formula "-SH".

[0066] The term "alkylthio" as used herein alone or as part of a group refers to an "alkyl-S-" group, with alkyl as defined above. Examples of alkylthio group include, but are not limited to, methylthio, ethylthio, *n*-propylthio, isopropylthio, *n*-butylthio and *t*-butylthio.

[0067] The term "arylthio" as used herein alone or as part of a group refers to an "aryl-S-" group, with aryl as defined above. Examples of arylthio group include, but are not limited to, phenylthio, naphthylthio, and anthracylthio.

[0068] The term "alkylsulfinyl" as used herein alone or as part of a group refers to an "alkyl-SO-" group, with alkyl as defined above. Examples of alkylsulfinyl groups include, but are not limited to, methylsulfinyl, ethylsulfinyl, *n*-propylsulfinyl, isopropylsulfinyl, *n*-butylsulfinyl and *sec*-butylsulfinyl.

[0069] The term "alkylsulfonyl" as used herein alone or as part of a group refers to an "alkyl-SO_2-" group. Examples of alkylsulfonyl groups include, but are not limited to, methylsulfonyl, ethylsulfonyl, *n*-propylsulfonyl, isopropylsulfonyl, *n*-butylsulfonyl, and *t*-butylsulfonyl.

[0070] The terms "phenylthio", "phenylsulfinyl", and "phenylsulfonyl" as used herein alone or as part of a group refer to a "phenyl-S-", "phenyl-SO-", and "phenyl-SO_2-" group, phenyl as defined herein.

[0071] The term "amine" as used herein refers to a compound that comprises an amino group. The term "amino" as used herein alone or as part of a group refers to the $-NH_2$ radical.

[0072] The term "cyano" as used herein alone or as part of a group refers to the -CN radical.

[0073] The term "hydroxy" as used herein alone or as part of a group refers to the -OH radical.

[0074] The term "imine" as used herein refers to a compound that comprises an imino group. The term "imino" as used herein alone or as part of a group refers to the =NH substituent.

[0075] The term "nitro" as used herein alone or as part of a group refers to the $-NO_2$ radical.

[0076] The term "oxo" as used herein alone or as part of a group refers to the =O substituent.

[0077] The term "thioxo" as used herein alone or as part of a group refers to the =S substituent.

[0078] The term "trifluoromethyl" as used herein alone or as part of a group refers to the $-CF_3$ radical.

[0079] The term "optional" or "optionally" as used herein means that the subsequently described event of circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not.

[0080] Unless otherwise indicated, when a substituent is deemed to be "optionally substituted", it is meant that the substituent is a group that may be substituted with one or more group(s) individually and independently selected from morpholinoalkanoate, cycloalkyl, aryl, heteroaryl, heterocyclyl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, cyano, halo, carbonyl, 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, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino

groups, and the protected derivatives thereof.

[0081] For example, "optionally substituted aryl" means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0082] The term "transition metal" as used herein refers to any element in the d-block of the periodic table of the elements. This corresponds to groups 3 (IIIB) to 12 (IIB) on the periodic table.

[0083] The term "ligand" in chemistry generally refers to an atom, ion, or molecule that bonds to a central metal, generally involving formal donation of one or more of its electrons. The metal-ligand bonding ranges from covalent to more ionic.

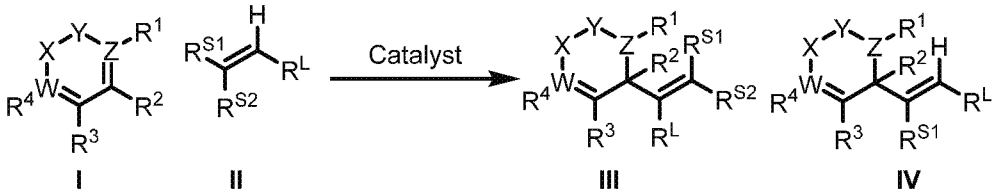
[0084] The term "carbene(s)" as used herein refers to an organic molecule containing a carbon atom with six valence electrons and having the general formula RR'C:.

[0085] Metalloid, or semi metal, is a term used in chemistry when classifying the chemical elements. On the basis of their general physical and chemical properties, nearly every element in the periodic table can be termed either a metal or a nonmetal. However, a few elements are referred to as metalloids. There is no rigorous definition of the term, but the following properties are usually considered characteristic of metalloids: (1) metalloids often form amphoteric oxides; and (2) metalloids often behave as semiconductors (B, Si, Ge).

[0086] The following elements are generally considered metalloids: Boron (B), Silicon (Si), Germanium (Ge), Arsenic (As), Antimony (Sb), Tellurium (Te), and Polonium (Po).

[0087] The term "endocyclic dienes" as used herein alone or as part of a group means any unbranched or branched, substituted or unsubstituted, pure hydrocarbon or heteroatom substituted n-member rings with 2 or more unsaturated bonds within the rings, where n is equal to an integer with a numerical range such as "4 to 20". By way of example only, this included by not limited to cyclohexadiene, cycloheptadiene, α-phellandrene, α-terpinene, 1,2-dihydropyridine, 2,3-dihydropyridine, 2H-pyran and the like.

[0088] In one aspect, the present application is directed to a process for preparing compounds of formula (III) and (IV) with a compound of formula (I) and a compound of formula (II) in the presence of a transition metal catalyst or a precursor thereof,



I II III IV

wherein,

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y are linkers that connects the diene to form a n-member ring, and n is an integer, and they are each independently selected from the group consisting of Group 13-16 elements, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and the substituents are optionally linked together and

W, Z are each independently selected from the group consisting of substituted Group 13-15 elements, and

R^{S1}, R^{S2} and R^L are not all equal to H, and thereafter are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y, R^1, R^2, R^3, R^4, R^{S1}, R^{S2} and R^L are each independently selected from the above and optionally linked together.

[0089] In some embodiments of the present application, R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of alkyl, aryl and alkoxyl.

[0090] Examples of the compounds of formula (I) that may be used in the present invention include, but are not limited to cyclohexadiene, cycloheptadiene, α-phellandrene, α-terpinene, 1,2-dihydropyridine, 2,3-dihydropyridine, 2H-pyran and the

like.

[0091] Examples of the compounds of formula (II) that may be used in the present invention include, but are not limited to 1-hexene/1-octene (straight chain monoene), vinylcyclohexane, 4-methyl-1-pentene (branched chain monoene), 2-hexene (acyclic internal olefins), styrene, allylbenzene (aromatic alkenes), vinylsilanes (vinylmetalloids), benzyl vinylethers (vinylethers), cyclohexenes and 1,2-dihydrofurans (cyclic olefins), and their substituted derivatives thereof, more highly substituted alkenes, and the like.

[0092] The methods of the present invention may be used to catalytically couple one diene and one alkene to form a skipped diene in one-pot. In some embodiments of the present application, the method is used to combine less reactive alkenes such as monoene or internal alkenes to build a more reactive one such as 1,1'-disubstituted alkenes, 1,2-disubstituted alkenes and tri-substituted alkenes.

[0093] In some embodiments of the present application, the method is used to comprise two different alkenes in a single reaction chamber in the presence of a catalyst to form a skipped diene in nearly quantitative yield.

[0094] In one embodiment, the reaction may be intermolecular, i.e. the two reactants are not joined by a bond prior to the coupling reaction. In another embodiment, the reaction may be intramolecular.

[0095] The transition metal catalyst of the present invention may include any catalytic transition metal and/or catalyst precursor as it is introduced into the reaction vessel and which may be, if needed, converted in situ into active form, as well as the active form of the catalyst which participates in the reaction. In some embodiments, the transition metal catalyst is provided in the reaction in a catalytic amount.

[0096] In some embodiments of the present application, the transition metal is selected from Groups 3 to 12 of the Periodic Table of Elements.

[0097] Exemplary transition metal that can be used in the present application includes, but is not limited to, Scandium (Sc), Titanium (Ti), Vanadium (V), Chromium (Cr), Manganese (Mn), Iron (Fe), Cobalt (Co), Nickel (Ni), Copper (Cu), Zinc (Zn), Yttrium (Y), Zirconium (Zr), Niobium (Nb), Molybdenum (Mo), Technetium (Tc), Ruthenium (Ru), Rhodium (Rh), Palladium (Pd), Silver (Ag), Cadmium (Cd), Hafnium

(Hf), Tantalum (Ta), Tungsten (W), Rhenium (Re), Osmium (Os), Iridium (Ir), Platinum (Pt), Gold (Au), Mercury (Hg), Rutherfordium (Rf), Dubnium (Db), Seaborgium (Sg), Bohrium (Bh), Hassium (Hs), Meitnerium (Mt), Darmstadtium (Ds), Roentgenium (Rg), and Ununbium (Uub).

[0098] In some embodiments of the present application, the transition metal is selected from Group 10 of the Periodic Table of Elements.

[0099] In some embodiments of the present application, the transition metal is selected from the group consisting of Nickel (Ni), Palladium (Pd) and Platinum (Pt). In some embodiments of the present application, the transition metal is Nickel (Ni).

[00100] The catalysts of the present invention may also include heterogeneous catalysts that containing different forms of these above elements.

[00101] Ligands on the metal catalyst may include chelating ligands, such as (heterocyclic) carbene derivatives, and/or biscarbenes, bisheterocyclic carbenes, phosphines, amines, imines, arsines and derivatives thereof, including hybrids of the above.

[00102] In some embodiments of the present application, the ligand or metal bears a weakly or non-nucleophilic stabilizing ion, including but not limited to halogen, borates, sulfonates, and phosphonates. Weakly or non-nucleophilic stabilizing ions are preferred to avoid complicating side reaction of the counter ion, for example, attacking or adding to the electrophilic center of the substrates.

[00103] Exemplary amines that can be used in the present application include, but are not limited to, aliphatic amines, and aromatic amines. Exemplary aliphatic amines that can be used in the present application include, but are not limited to, primary amines, secondary amines, and tertiary amines. Exemplary aliphatic amines that can be used in the present application include, but are not limited to, methylamine, ethanolamine, dimethylamine, methylethanolamine, trimethylamine, aziridine, piperidine, *N*-methylpiperidine, and the like. Exemplary aromatic amines that can be used in the present application include, but are not limited to, aniline, *o*-toluidine, 2,4,6-trimethylaniline, anisidine, 3-trifluoromethylaniline, and the like.

[00104] In some embodiments of the present application, additional ligands may be

included in the catalyst to obtain a stable complex.

[00105] The ligand can be added to the reaction mixture in the form of a metal complex, or added as separate reagent relative to the addition of the metal. The ligand, if chiral, can be provided as a racemic mixture or a purified stereoisomer. The ligands are commercially available or can be prepared by the methods similar to processes known in the art.

[00106] In some embodiments of the present application, the transition metal catalyst is provided in the reaction in a catalytic amount. In certain embodiments, that amount is in the range of < 2 mol%, with respect to the limiting reagent, which may be either the compound of formula (I) or the compound of formula (II), depending upon which reagent is in stoichiometric excess.

[00107] In some embodiments of the present application, the reaction is carried out in a solvent which is selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, alicyclic hydrocarbons, halohydrocarbons, alcohols, ethers, esters, ketones, nitriles and diol derivatives, and ionic liquids such as imidazolium salts.

[00108] Exemplary aromatic hydrocarbons that can be used in the present application include, but are not limited to, benzene, toluene, xylene, and the like. Exemplary aliphatic hydrocarbons that can be used in the present application include, but are not limited to, pentane, hexane, heptane, octane, and the like. Exemplary alicyclic hydrocarbons that can be used in the present application include, but are not limited to, cyclohexane, cyclohexanone, methylcyclohexanone, and the like. Exemplary aliphatic hydrocarbons that can be used in the present application include, but are not limited to, pentane, hexane, heptane, octane, and the like. Exemplary halohydrocarbons that can be used in the present application include, but are not limited to, methylene chloride, chloroform, and the like. Exemplary alcohols that can be used in the present application include, but are not limited to, methanol, ethanol, isopropanol, and the like. Exemplary ethers that can be used in the present application include, but are not limited to, diethyl ether, methyl ethyl ether, propyl ether, propylene oxide, and the like. Exemplary esters that can be used in the present application include, but are not limited to, methyl formate, ethyl formate, butyl formate, pentyl formate, methyl acetate, ethyl

acetate, propyl acetate, benzyl phenylacetate, and the like. Exemplary ketones that can be used in the present application include, but are not limited to, acetone, methylbutanone, methyl isobutyl ketone, and the like. Exemplary nitriles that can be used in the present application include, but are not limited to, acetonitrile, propionitrile, acrylonitrile, and the like. Exemplary diol derivatives that can be used in the present application include, but are not limited to, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether, ethylene glycol monobutyl ether, and the like.

[00109] In some embodiments of the present application, the solvent is an aromatic hydrocarbon. In some embodiments of the present application, the solvent is selected from the group consisting of benzene, toluene and xylene. In some embodiments of the present application, the solvent is toluene.

[00110] Alternatively, the reaction can be carried out in the alkene substrates themselves (neat condition). Ionic liquid, such as imidazolium salts, can be also used as reaction medium.

[00111] In some embodiments of the present application, the process may be carried out optionally in a buffer to minimize the problems related to isomerization, oligomerization and polymerization. Examples of the buffer which can be used in the present application include but not limited to ammonium salt, phosphorous buffer, carbonates.

EXAMPLES

[00112] The active catalyst was generated by using a transition metal with a (heterocyclic) carbene ligand and an allyl or substituted allyl precursor or equivalent, with a general structure of [carbene-M(allyl)]X or the corresponding hydride equivalent [carbene-MH]X by general procedure.

[00113] The reaction was achieved by adding the corresponding dienes and alkenes to the catalyst solution, stirring at room temperature for 24 hrs under nitrogen atmosphere.

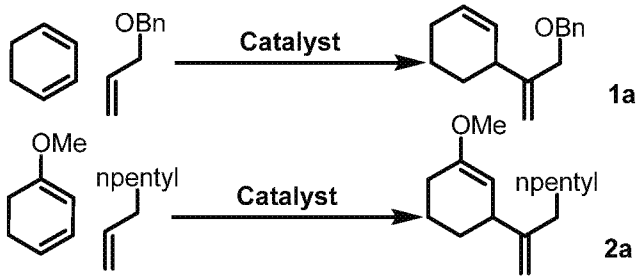
[00114] A buffer may be used to minimize the problems related to isomerization,

oligomerization and polymerization.

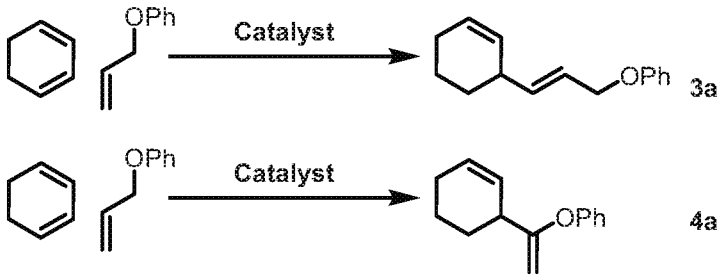
[00115] Typical procedure for the in situ catalyst generation: under a nitrogen/inert atmosphere, to a solution of a carbene (2 mol%) and $Ni(cod)_2$ (2 mol%) in 2 mL toluene in a typical round bottom flask equipped with a magnetic stir bar, 1-octene (10 mol%), triethylamine (12 mol%), p-anisaldehyde (2 mol%) and silyl triflate (4 mol%) were added sequentially at room temperature. The catalyst was generated after 30 mins of stirring at room temperature using normal bench-top apparatus. In situ catalyst generation can be done alternatively using a compound with a general formula of benzyl or allyl-X to replace the carbonyl compounds, where X equal to leaving group. Also the catalyst could be generated by oxidative addition using the corresponding ionic liquid and $Ni(cod)_2$.

[00116] Typical skipped diene preparation procedure for illustration purpose:

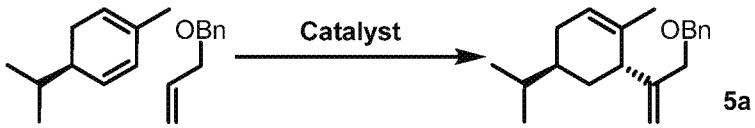
[00117] Example 1: Equal molar amount of diene and alkene substrates was added to the catalyst mixture after the catalyst generation. Keep on stirring for another 24 hrs at rt and normal pressure on bench top, work up by filtering it through a pad of silica gel and concentrate in vacuum. (e.g. Commercially available cyclohexadiene and allyl benzyl ether, or 1-methoxy-cyclohexadiene and 1-octene, 100% conversion, quantitative yield with the corresponding skipped diene (III) formed as exclusive isomer 1a and 2a).



[00118] Example 2: Similar to the above general procedure, skipped diene (IV) was obtained by using a different carbene catalyst or substrates. (e.g. cyclohexadiene and allyl phenyl ether, 100% conversion, 93% yield).



[00119] Example 3: Similar to the above general procedure, by using a different carbene catalyst that bears a weakly or non-nucleophilic stabilizing ion, skipped diene (III) and (IV) were provided selectively as a racemic mixture or a purified stereoisomer. (e.g. α-phellandrene, and allyl benzyl ether, BArF anion tetrakis(3,5-bis(trifluoromethyl)phenyl)borate, 100% conversion, > 20:1 diastereoselectivity).



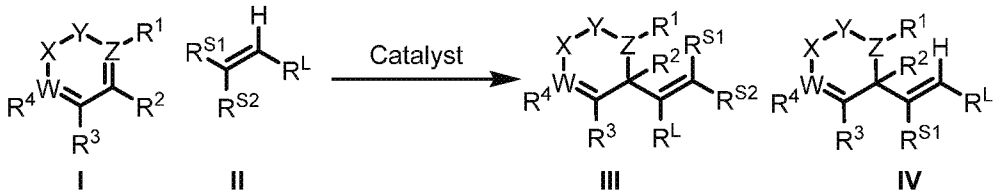
[00120] Following the above procedure, the compound (III) and (IV) were synthesized from the corresponding starting materials and the characterizations of the products thereof are provided (Figure 1-5).

[00121] All of the above U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification and/or listed in the Application Data Sheet, are incorporated herein by reference, in their entirety.

[00122] From the foregoing it will be appreciated that, although specific embodiments of the application have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the application. Accordingly, the application is not limited except as by the appended claims.

CLAIMS

1. A process for preparing a compound of formula (III) and (IV) with a compound of formula (I) and a compound of formula (II) in the presence of a transition metal catalyst or a precursor thereof,



I II III IV

wherein,

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y are linkers that connects the diene to form a n-member ring, and n is an integer, and they are each independently selected from the group consisting of Group 13-16 elements of the Periodic Table, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and the substituents are optionally linked together and

W, Z are each independently selected from the group consisting of substituted Group 13-15 elements of the Periodic Table, and

R^{S1}, R^{S2} and R^L are not all equal to H, and thereafter are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y, R^1, R^2, R^3, R^4, R^{S1}, R^{S2} and R^L are each independently selected from the above and optionally linked together.

2. A process of claim 1, wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together.

3. A process of claim 1, wherein the compound of formula (I) is selected from the group consisting of cyclohexadiene, cycloheptadiene, α-phellandrene, α-terpinene, 1,2-dihydropyridine, 2,3-dihydropyridine, 2H-pyran and the like.

4. A process of claim 1, wherein the compound of formula (II) is selected from the group consisting of straight chain monoenes such as 1-hexene/1-octene (straight chain monoene), 2-hexene (acyclic internal olefins), vinylcyclohexane, 4-methyl-1-pentene (branched chain monoene), styrene, allylbenzene (aromatic alkenes), vinylsilanes (vinylmetalloids), benzyl vinylethers (vinylethers), cyclohexenes and 1,2-dihydrofurans (cyclic olefins), and their substituted derivatives thereof, and the like.

5. A process of claim 1, wherein the transition metal is selected from Groups 3 to 12 of the Periodic Table of Elements.

6. A process of claim 1, wherein the transition metal is selected from Group 10 of the Periodic Table of Elements.

7. A process of claim 6, wherein the transition metal is Ni.

8. A process of claim 1, wherein the amount of the transition metal is in the range of < 2 mol%, with respect to the limiting reagent, which may be either the compound of formula (I) or the compound of formula (II), depending upon which reagent is in stoichiometric

excess.

9. A process of claim 1, wherein the compound of formula (I) and/or formula (II) if chiral, the compound of formula (III) and/or formula (IV) can be provided as a racemic mixture or a purified stereoisomer.

10. A process of claim 1, wherein a ligand on the transition metal catalyst is selected from the group consisting of carbenes, heterocyclic carbenes, biscarbenes, bisheterocyclic carbenes, phosphines, amines, imines, arsines and derivatives thereof.

11. A process of claim 10, wherein the ligand or metal bears a weakly or non-nucleophilic stabilizing ion is selected from the group consisting of halogen, borates, sulfonates, and phosphonates.

12. A process of claim 11, wherein the ligand, if chiral, the compound of formula (III) and/or formula (IV) can be provided as a racemic mixture or a purified stereoisomer.

13. A process of claim 12, wherein the ligand catalyst can be immobilized on a solid support.

14. A process of claim 1, wherein the process is carried out in a solvent and the solvent is selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, alicyclic hydrocarbons, halohydrocarbons, alcohols, ethers, esters, ketones, nitriles and diol derivatives, and ionic liquids such as imidazolium salts.

15. A process of claim 14, wherein the solvent is selected from the group consisting of benzene, toluene, and xylene.

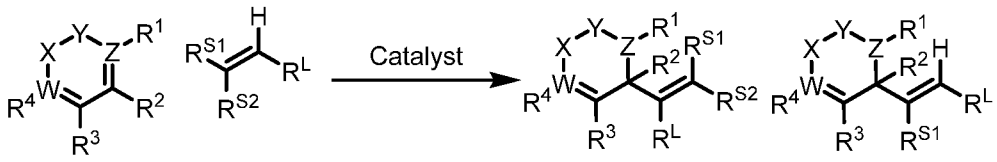
16. A process of claim 14, wherein the process is carried out in a flow reactor.

17. A process of claim 1, wherein the process is carried out in a buffer.

AMENDED CLAIMS
received by the International Bureau on 16 May 2018 (16.05.2018)

CLAIMS

1. An aluminum Lewis acid free process for preparing a compound of formula (III) and (IV) with a compound of formula (I) and a compound of formula (II) in the presence of a transition metal catalyst or a precursor thereof,



I II III IV

wherein,

R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y are linkers that connects the diene to form a n-member ring, and n is an integer, and they are each independently selected from the group consisting of Group 13-16 elements of the Periodic Table, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and the substituents are optionally linked together and

W, Z are each independently selected from the group consisting of substituted Group 13-15 elements of the Periodic Table, and

R^{S1}, R^{S2} and R^L are not all equal to H, and thereafter are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together, and

X, Y, R^1, R^2, R^3, R^4, R^{S1}, R^{S2} and R^L are each independently selected from the above and optionally linked together.

AMENDED SHEET (ARTICLE 19)

2. A process of claim 1, wherein R^1, R^2, R^3 and R^4 are each independently selected from the group consisting of H, substituted alkyl, alkenyl, aryl, arylalkyl, hydroxyl, alkoxyl, aroxyl, halogen, metalloids, amino, alkylamino, arylamino, mercapto, carbonyl, alkylthio and arylthio, and optionally linked together.

3. A process of claim 1, wherein the compound of formula (I) is selected from the group consisting of cyclohexadiene, cycloheptadiene, α-phellandrene, α-terpinene, 1,2-dihydropyridine, 2,3-dihydropyridine, 2H-pyran and the like.

4. A process of claim 1, wherein the compound of formula (II) is selected from the group consisting of straight chain monoenes such as 1-hexene/1-octene (straight chain monoene), 2-hexene (acyclic internal olefins), vinylcyclohexane, 4-methyl-1-pentene (branched chain monoene), styrene, allylbenzene (aromatic alkenes), vinylsilanes (vinylmetalloids), benzyl vinylethers (vinylethers), cyclohexenes and 1,2-dihydrofurans (cyclic olefins), and their substituted derivatives thereof, and the like.

5. A process of claim 1, wherein the transition metal is selected from Groups 3 to 12 of the Periodic Table of Elements.

6. A process of claim 1, wherein the transition metal is selected from Group 10 of the Periodic Table of Elements.

7. A process of claim 6, wherein the transition metal is Ni.

8. A process of claim 1, wherein the amount of the transition metal is in the range of < 2 mol%, with respect to the limiting reagent, which may be either the compound of formula (I) or the compound of formula (II), depending upon which reagent is in stoichiometric

AMENDED SHEET (ARTICLE 19)

excess.

9. A process of claim 1, wherein the compound of formula (I) and/or formula (II) if chiral, the compound of formula (III) and/or formula (IV) can be provided as a racemic mixture or a purified stereoisomer.

10. A process of claim 1, wherein a ligand on the transition metal catalyst is selected from the group consisting of carbenes, heterocyclic carbenes, biscarbenes, bisheterocyclic carbenes, phosphines, amines, imines, arsines and derivatives thereof.

11. A process of claim 10, wherein the ligand or metal bears a weakly or non-nucleophilic stabilizing ion is selected from the group consisting of halogen, borates, sulfonates, and phosphonates.

12. A process of claim 11, wherein the ligand, if chiral, the compound of formula (III) and/or formula (IV) can be provided as a racemic mixture or a purified stereoisomer.

13. A process of claim 12, wherein the ligand catalyst can be immobilized on a solid support.

14. A process of claim 1, wherein the process is carried out in a solvent and the solvent is selected from the group consisting of aromatic hydrocarbons, aliphatic hydrocarbons, alicyclic hydrocarbons, halohydrocarbons, alcohols, ethers, esters, ketones, nitriles and diol derivatives, and ionic liquids such as imidazolium salts.

15. A process of claim 14, wherein the solvent is selected from the group consisting of benzene, toluene, and xylene.

AMENDED SHEET (ARTICLE 19)

16. A process of claim 14, wherein the process is carried out in a flow reactor.

17. A process of claim 1, wherein the process is carried out in a buffer.

AMENDED SHEET (ARTICLE 19)

Statement under Article 19(1)

Given that D1 clearly indicated organoaluminum Lewis acid is **essential** (p185, 2nd column last paragraph) for the desired reactivity, i.e. skipped diene formation (cpd 3 in D1, formula (III) and (IV) in claim 1), one of the key inventive steps of the current invention as compared to the D1 prior art is that it does not require an organoaluminum Lewis acid to prepare the target products. So we indicated that is an "aluminum lewis acid free" process in both Claim 1 and the abstract as provided, no matter which kinds of addition products are prepared. And therefore the additional features defined in other claims 2-15 are also not obvious to a person skilled in the art in the absence of organoaluminum Lewis acid.

Actually, the info in prior art D1 highlighted the importance of the above inventive step. First, D1 showed that the nature and size of the P ligand employed (a reflection of vinyl substitutent and ligand steric interaction, p186 Table 1) will affect only the product distribution of the cpd 3 and cpd 4 (a homo-dimer of VTMS, p185, 2nd column last paragraph), but not able to produce a product of formula (IV) in this invention. Therefore, the interplay of the number and size of vinyl substituents (the other is same or similar to R^L) are expected not applicable to yield formula (IV) according to a person skilled in the art no matter it was run under the aluminum Lewis acid free system or D1. Second, there are no examples provided in the D1 that the choice of acyclic olefin can be used other than VTMS or vinylsilane in general. It is well known for a skilled person to anticipate the simpler olefins like those in Claim 4 are not compatible with the D1 protocol. It is because the alike condition is known to isomerize acyclic olefin prior to the desired codimerization (please see Chem Rev. 2003, 103, 2845, even when (II) was tested with more reactive ethylene).

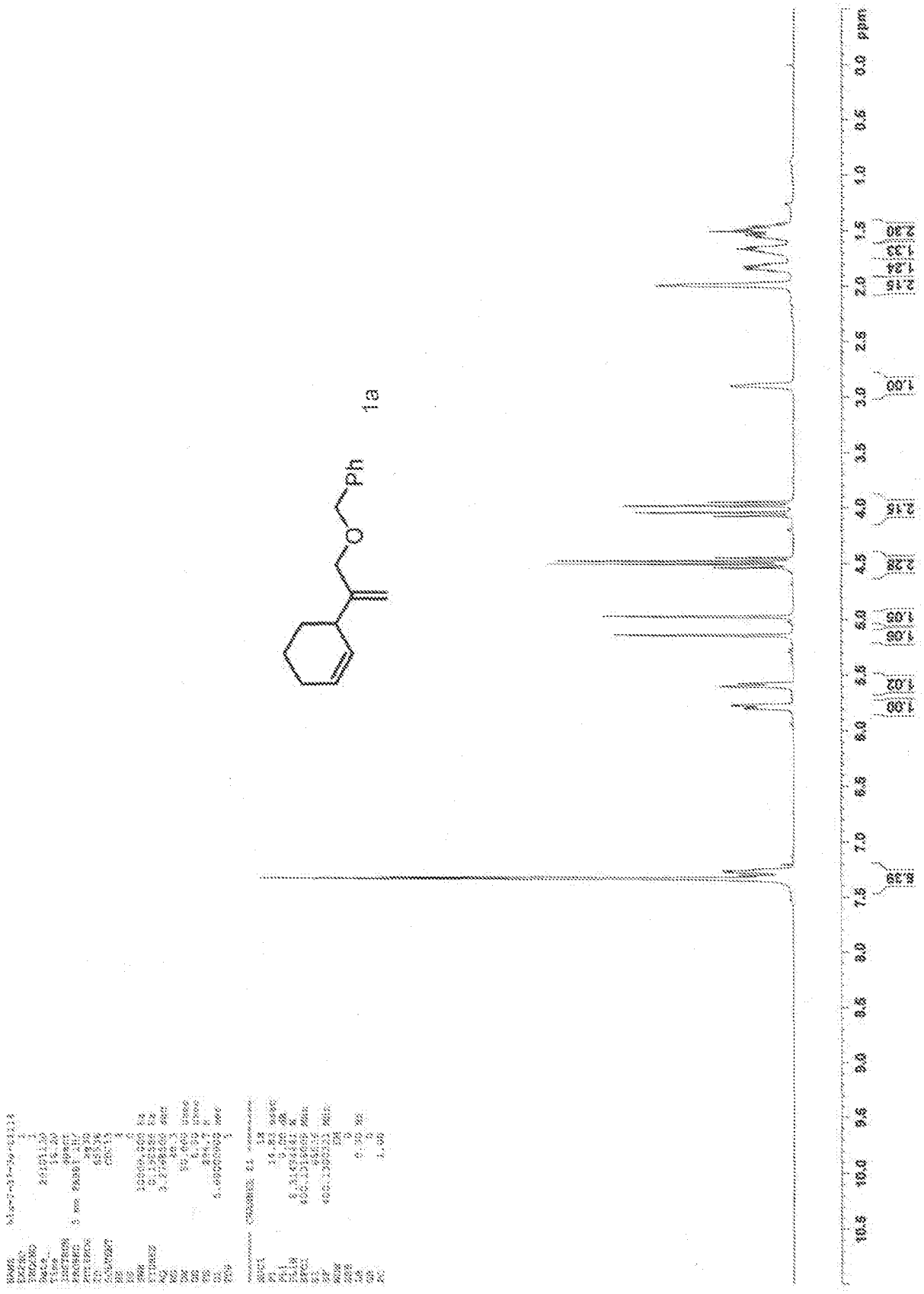
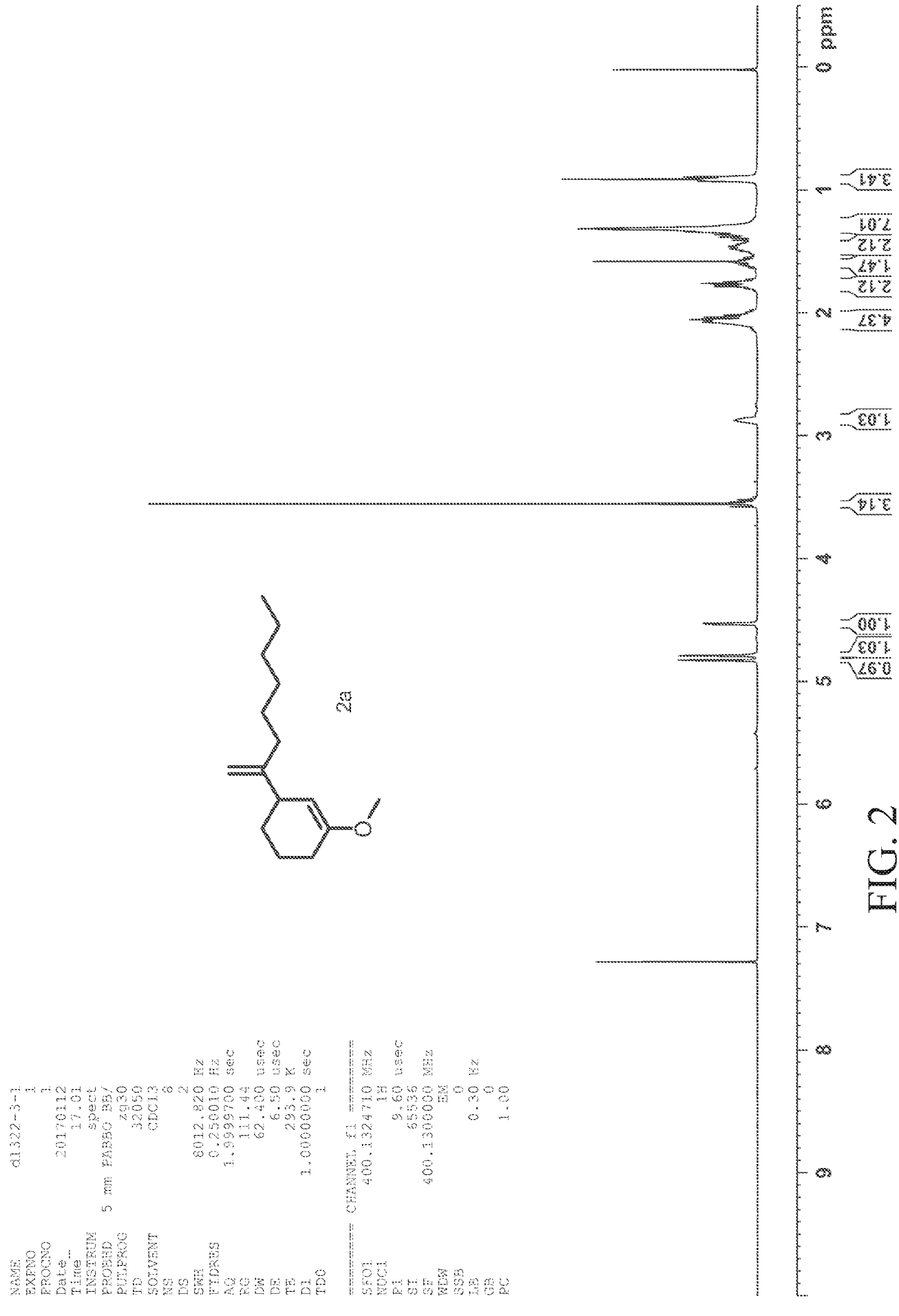


FIG. 1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SOLVENT CDCl3
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DS 2
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FIDRES 0.250010 Hz
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RG 111.44
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DE 6.50 usec
TE 293.9 K
D1 1.0000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 400.1324710 MHz
NUC1 1H
P1 9.60 usec
SI 65536
SF 400.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
2a
0 ppm
1
2
3
4
5
6
7
8
9
3.41
7.01
2.12
1.47
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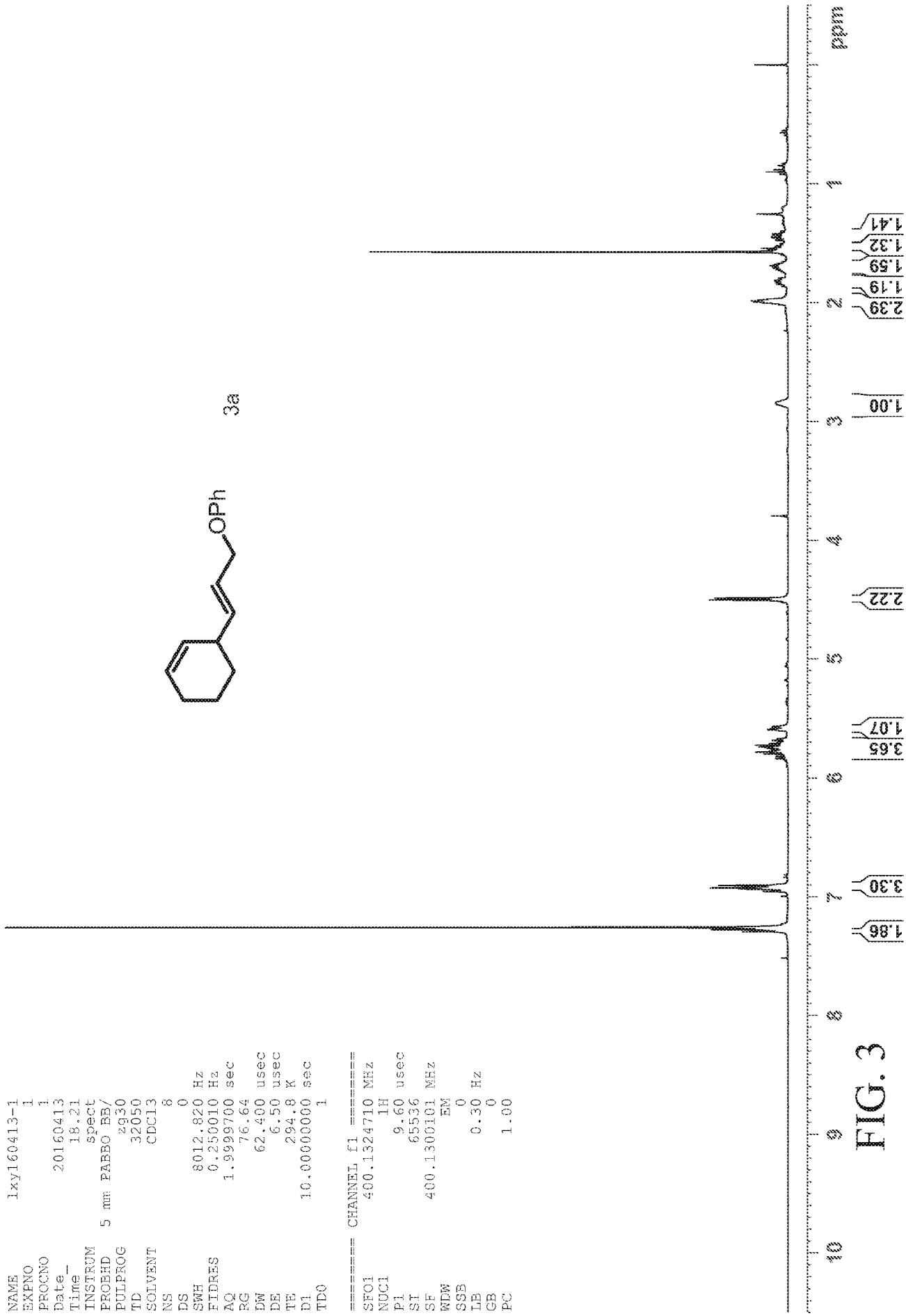
1.03
1.00

FIG. 2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SOLVENT CDCl3
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FIDRES 0.250010 Hz
AQ 1.9999700 sec
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DE 6.50 usec
TE 294.8 K
D1 10.00000000 sec
TD0 1
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P1 9.60 usec
SI 65536
SF 400.1300101 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OPh
3a
1.86
3.30
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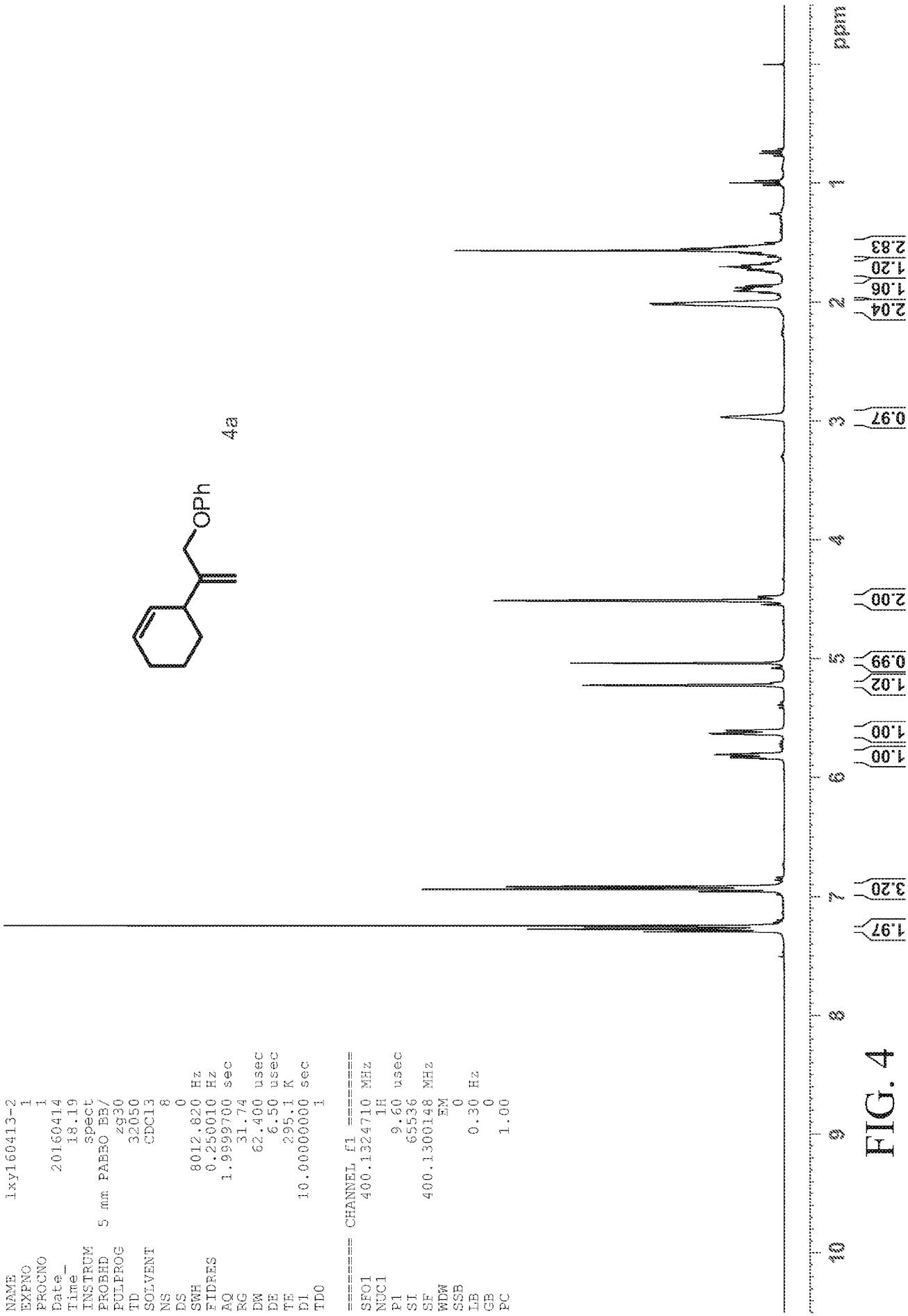
2.22
1.00
2.39
1.19
1.59
1.32
1.41
ppm

FIG. 3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FIDRES 0.250010 Hz
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DW 62.400 usec
DE 6.50 usec
TE 295.1 K
D1 10.00000000 sec
TD0 1
======== CHANNEL f1 ========
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NUC1 1H
P1 9.60 usec
SI 65536
SF 400.1300148 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
OPh
4a
1.97
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1.02
0.99
2.00
0.97
2.04
1.06
1.20
2.83
ppm

FIG. 4

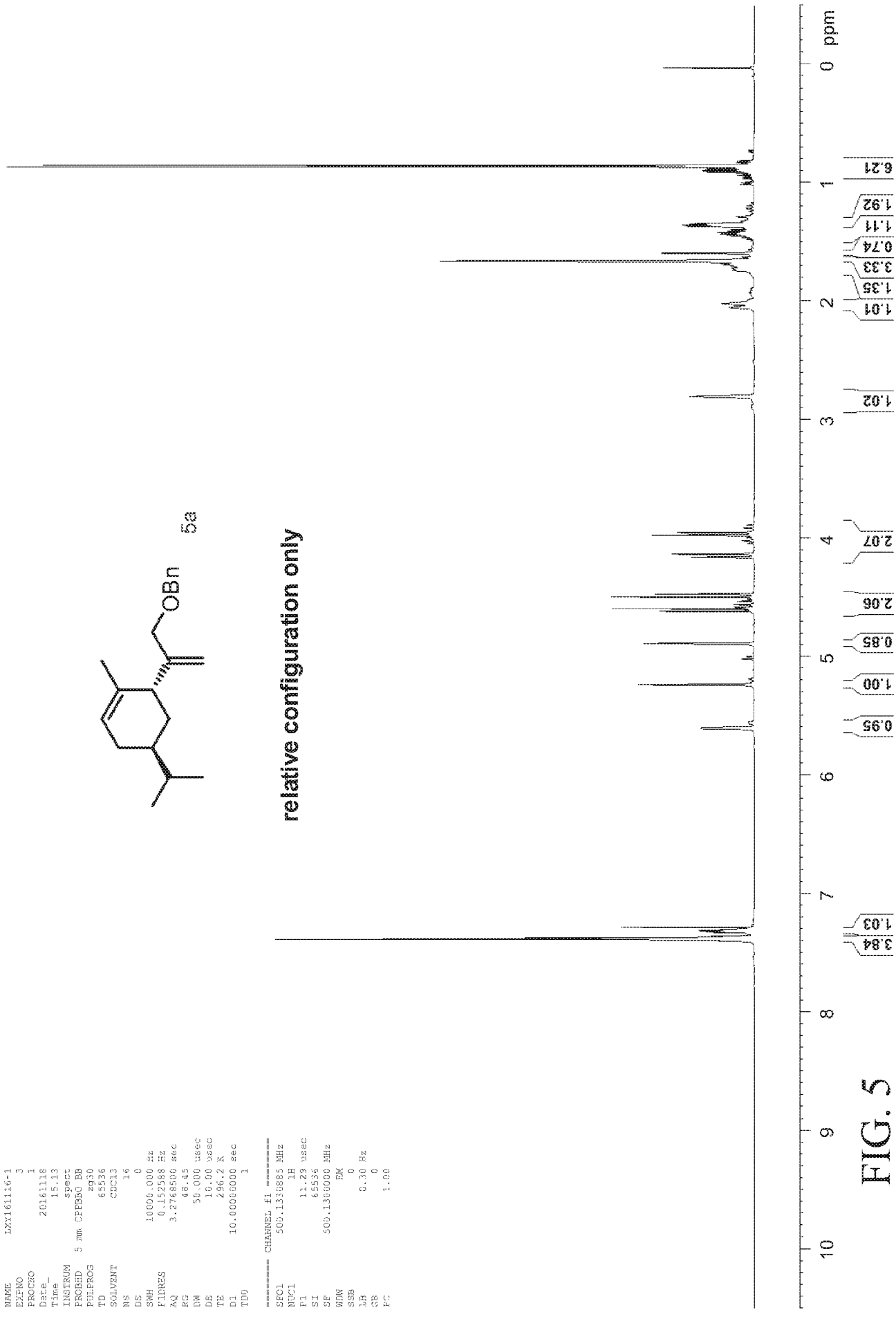
OBn
5a
relative configuration only
6.21
1.92
1.11
0.74
3.33
1.35
1.01
1.02
2.07
2.06
0.85
1.00
0.95
3.84
1.03
0 ppm
1
2
3
4
5
6
7
8
9
10

FIG. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2017/085650

A. CLASSIFICATION OF SUBJECT MATTER

C07B 37/02(2006.01)i; C07C 37/14(2006.01)i; C07C 13/20(2006.01)i

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)

C07B, C07C, C07D

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)

CNKI,CNABS,DWPI,SIPOABS,CASREACT(STN): diene,alkene,cyclohexadiene, cyclohetadiene, dihyropyridine, dihydropyridine,pyran, vinyl,reaction search based on claim 1

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHILIPPE C., et al. "Nickel-Catalyzed Codimerization of 1, 3-Cyclohexadiene and Vinyltrimethylsilane. Effects of Organophosphorus Ligands" *J. Org. Chem.*, Vol. 53, 31 December 1988 (1988-12-31), page 185, second paragraph in right column, page 186, scheme 1, table I, II	1-17
A	SOUVAGYA B., et al. "Triarylphosphine Ligands with Hemilabile Alkoxy Groups: Ligands for Nickel(II)-Catalyzed Olefin Dimerization Reactions. Hydrovinylation of Vinylarenes, 1, 3-Dienes, and Cycloisomerization of 1, 6-Dienes" *Adv. Synth. Catal.*, Vol. 356, 04 June 2014 (2014-06-04), pages 2281-2292	1-17

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* 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
12 February 2018	**24 February 2018**

Name and mailing address of the ISA/CN	Authorized officer
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