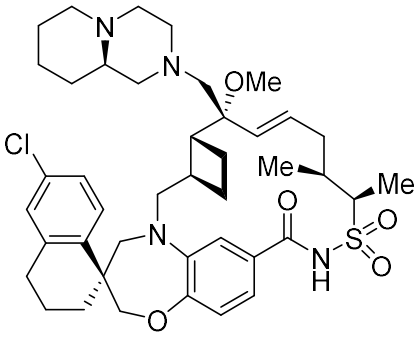
[14.7.2.$0^{3,6}$.$0^{19,24}$]pentacosa[8,16,18,24]tetraen]-15'-one 13',13'-dioxide (compound A2), is useful as an inhibitor of myeloid cell leukemia 1 (Mcl-1):



(A2).

[005] One common characteristic of human cancer is overexpression of Mcl-1. Mcl-1 overexpression prevents cancer cells from undergoing programmed cell death (apoptosis), allowing the cells to survive despite widespread genetic damage.

[006] Mcl-1 is a member of the Bcl-2 family of proteins. The Bcl-2 family includes pro-apoptotic members (such as BAX and BAK) which, upon activation, form a homo-oligomer in the outer mitochondrial membrane that leads to pore formation and the escape of mitochondrial contents, a step in triggering apoptosis. Antiapoptotic members of the Bcl-2 family (such as Bcl-2, Bcl-XL, and Mcl-1) block the activity of BAX and BAK. Other proteins (such as BID, BIM, BIK, and BAD) exhibit additional regulatory functions. Research has shown that Mcl-1 inhibitors can be useful for the treatment of cancers. Mcl-1 is overexpressed in numerous cancers.

[007] U.S. Patent No. 9,562,061, which is incorporated herein by reference in its entirety, discloses compound A1 as an Mcl-1 inhibitor and provides a method for preparing it. However, improved synthetic methods that result in greater yield and purity of compound A1 are desired, particularly for the commercial production of compound A1.

[008] U.S. Patent No. 10,300,075, which is incorporated herein by reference in its entirety, discloses compound A2 as an Mcl-1 inhibitor and provides a method for preparing it. However, improved synthetic methods that result in greater yield and purity of compound A2 are desired, particularly for the commercial production of compound A2.

SUMMARY ~~OF THE INVENTION~~

[009] In one aspect, the ~~invention~~ present disclosure provides a method of synthesizing a compound of Formula BI, the compound of Formula BI having the formula

or 3 substituents selected from -OH, -O-C_1-C_6 alkyl, -O-Si(C_1-C_6 alkyl)$_3$, halo, or C_1-C_6 haloalkyl;

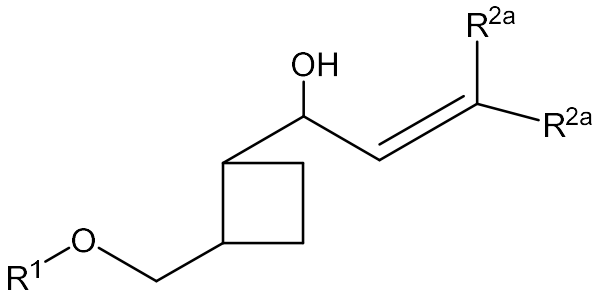
or R^{1a} and R^{1b} may join to form a ring comprising 3, 4, 5, 6, 7, or 8 ring members comprising 0 or 1 oxygen atom, wherein the ring is unsubstituted or is substituted with 1 or 2 substituents selected from -OR^{1e} or -C_1-C_6-OR^{1e};

R^{1e} is selected from -H, -C_1-C_6 alkyl, -CH_2-aryl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, aryl, or -C=O-C_1-C_6 alkyl, wherein the aryl of an R^{1e} group is a C_6-C_{10} aromatic ring that is unsubstituted or is substituted with 1, 2, or 3 substituents selected from -OR^{1f}, -halo, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, or -C=O-C_1-C_6 alkyl;

R^{1f} is selected from -H, -C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, or –(C_1-C_6 alkyl)-aryl, wherein the aryl of an R^{1f} group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from -OH, -O-C_1-C_6 alkyl, -O-Si(C_1-C_6 alkyl)$_3$, halo, or C_1-C_6 haloalkyl; and

b) reacting the product mixture with an oxidizing agent to oxidize the phosphine moieties in the phosphine to phosphine oxides to produce an oxidized phosphine.

[010] In another aspect, the ~~invention~~ present disclosure provides a method of synthesizing a compound of Formula IA', the compound of Formula IA' having the formula:



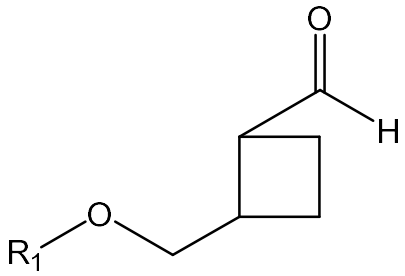
IA',

wherein the method comprises:

reacting a compound of Formula IIA with an alkenyl boron compound and a catalyst in the presence of a base and an optional solvent to form a product mixture comprising the compound of Formula IA', wherein the catalyst is prepared from a copper I salt or a copper II salt and a phosphine, wherein the phosphine is at least two equivalents of a monophosphine or at least one equivalent of a diphosphine with respect to the copper I salt or is at least four equivalents of a monophosphine or at least two equivalents of a disphosphine with respect to the copper II salt,

and further wherein the sp^2 hybridized carbon atom of the alkenyl group that is not directly bonded to the boron atom of the alkenyl boron compound is bonded to 2 R^{2a} groups, wherein each R^{2a} is independently selected from -H, -C_1-C_6 alkyl, or a -C_6-C_{10} aryl group, wherein the aryl group is unsubstituted or is substituted with 1 or 2 R^{3a} groups independently selected from -C_1-C_6 alkyl, -NO_2, halo, or -O-C_1-C_6 alkyl; and further wherein if one of the R^{2a} groups is an aryl group, then the other R^{2a} group is not an aryl group;

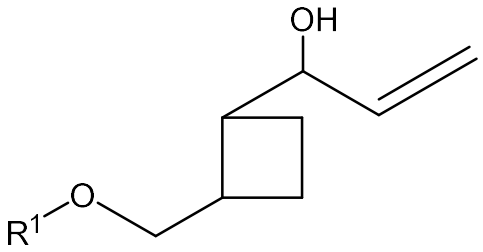
wherein the compound of Formula IIA has the structure



IIA;

wherein R^1 is selected from -H, -C_1-C_6 alkyl, -C=O-C_1-C_6 alkyl, -C=O-aryl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, or -C_1-C_6 alkyl-aryl, wherein the aryl group in an R^1 group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from -OH, NO_2, -O-C_1-C_6 alkyl, halo, or C_1-C_6 haloalkyl.

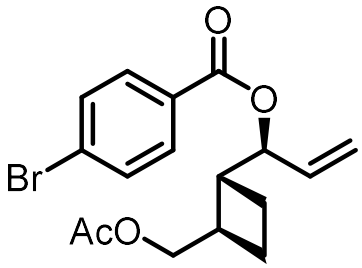
[011] In another aspect, the ~~invention~~ present disclosure provides a compound of Formula IA having the formula



IA

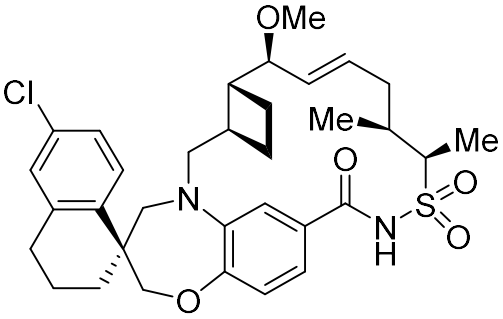
wherein R^1 is selected from -H, -C_1-C_6 alkyl, C=O-C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, -C_1-C_6 alkyl-aryl, wherein the aryl in an R^1 group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from -OH, -O-C_1-C_6 alkyl, halo, or C_1-C_6 haloalkyl.

[012] In ~~yet another aspect~~an example, the ~~invention~~ present disclosure provides a method for synthesizing compound A3 using compound IA, wherein the compound A3 has the following structure:



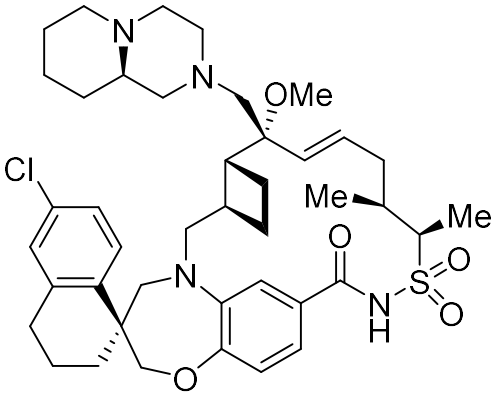
A3.

[013] In ~~yet~~ another ~~aspect~~another example, the ~~invention~~ disclosure provides a method for synthesizing compound A1 using compound IA, wherein the compound A1 has the following structure:



A1.

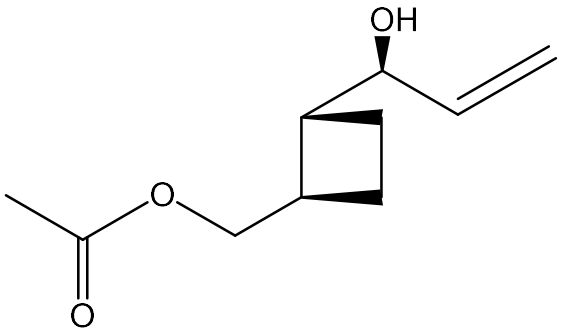
[014] In yet another ~~aspect~~example, the ~~invention~~ disclosure provides a method for synthesizing compound A2 using compound IA, wherein the compound A2 has the following structure:



A2.

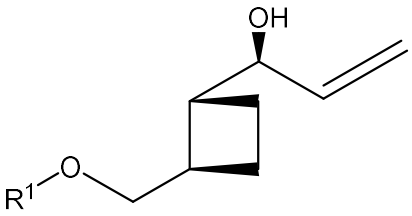
[015] Other objects, features and advantages of the ~~invention~~ disclosure will become apparent to those skilled in the art from the following description and claims.

[061] In embodiment 19, the invention provides the method of embodiment 15, wherein the compound of Formula BI has the Formula IE

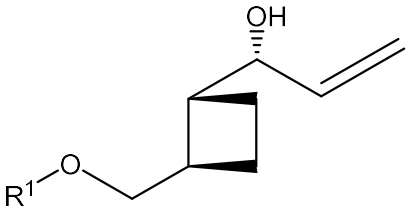


IE.

[062] In embodiment 20, the invention provides the method of embodiment 15, wherein the compound of Formula BI is formed as a mixture of the compounds of Formula ID and ID', wherein the compounds of formula ID and ID' have the structures:



ID



ID'.

[063] In embodiment 21, the invention provides the method of embodiment 20, wherein the amount of ID to ID' or the amount of ID' to ID ranges from 60:40 to 100:0.

[064] In embodiment 22, the invention provides the method of embodiment 20, wherein the amount of ID to ID' or the amount of ID' to ID ranges from 65:35 to 99.9:0.1.

[065] In embodiment 23, the invention provides the method of embodiment 20, wherein the amount of ID to ID' or the amount of ID' to ID ranges from 70:30 to ~~99.1~~99.9:0.1.

[098] In embodiment 56, the invention provides the method of embodiment 54, wherein the amount of ID to ID' or the amount of ID' to ID ranges from 65:35 to 99.9:0.1.

[099] In embodiment 57, the invention provides the method of embodiment 54, wherein the amount of ID to ID' or the amount of ID' to ID ranges from 70:30 to ~~99.1~~99.9:0.1.

[0100] In embodiment 58, the invention provides the method of embodiment 54, wherein the amount of ID to ID' or the amount of ID' to ID ranges from 75:25 to 99.9:0.1.

[0101] In embodiment 59, the invention provides the method of embodiment 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is 60% or greater.

[0102] In embodiment 60, the invention provides the method of embodiment 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is 70% or greater.

[0103] In embodiment 61, the invention provides the method of embodiment 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is 80% or greater.

[0104] In embodiment 62, the invention provides the method of embodiment 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is 85% or greater.

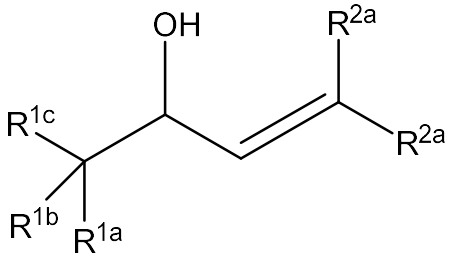
[0105] In embodiment 63, the invention provides the method of embodiment 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is 90% or greater.

[0106] In embodiment 64, the invention provides the method of embodiment 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is 95% or greater.

[0107] In embodiment 65, the invention provides the method of embodiment 54, wherein the compound of Formula ID has the structure IE and the compound of ID' has the structure IE',

WHAT IS CLAIMED:

1. A method of synthesizing a compound of Formula BI, the compound of Formula BI having the formula



BI,

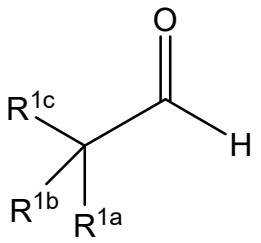
wherein the method comprises:

a) reacting a compound of Formula BII with an alkenyl boron compound and a catalyst in the presence of a base and optionally a solvent to form a product mixture comprising the compound of Formula BI, wherein the catalyst is prepared from a copper I salt or a copper II salt and a phosphine;

wherein the phosphine is at least two equivalents of a monophosphine or at least one equivalent of a diphosphine with respect to the copper I salt or is at least four equivalents of a monophosphine or at least two equivalents of a disphosphine with respect to the copper II salt;

and further wherein the sp^2 hybridized carbon atom of the alkenyl group that is not directly bonded to the boron atom of the alkenyl boron compound is bonded to 2 R^{2a} groups, wherein each R^{2a} is independently selected from the group consisting of -H, -C_1-C_6 alkyl, ~~or~~ and a -C_6-C_{10} aryl group, wherein the aryl group is unsubstituted or is substituted with 1 or 2 R^{3a} groups independently selected from the group consisting of -C_1-C_6 alkyl, -NO_2, halo, ~~or~~ and -O-C_1-C_6 alkyl; and further wherein if one of the R^{2a} groups is an aryl group, then the other R^{2a} group is not an aryl group;

wherein, BII has the formula



BII

wherein

$R^{1a,}$ R^{1b} and R^{1c} are independently selected from the group consisting of -H, or -C_1-C_6 alkyl, ~~or~~ and OR^{1d} wherein R^{1d} is selected from the group consisting of -H, -C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, ~~or~~ and C_1-C_6 alkyl-aryl, wherein the aryl in an R^{1d} group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from the group consisting of -OH, -O-C_1-C_6 alkyl, -O-Si(C_1-C_6 alkyl)$_3$, halo, ~~or~~ and C_1-C_6 haloalkyl;

or R^{1a} and R^{1b} may join to form a ring comprising 3, 4, 5, 6, 7, or 8 ring members comprising 0 or 1 oxygen atom, wherein the ring is unsubstituted or is substituted with 1 or 2 substituents selected from the group consisting of -OR^{1e} ~~or~~ and -C_1-C_6-OR^{1e};

R^{1e} is selected from the group consisting of -H, -C_1-C_6 alkyl, -CH_2-aryl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, aryl, ~~or~~ and -C=O-C_1-C_6 alkyl, wherein the aryl of an R^{1e} group is a C_6-C_{10} aromatic ring that is unsubstituted or is substituted with 1, 2, or 3 substituents selected from the group consisting of -OR^{1f}, -halo, -C_1-C_6 alkyl, -C_1-C_6 haloalkyl, ~~or~~ and -C=O-C_1-C_6 alkyl;

R^{1f} is selected from the group consisting of-H, -C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, ~~or~~ and -(C_1-C_6 alkyl)-aryl, wherein the aryl of an R^{1f} group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from the group consisting of -OH, -O-C_1-C_6 alkyl, -O-Si(C_1-C_6 alkyl)$_3$, halo, ~~or~~ and C_1-C_6 haloalkyl; and

b) reacting the product mixture with an oxidizing agent to oxidize the phosphine moieties in the phosphine to phosphine oxides to produce an oxidized phosphine.

2. The method of claim 1, wherein the method further comprises: separating crystals of the oxidized phosphine from the ~~reaction~~ product mixture; and optionally reacting the separated oxidized phosphine oxide with a reducing agent to provide the phosphine.

3. The method of claim 1 or claim 2 wherein the oxidizing agent is selected from the group consisting of H_2O_2, HOF, Ru(III)/O_2, ~~or~~ and NaOCl~~.~~, optionally

~~4. The method of claim 3,~~ wherein the oxidizing agent is an aqueous solution of H_2O_2.

~~5. The method of claim 2, wherein the method further comprises: reacting the separated oxidized phosphine oxide with a reducing agent to provide the phosphine.~~

~~6~~4. The method of claim 2~~5~~, wherein the reducing agent is selected from the group consisting of $HSiCl_3$, $HSiCl_3$:$N(C_1$-C_6 alkyl$)_3$, Si_2Cl_6, $PhSiH_3$, Ph_2SiH_2, Me_3SiH, Et_3SiH, $PhMe_2SiH$, Ph_3SiH, $(Me_3Si)_3Si$-H, $PhCH_2SiH_3$, naphthylsilane, bis(naphthyl)silane, bis(4-methylphenyl)silane, bis(fluorenyl)silane, $HSi(OEt)_3$, $HSi(OEt)_3$ with $Ti(C_1$-C_6 alkoxide$)_4$, 1,3-diphenyldisiloxane, hexamethyldisilane, $TfOSi(H)(CH_3)_2$, $(CH_3)_2Si(H)$-O-$Si(CH_3)_2(H)$ with $Cu(OTf)_2$, tetramethyldisiloxane, polymethylhydrosiloxane, dialkylphosphite with I_2 and $P(OPh)_3$, AlH_3 with diisobutylaluminum hydride, and~~or~~ borane reducing agents, wherein Tf is triflate~~.~~, optionally

~~7. The method of claim 6,~~ wherein the reducing agent is $HSiCl_3$.

~~8~~5. The method of any one of claims 1-~~7~~4, wherein R^{1a} and R^{1b} join to form a substituted or unsubstituted ring with 3, 4, 5, or 6 ring members each of which is a carbon atom~~.~~, optionally

~~9. The method of claim 8,~~ wherein R^{1a} and R^{1b} join to form a substituted or unsubstituted ring with 4 ring members each of which is a carbon atom; ~~.~~optionally

~~10. The method of claim 8 or claim 9,~~ wherein R^{1c} is -H.

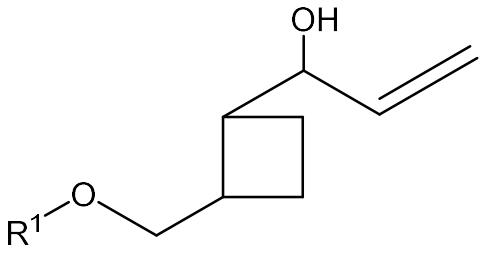
~~11~~6. The method of ~~any one of claims 8-10~~claim 5, wherein R^{1a} and R^{1b} join to form a 4 membered ring that is substituted with 1 -C_1-C_6-OR^{1e} substituent; optionally~~.~~

~~12. The method of claim 1,~~ wherein R^{1a} and R^{1b} join to form a 4 membered ring that is substituted with 1 -CH_2-OR^{1e} substituent, ~~.~~optionally

~~13. The method of claim 12,~~ wherein R^{1a} and R^{1b} join to form a 4 membered ring that is substituted with 1 -CH_2-O-C=O-C_1-C_6 alkyl substituent, optionally~~.~~

~~14. The method of claim 13,~~ wherein R^{1a} and R^{1b} join to form a 4 membered ring that is substituted with 1 -CH_2-O-C=O-CH_3 substituent.

~~15~~7. The method of any one of claims 1-~~8~~6, wherein the compound of formula BI, has the formula IA



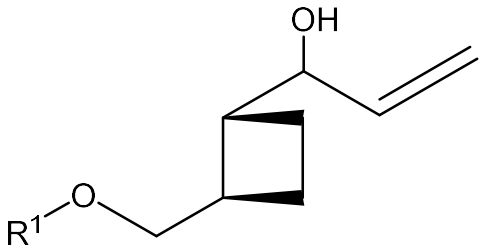
IA,

wherein R^1 is a -C=O-C_1-C_6 alkyl group.

~~16.~~8. The method of claim ~~15~~10~~8~~7, wherein:

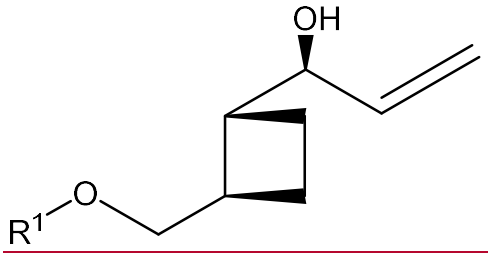
(A) the compound of Formula BI has:

(i) the Formula IB



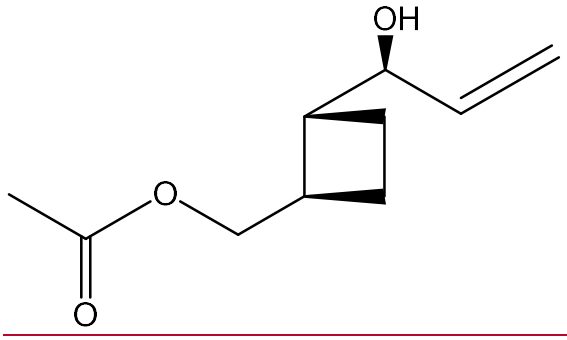
IB, or

(ii) the Formula ID



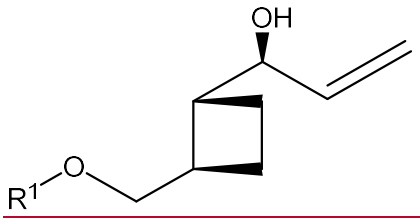
ID, or

(iii) the Formula IE

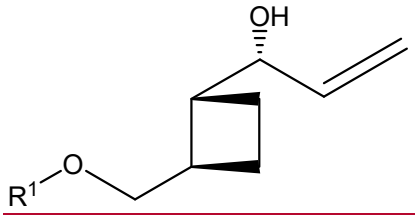


IE, or

(iv) is formed as a mixture of the compounds of Formula ID and ID', wherein the compounds of formula ID and ID' have the structures:

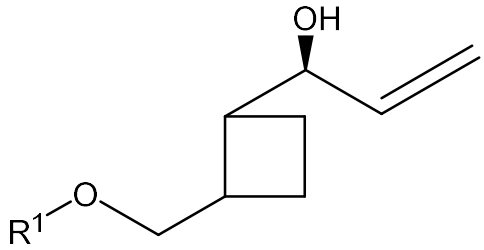


ID



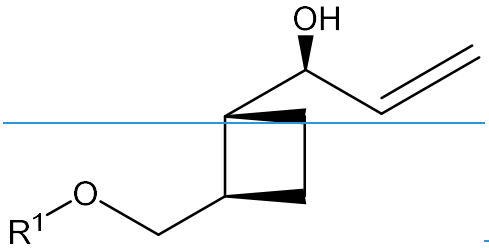
ID' and/or

17. The method of claim 15, wherein (B) the compound of Formula IA has the Formula IC



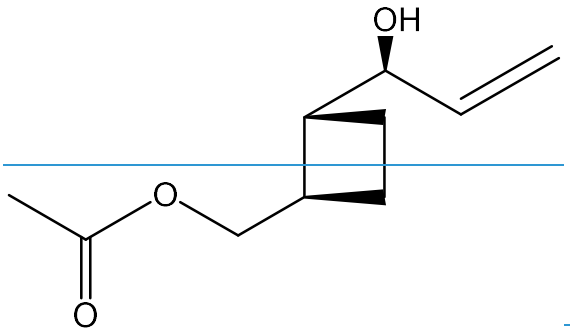
IC.

18. The method of claim 15, wherein the compound of Formula BI has the Formula ID



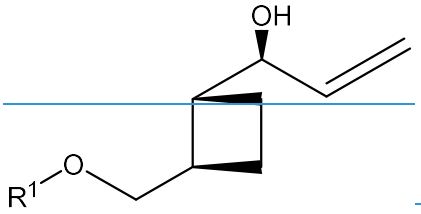
ID.

19. The method of claim 15, wherein the compound of Formula BI has the Formula IE

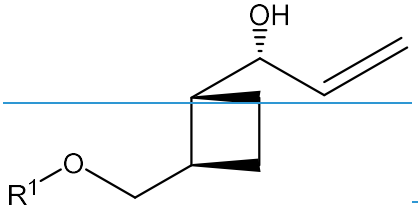


~~IE.~~

~~20. The method of claim 15, wherein the compound of Formula BI is formed as a mixture of the compounds of Formula ID and ID', wherein the compounds of formula ID and ID' have the structures:~~



~~ID~~



~~ID'.~~

~~21~~9. The method of claim ~~20~~8, wherein the amount of ID to ID' or the amount of ID' to ID ranges from any one of 60:40 to 100:0, ~~.~~

~~22. The method of claim 20, wherein the amount of ID to ID' or the amount of ID' to ID ranges from~~ 65:35 to 99.9:0.1~~,~~.

~~23. The method of claim 20, wherein the amount of ID to ID' or the amount of ID' to ID ranges from~~ 70:30 to ~~99.1~~99.9:0.1~~.~~, or

~~24. The method of claim 20, wherein the amount of ID to ID' or the amount of ID' to ID ranges from~~ 75:25 to 99.9:0.1.

~~25~~10. The method of claim ~~20~~8, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is any one of 60% or greater~~.~~

~~26. The method of claim 20, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is ,~~ 70% or greater~~.~~

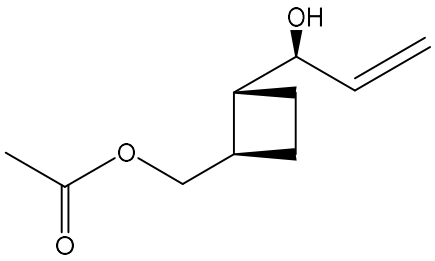
~~27. The method of claim 20, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is ,~~ 80% or greater~~.~~

~~28. The method of claim 20, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is ,~~ 85% or greater~~.~~

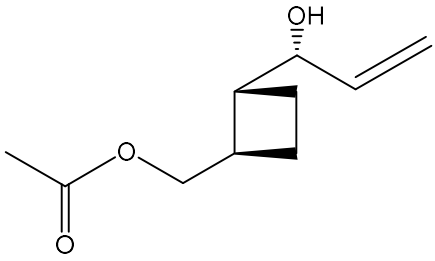
~~29. The method of claim 20, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is ,~~90% or greater~~.~~

~~30. The method of claim 20, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is , or~~ 95% or greater.

~~31~~11. The method of claim ~~20~~8, wherein the compound of Formula ID has the structure IE and the compound of ID' has the structure IE',



IE



IE'.

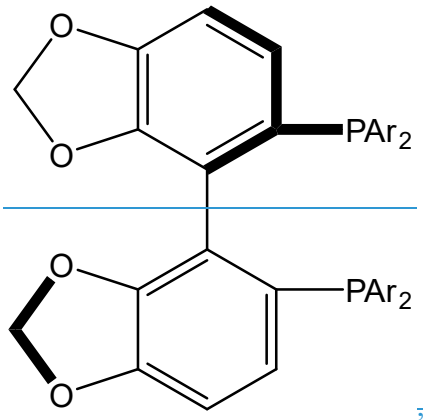
~~32. The method of any one of claims 1-19, wherein the phosphine has at least one chiral center.~~

~~33. The method of any one of claims 1-32, wherein the phosphine is a monophosphine.~~

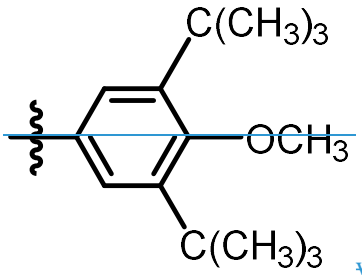
~~34. The method of any one of claims 1-32, wherein the phosphine is a diphosphine.~~

35. The method of any one of claims 1-34, wherein the phosphine is selected from (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((R)-BINAP), 4(*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[diphenylphosphine] ((R)-SEGPHOS), 1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf), 1,3-bis(diphenylphosphino)propane (dppp), 1,2-bis(diphenylphosphino)ethane (dppe), PPh_3, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (TolBINAP), 2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl (XylBINAP), 5,5′-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole (DM-SEGPHOS), or (*R*)-1,13-bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[f,h][1,5]dioxonin ((R)-C3-TunePhos).

36. The method of any one of claims 1-32, wherein the phosphine is (*R*)-DTBM-SEGPHOS having the structure



, wherein Ar has the structure



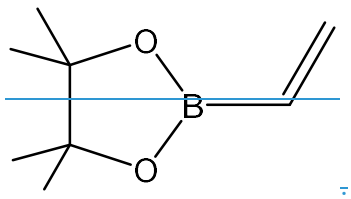
wherein the 〰 indicates the point of attachment to the rest of the molecule.

37. The method of any one of claims 1-36, wherein the copper I salt or the copper II salt is selected from copper(I) hexafluorophosphate, copper(I) tetrafluoroborate, $CuF(PPh_3)_3$, CuF_2, CuF, CuI, $Cu(OTf)_2$, or Cu(OTf), wherein Tf is triflate.

~~38. The method of any one of claims 1-36, wherein the catalyst is formed from a copper I salt and the copper I salt is copper(I) hexafluorophosphate or copper(I) tetrafluoroborate.~~

~~39. The method of any one of claims 1-38, wherein the alkenyl boron compound is selected from 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane, vinylBF_3K, 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane, vinyl$B(OH)_2$, vinylboronic anhydride, vinylboronic acid MIDA ester, (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane, (E)-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane, (E)-2-(3,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, or (E)-4,4,5,5-tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane.~~

~~40. The method of any one of claims 1-38, wherein the alkenyl boron compound is~~



~~41. The method of any one of claims 1-40, wherein the reaction is conducted in the presence of an organic solvent.~~

~~42. The method of claim 41, wherein the solvent is selected from isopropyl acetate, toluene, ethyl acetate, xylene, 2-methyltetrahydrofuran, tetrahydrofuran, cyclopentyl methyl ether, or t-butyl methyl ether.~~

~~43. The method of any one of claims 1-40, wherein the reaction is conducted in a solvent and the solvent is isopropyl acetate.~~

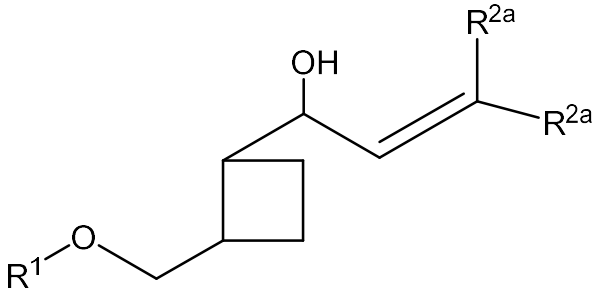
~~44~~12. The method of any one of claims 1-~~43~~11, wherein the compound of Formula BII is reacted with the alkenyl boron compound and the catalyst in the presence of the base and the base is selected from the group consisting of K_3PO_4. CsF, Cs_2CO_3, Na_2CO_3, K_2CO_3, NaF, KF, Na_3PO_4, ~~or~~ and Cs_3PO_4~~.~~

~~45. The method of any one of claims 1-43~~, optionally wherein the compound of Formula BII is reacted with the alkenyl boron compound and the catalyst in the presence of the base and the base is K_3PO_4.

~~46~~13. The method of any one of claims 1-12~~45~~, wherein the compound of Formula BII is reacted with the alkenyl boron compound and the catalyst at a temperature ranging from 15°C to 50°C or ~~.~~

~~47. The method of claim 46, wherein the compound of Formula BII is reacted with the alkenyl boron compound and the catalyst at a temperature ranging~~ from 20°C to 40°C.

~~48~~14. A method of synthesizing a compound of Formula IA', the compound of Formula IA' having the formula



IA',

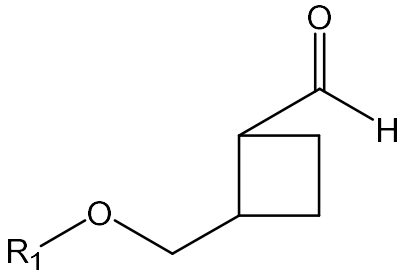
wherein the method comprises:

reacting a compound of Formula IIA with an alkenyl boron compound and a catalyst in the presence of a base and an optional solvent to form a product mixture comprising the compound of Formula IA', wherein the catalyst is prepared from a copper I salt or a copper II salt and a phosphine, wherein the phosphine is at least two equivalents of a monophosphine or at least one equivalent of a diphosphine with respect to the copper I salt or is at least four equivalents of a monophosphine or at least two equivalents of a disphosphine with respect to the copper II salt,

and further wherein the sp^2 hybridized carbon atom of the alkenyl group that is not directly bonded to the boron atom of the alkenyl boron compound is bonded to 2 R^{2a} groups, wherein each R^{2a} is independently selected from the group consisting of -H, -C_1-C_6 alkyl, ~~or~~ and a -C_6-C_{10} aryl group, wherein the aryl group is unsubstituted or is substituted with 1 or 2 R^{3a} groups independently selected from the group consisting of -

C_1-C_6 alkyl, -NO_2, halo, ~~or~~ and -O-C_1-C_6 alkyl; and further wherein if one of the R^{2a} groups is an aryl group, then the other R^{2a} group is not an aryl group;

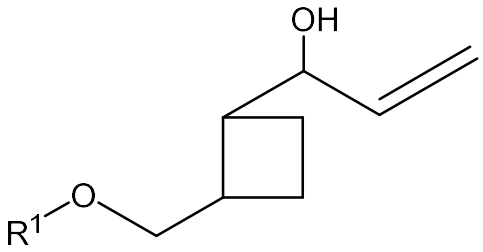
wherein the compound of Formula IIA has the structure



IIA;

wherein R^1 is selected from the group consisting of -H, -C_1-C_6 alkyl, -C=O-C_1-C_6 alkyl, -C=O-aryl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, ~~or~~ and -C_1-C_6 alkyl-aryl, wherein the aryl group in an R^1 group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from the group consisting of -OH, NO_2, -O-C_1-C_6 alkyl, halo, ~~or~~ and C_1-C_6 haloalkyl.

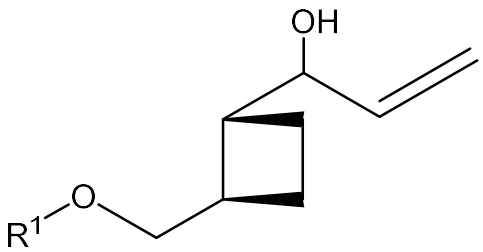
~~49~~15. The method of claim ~~48~~14, wherein the compound of Formula IA' has the Formula IA



IA.

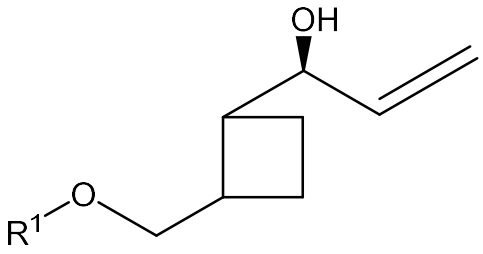
~~50~~16. The method of claim ~~49~~15, wherein the compound of Formula IA' has

the Formula IB



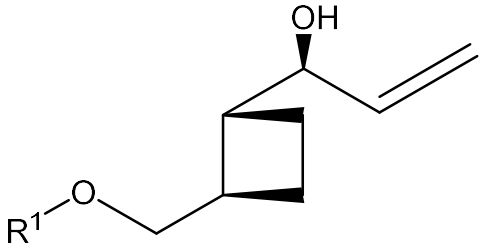
IB, or~~,~~

~~51. The method of claim 49, wherein the compound of Formula IA' has~~ the Formula IC



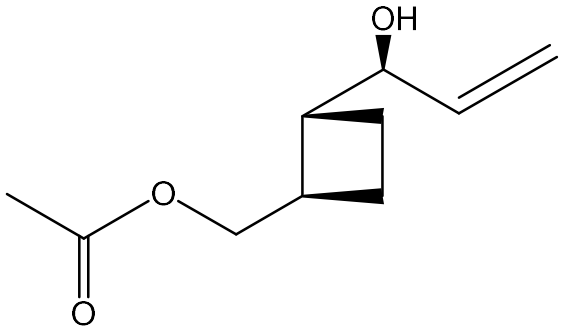
IC~~,~~ or,

~~52. The method of claim 49, wherein the compound of Formula IA' has~~ the Formula ID



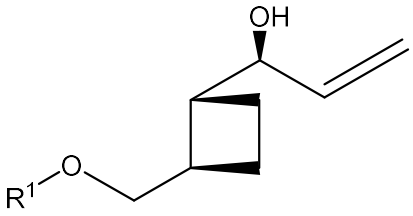
ID, or~~,~~

~~53. The method of claim 49, wherein the compound of Formula IA' has~~ the Formula IE

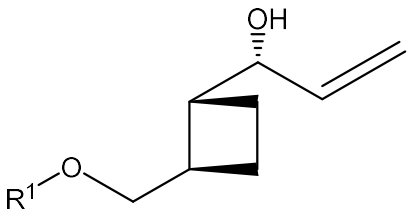


IE, or~~,~~

~~54. The method of claim 49, wherein~~ the compound of Formula IA' is formed as a mixture of the compounds of Formula ID and ID', wherein the compounds of Formula ID and Formula ID' have the structures:



ID



ID'.

~~55~~17. The method of claim ~~54~~16, wherein the amount of ID to ID' or the amount of ID' to ID ranges from any one of 60:40 to 100:0~~.~~

~~56. The method of claim 54, wherein the amount of ID to ID' or the amount of ID' to ID ranges from~~, 65:35 to 99.9:0.1~~.~~

~~57. The method of claim 54, wherein the amount of ID to ID' or the amount of ID' to ID ranges from~~ , 70:30 to ~~99.1~~99.9:0.1~~.~~

~~58. The method of claim 54, wherein the amount of ID to ID' or the amount of ID' to ID ranges from~~, or 75:25 to 99.9:0.1.

~~59~~18. The method of claim ~~54~~16, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID' is any one of 60% or greater~~.~~

~~60. The method of claim 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID'~~, ~~is~~ 70% or greater~~.~~

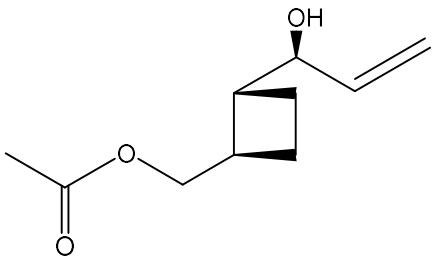
~~61. The method of claim 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID'~~, ~~is~~ 80% or greater~~.~~

~~62. The method of claim 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID'~~ , ~~is~~ 85% or greater~~.~~

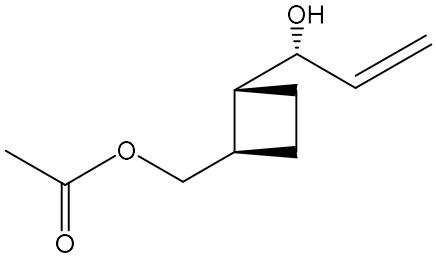
~~63. The method of claim 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID'~~, ~~is~~ 90% or greater~~.~~

~~64. The method of claim 54, wherein the percent of ID present in the mixture based on the total of the amount of ID and ID'~~, or ~~is~~ 95% or greater.

~~65~~19. The method of claim ~~54~~16, wherein the compound of Formula ID has the structure IE and the compound of ID' has the structure IE',



IE



IE'.

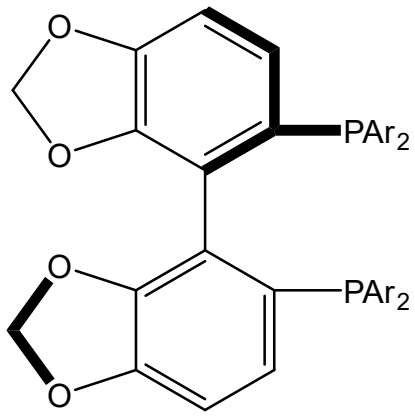
~~66~~20. The method of any one of claims ~~48-65~~1-11 and 14-19, wherein the phosphine has at least one chiral center.

~~67~~21. The method of any one of claims ~~48-65~~1-11 and 14-19, wherein the phosphine is a monophosphine~~.~~

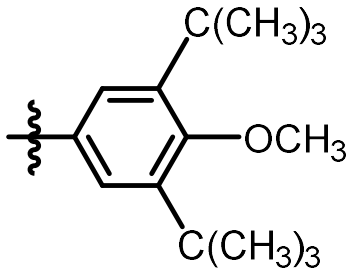
~~68. The method of any one of claims 48-65, wherein the phosphine is~~or a diphosphine~~.~~; optionally

~~69. The method of any one of claims 48-65,~~ wherein the phosphine is selected from the group consisting of (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((R)-BINAP), 4(*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[diphenylphosphine] ((R)-SEGPHOS), 1,1′-ferrocenediyl-bis(diphenylphosphine) (dppf), 1,3-bis(diphenylphosphino)propane (dppp), 1,2-bis(diphenylphosphino)ethane (dppe), PPh_3, 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl (TolBINAP), 2,2'-bis[di(3,5-xylyl)phosphino]-1,1'-binaphthyl (XylBINAP), 5,5′−bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole (DM-SEGPHOS), ~~or~~ and (*R*)-1,13-bis(diphenylphosphino)-7,8-dihydro-6*H*-dibenzo[f,h][1,5]dioxonin ((R)-C3-TunePhos).

~~70~~22. The method of any one of claims ~~48-65~~1-11 and 14-19, wherein the phosphine is (*R*)-DTBM-SEGPHOS having the structure



, wherein Ar has the structure



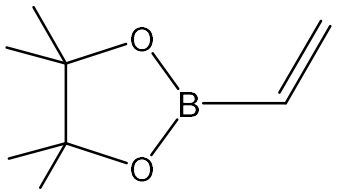
wherein the ~~~ indicates the point of attachment to the rest of the molecule.

~~71~~23. The method of any one of claims ~~48-70~~1-11 and 14-19, wherein the copper I salt or copper II salt is selected from the group consisting of copper(I) hexafluorophosphate, copper(I) tetrafluoroborate, $CuF(PPh_3)_3$, CuF_2, CuF.CuI, $Cu(OTf)_2$, ~~or~~ and Cu(OTf), wherein Tf is triflate.

~~72~~24. The method of any one of claims ~~48-70~~1-11 and 14-19, wherein the catalyst is formed from a copper I salt and the copper I salt is copper(I) hexafluorophosphate or copper(I) tetrafluoroforate.

~~73~~25. The method of any one of claims ~~48-72~~1-11 and 14-19, wherein the alkenyl boron compound is selected from the group consisting of 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane. vinylBF_3K, 4,4,6-trimethyl-2-vinyl-1,3,2-dioxaborinane, vinyl$B(OH)_2$, vinylboronic anhydride, vinylboronic acid MIDA ester, (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane, (E)-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane, (E)-2-(3,3-dimethylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, ~~or~~ and (E)-4,4,5,5-tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane~~.~~

~~74. The method of any one of claims 48-72~~, optionally wherein the alkenyl boron compound is



.

~~75~~26. The method of any one of claims ~~48-74,~~14-25 wherein the compound of Formula IIA is reacted with the alkenyl boron compound and the catalyst in the presence of the base and the solvent, wherein the solvent is selected from the group consisting of isopropyl acetate, toluene, ethyl acetate, xylene, 2-methyltetrahydrofuran, tetrahydrofuran, cyclopentyl methyl ether, ~~or~~ and t-butyl methyl ether~~.~~

~~76. The method of any one of claims 48-74~~, optionally wherein the compound of Formula IIA is reacted with the alkenyl boron compound and the catalyst in the presence of the base and the solvent, wherein the solvent is isopropyl acetate.

~~77~~27. The method of any one of claims ~~48-76~~14-26, wherein the base is selected from the group consisting of K_3PO_4, CsF, Cs_2CO_3, Na_2CO_3, K_2CO_3, NaF, KF, Na_3PO_4, ~~or~~ and Cs_3PO_4~~.~~

~~78. The method of any one of claims 48-76~~, optionally wherein the base is K_3PO_4.

~~79~~28. The method of any one of claims ~~48-78~~14-27, wherein the compound of Formula BII is reacted with the alkenyl boron compound and the catalyst at a temperature ranging from 15°C to 50°C or ~~.~~

~~80. The method of claim 79, wherein the compound of Formula BII is reacted with the alkenyl boron compound and the catalyst at a temperature ranging~~ from 20°C to 40°C.

~~81~~29. The method of any one of claims ~~48-80~~14-27, wherein the method further comprises: reacting the product mixture with an oxidizing agent to oxidize the phosphine moieties in the phosphine to phosphine oxides to produce an oxidized phosphine; ~~.~~

~~82. The method of claim 81, wherein the method further comprises~~ and optionally separating crystals of the oxidized phosphine from the ~~reaction~~ product mixture.

8330. The method of claim 2981 or claim 82 wherein the oxidizing agent is selected from the group consisting of H_2O_2, HOF, Ru(III)/O_2, or and NaOCl.

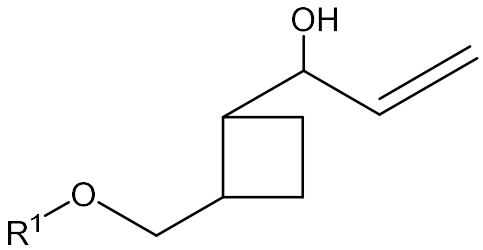
84. The method of claim 81 or claim 82, optionally wherein the oxidizing agent is an aqueous solution of H_2O_2.

8531. The method of any one of claims 82-84 claim 30, wherein the method further comprises: reacting the separated oxidized phosphine with a reducing agent to provide the phosphine.

86. The method of claim 85, optionally wherein the reducing agent is selected from selected from the group consisting of $HSiCl_3$, $HSiCl_3$:N(C_1-C_6 alkyl)$_3$, Si_2Cl_6, $PhSiH_3$, Ph_2SiH_2, $PhCH_2SiH_3$, Me_3SiH, Et_3SiH, $PhMe_2SiH$, Ph_3SiH, $(Me_3Si)_3Si$-H, naphthylsilane, bis(naphthyl)silane, bis(4-methylphenyl)silane, bis(fluorenyl)silane, $HSi(OEt)_3$, $HSi(OEt)_3$ with Ti(C_1-C_6 alkoxide)$_4$, 1,3-diphenyldisiloxane, hexamethyldisilane, $TfOSi(H)(CH_3)_2$, $(CH_3)_2Si(H)$-O-$Si(CH_3)_2(H)$ with $Cu(OTf)_2$, tetramethyldisiloxane, polymethylhydrosiloxane, dialkylphosphite with I_2 and $P(OPh)_3$, AlH_3 with diisobutylaluminum hydride, or and borane reducing agents, wherein Tf is triflate.

87. The method of claim 86, optionally wherein the reducing agent is $HSiCl_3$.

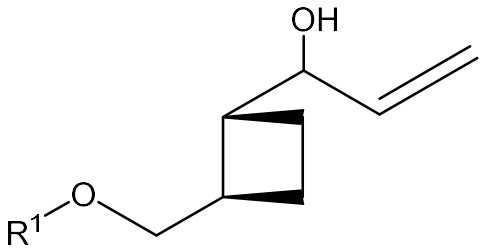
8832. A compound of Formula IA having the formula



IA

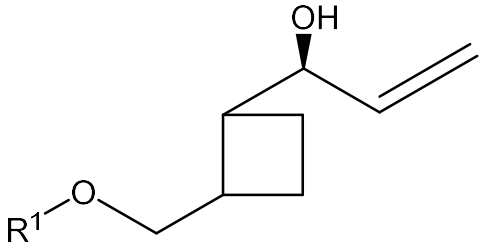
wherein R^1 is selected from the group consisting of -H, -C_1-C_6 alkyl, C=O-C_1-C_6 alkyl, -Si(C_1-C_6 alkyl)$_3$, tetrahydropyranyl, and -C_1-C_6 alkyl-aryl, wherein the aryl in an R^1 group is a C_6-C_{10} aromatic ring that is unsubstituted, or is substituted with 1, 2, or 3 substituents selected from the group consisting of -OH, -O-C_1-C_6 alkyl, halo, or and C_1-C_6 haloalkyl.

8933. The compound of claim 8832, wherein the compound of Formula IA has any one of the Formula IB



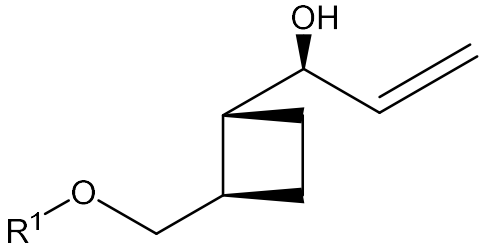
IB, or

~~90. The compound of claim 88, wherein the compound of Formula IA has~~ the Formula IC



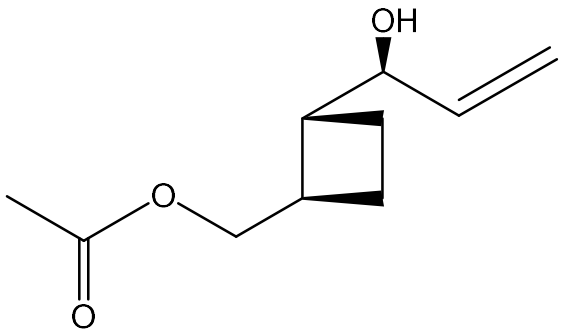
IC, or

~~91. The compound of claim 88, wherein the compound of Formula IA has~~ the Formula ID



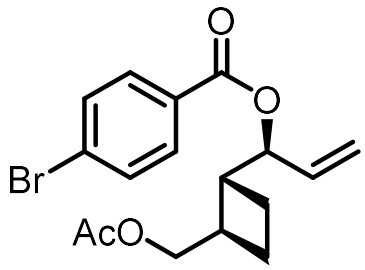
ID, or

~~92. The compound of claim 88, wherein the compound of Formula IA has~~ the Formula IE



IE.

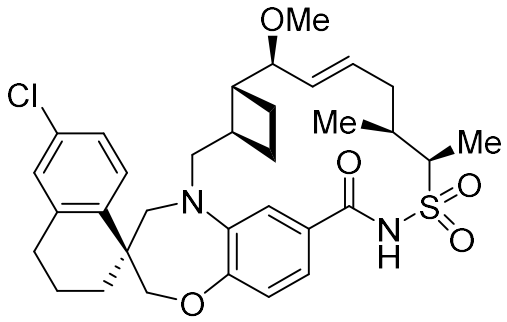
~~93~~34. The method of any one of claims ~~15-47 or 48-87~~7-31, further comprising: (i) synthesizing compound A3 using compound IA, wherein the compound A3 has the following structure:



A3~~.~~;and/or

~~94. The method of any one of claims 15-47 or 48-87, further comprising~~

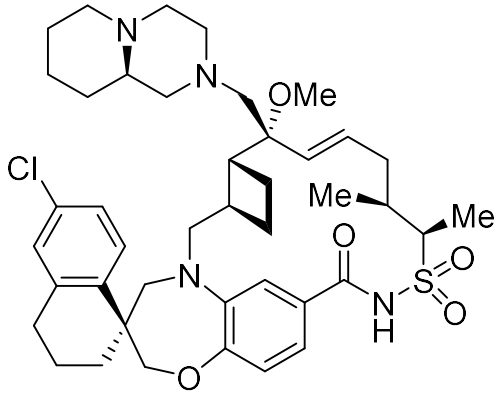
(ii) synthesizing compound A1 or a salt or solvate thereof using compound IA, wherein the compound A1 has the following structure:



A1~~.~~; and/or

~~95. The method of any one of claims 15-47 or 48-87, further comprising~~

(iii) synthesizing compound A2 or a salt or solvate thereof using compound IA, wherein the compound A2 has the following structure:



A2.