

BORONIC COMPOUNDS

The invention relates to boronic compounds, in particular to novel diboron derivatives and organic boronic acid derivatives prepared therefrom. The invention also relates to processes for the preparation of these derivatives. These diboron derivatives and organic
5 boronic acid derivatives are useful intermediates in processes for covalently linking organic compounds.

Processes for forming covalent bonds between organic compounds, both inter- and intra-molecular, are of particular importance to the synthetic organic chemist. Many such
10 reactions are known, each requiring its own special reaction conditions, solvents, catalysts, ring activating groups etc. Some known types of coupling reactions include the Grignard reaction, Heck reactions and Suzuki reactions (N. Migaura and A. Suzuki, Chem. Rev. 1995, 95, 2457-2483).

15 Substituted bi- and tri-aryl compounds are of great interest to the pharmaceutical and agrochemical industries. A great number of these compounds have been found to possess pharmaceutical activity, while others have been found to be useful herbicides. There is also interest from the polymer industry in polymers prepared by the linking together of organic compounds.

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Conventional methods for covalently linking aromatic rings, such as by reaction of an appropriate Grignard reagent, involve harsh conditions and are not suitable for aromatic rings with active hydrogen containing substituents. Substituents with active hydrogen atoms also can become involved in unwanted side reactions leading to undesirable
25 products. Such substituents need to be protected prior to reaction. Boronic acid derivatives required for the Suzuki reaction are traditionally synthesized through highly reactive organo metallic intermediates.

In view of the severity of the reaction conditions the range of substituents which could be
30 present during the linking reaction was considerably limited, and the range of useful

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reaction media (solvents) was restricted to those which can be expensive, difficult to remove and/or toxic.

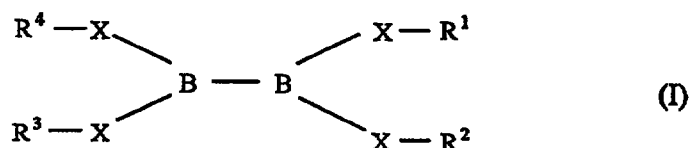
A difficulty associated with the known coupling reactions is the limited control of the functionality of the products, leading to complex mixtures which can be difficult to separate.

Some known diboron derivatives are relatively unstable compounds, which decompose readily in aqueous solution or on exposure to air. For this reason, and a perceived difficulty in making the compounds, their use in chemical reaction is relatively unexplored.

It has now been found that diboron derivatives can be quite stable and useful in the preparation of organic boronic acid derivatives, and that properties of the diboron derivatives can be adjusted to suit particular reaction conditions or to provide particular products by selection of appropriate substituents.

Accordingly in a first aspect of the present invention there is provided a diboron derivative of formula (I)

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where R^1 , R^2 , R^3 and R^4 are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, and a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer from 1 to 3, the or each R^5 is independently an optionally substituted C_1 - C_3 alkylene, R^6 is C_1 - C_3 alkyl or hydrogen and

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R^7 is hydrogen or C_1 - C_{12} alkyl; and

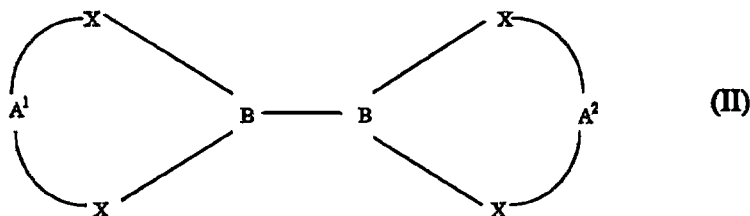
each X is independently selected from O, $S(O)_n$ and NR^7 , where n is an integer of 0 to 3 and R^7 is hydrogen or C_1 - C_{12} alkyl, or one or more of $-NR^1R^7$, $-NR^2R^7$, $-NR^3R^7$ and -

5 NR^4R^7 represent an optionally substituted 5 or 6 membered heterocyclyl group,

provided that when each X is O and R^1 to R^4 are identical, R^1 to R^4 are not unsubstituted straight chain alkyl, phenyl or naphthyl, isopropyl, or phenyl substituted with alkyl; when each X is $N(C_1-C_6 \text{ alkyl})$, R^1 to R^4 are not C_1 - C_6 alkyl and $-NR^1R^7$, $-NR^2R^7$, $-NR^3R^7$ and -
 10 NR^4R^7 are not unsubstituted piperidyl or unsubstituted pyrrolidinyl; when each X is NH, R^1 to R^4 are not C_1 - C_6 alkyl or unsubstituted phenyl; and when $-XR^1$ is $-OCH_3$, $-XR^2$ is $-N(CH_3)_2$ and $-XR^4$ is $-N(CH_3)_2$, $-XR^3$ is not OCH_3 .

In a second aspect of the invention there is provided a diboron derivative of formula (II)

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where X is independently selected from O, $S(O)_n$ and NR^7 where n is an integer from 0 to 2, R^7 is hydrogen or C_1 - C_{12} alkyl, and A^1 and A^2 are divalent groups which may be the same or different, provided that when each X is O, A^1 and A^2 are not unsubstituted C_1 - C_3 alkylene, 1,1,2,2-tetramethylethylene, 2,2-dimethylpropylene,

25 1,2-dialkoxycarbonylethylene, 1,2 diphenylethylene, 1 phenylethylene, unsubstituted phenylene or phenylene mono- or di-substituted with C_1 - C_4 alkyl; and when each X is S or NMe, both of A^1 and A^2 are not ethylene.

Preferably A^1 and A^2 are independently selected from optionally substituted alkylene,

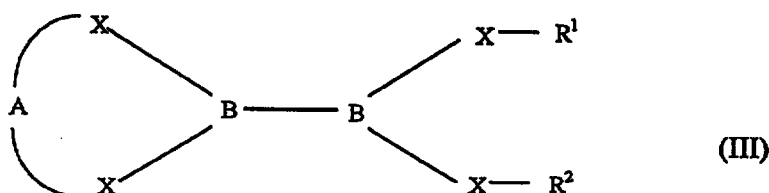
30 optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted

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arylene, optionally substituted alkylarylene, optionally substituted cycloalkylene, optionally substituted cycloalkenylene, or a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, R^5 and R^6 are independently an optionally substituted C_1 - C_3 alkylene, and R^7 is hydrogen or C_1 - C_{12} alkyl. The divalent groups, A^1 and A^2 , may include a fused 5 or 6 membered aliphatic or aromatic ring.

In a third aspect of the present invention there is provided a diboron derivative of formula (III)

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15 where R^1 and R^2 are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, the
 20 or each R^5 is independently an optionally substituted C_1 - C_3 alkylene, R^6 is hydrogen or C_1 - C_3 alkyl, and R^7 is hydrogen or C_1 - C_{12} alkyl;

each X is independently selected from O, $S(O)_n$ and NR^7 , where n is an integer of 0 to 3 and R^7 is hydrogen or C_1 - C_{12} alkyl, or one or both of $-NR^1R^7$ and $-NR^2R^7$ represent an
 25 optionally substituted 5 or 6 membered heterocyclyl group; and

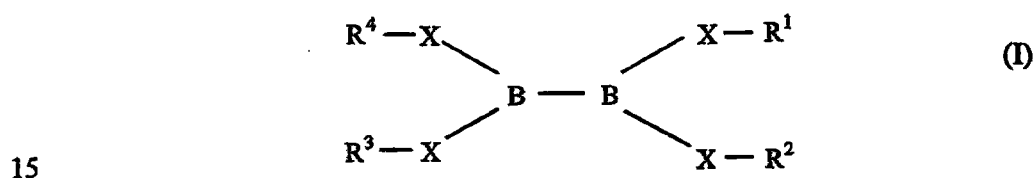
A is a divalent group;

provided that when R^1 and R^2 are Me and each X is NMe then A is not unsubstituted
 30 ethylene.

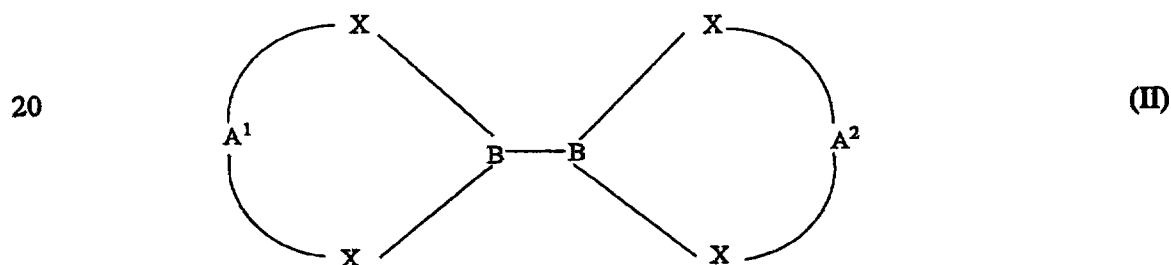
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Preferably A is independently selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted cycloalkenylene, or a group of the formula $-(R^5Q)_mR^6$ - where Q is
 5 selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, R^5 and R^6 are independently an optionally substituted C_1 - C_3 alkylene, and R^7 is hydrogen or C_1 - C_{12} alkyl. The divalent group A, may include a fused aliphatic or aromatic ring or ring system.

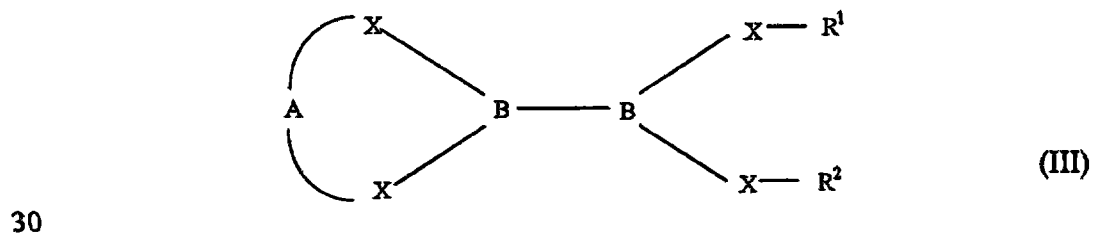
10 The invention also provides a diboron derivative of formula (I)



or a diboron derivative of formula (II)



25 or a diboron derivative of formula (III)



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where R^1 , R^2 , R^3 and R^4 are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, a group of the
 5 formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, the or and each R^5 is independently an optionally substituted C_1 - C_3 alkylene, R^6 is C_1 - C_3 alkyl or hydrogen, and R^7 is hydrogen or C_1 - C_{12} alkyl;

10 each X is independently selected from O, $S(O)_n$ and NR^7 , where n is an integer from 0 to 3, R^7 is hydrogen or C_1 - C_{12} alkyl, or one or more of $-NR^1R^7$, $-NR^2R^7$, $-NR^3R^7$ and $-NR^4R^7$ represent an optionally substituted 5 or 6 membered heterocyclyl group,

and A, A^1 and A^2 are divalent groups which may or may not be different, wherein said
 15 derivative has one or more chiral centres and there is an enantiomeric excess of one form.

Preferably the enantiomeric excess is greater than 80%, and more preferably greater than 90%.

20 In the above definitions, the term "alkyl", used either alone or in compound words such as "alkenyloxyalkyl", "alkylthio", "alkylamino" and "dialkylamino" denotes straight chain or branched alkyl, preferably C_1 - C_{20} alkyl. Examples of straight chain and branched alkyl include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethyl-propyl, hexyl, 4-methylpentyl, 1-
 25 methylpentyl, 2-methylpentyl, 3-methylpentyl, 1,1-dimethylbutyl, 2,2-dimethylbutyl, 3,3-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 1,2,2-trimethylpropyl, 1,1,2-trimethylpropyl, heptyl, 5-methoxyhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethyl-pentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl,
 30 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or

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7-methyl-octyl, 1-, 2-, 3-, 4- or 5-ethylheptyl, 1-, 2- or 3-propylhexyl, decyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- and 8-methylnonyl, 1-, 2-, 3-, 4-, 5- or 6-ethyloctyl, 1-, 2-, 3- or 4-propylheptyl, undecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-methyldecyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-ethylnonyl, 1-, 2-, 3-, 4- or 5-propyloctyl, 1-, 2- or 3-butylheptyl, 1-pentylhexyl, 5 dodecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-methylundecyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-ethyldecyl, 1-, 2-, 3-, 4-, 5- or 6-propylnonyl, 1-, 2-, 3- or 4-butyloctyl, 1-2-pentylheptyl and the like.

The term "alkylene" denotes a divalent alkyl group as defined above.

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The term "cycloalkyl" denotes cyclic alkyl groups, preferably C_{3-20} cycloalkyl. Examples of cycloalkyl include mono- or polycyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl and the like.

15 The term "cycloalkylene" denotes a divalent cycloalkyl group as defined above.

The term "alkenyl" denotes groups formed from straight chain or branched alkenes including ethylenically mono-, di- or poly-unsaturated alkyl or groups as previously defined, preferably C_{2-20} alkenyl. Examples of alkenyl include vinyl, allyl, 1- 20 methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, 1-hexenyl, 3-hexenyl, 1-heptenyl, 3-heptenyl, 1-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 3-decenyl, 1,3-butadienyl, 1,4-pentadienyl, 1,3-hexadienyl, 1,4-hexadienyl.

The term "alkenylene" denotes a divalent alkenyl group as defined above.

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The term "cycloalkenyl" denotes cyclic alkene groups, preferably C_{5-20} cycloalkenyl. Examples of cycloalkenyl include (cyclopentenyl, methyl cyclopentenyl, cyclohexenyl, cyclooctenyl, 1,3-cyclopentadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

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The term "cycloalkenylene" denotes a divalent cycloalkenyl group as defined above.

The term "aryl" is used herein in the broadest sense to refer to any aromatic ring or ring system, preferably having 3 to 20 carbon atoms. The ring or ring system may contain one or more heteroatoms selected from N, S, and O. The aromatic rings may be carbocyclic, heterocyclic or pseudo aromatic, and may be mono or polycyclic ring systems. Examples of suitable rings include but are not limited to benzene, biphenyl, terphenyl, quaterphenyl, naphthalene, tetrahydronaphthalene, 1-benzyl naphthalene, anthracene, dihydroanthracene, benzanthracene, dibenzanthracene, phenanthracene, perylene, pyridine, 4-phenylpyridine, 3-phenylpyridine, thiophene, benzothiophene, naphthothiophene, thianthrene, furan, pyrene, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, pyrazine, pyrimidine, pyridazine, indole, indolizine, isoindole, purine, quinoline, isoquinoline, phthalazine, quinoxaline, quinazoline, pteridine, carbazole, carboline, phenanthridine, acridine, phenanthroline, phenazine, isothiazole, isooxazole, phenoxazine and the like, each of which may be optionally substituted. The term "pseudoaromatic" refers to a ring system which is not strictly aromatic, but which is stabilized by means of delocalization of π electrons and behaves in a similar manner to aromatic rings. Examples of pseudoaromatic rings include but are not limited to furan, thiophene, pyrrole and the like.

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The term "aliphatic ring or ring system" as used herein refers to a non-aromatic carbocyclic or heterocyclic ring or ring system, preferably having from 3 to 20 carbon atoms. The ring or ring system may have one or more double or triple bonds. Examples of suitable aliphatic rings include but are not limited to cyclobutane, cyclopentadiene, cyclohexanone, cyclohexene, spiro-[4,5-decane] and hydrogenated or partially hydrogenated aromatic rings as described above.

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The term "arylene" as used herein denotes a divalent "aryl" moiety as defined above.

As used herein, an "olefinic" compound refers to any organic compound having at least

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one carbon to carbon double bond which is not part of an aromatic or pseudo aromatic system. The olefinic compounds may be selected from optionally substituted straight chain, branched or cyclic alkenes; and molecules, monomers and macromolecules such as polymers and dendrimers, which include at least one carbon to carbon double bond.

- 5 Examples of suitable olefinic compounds include but are not limited to ethylene, propylene, but-1-ene, but-2-ene, pent-1-ene, pent-2-ene, cyclopentene, 1-methylpent-2-ene, hex-1-ene, hex-2-ene, hex-3-ene, cyclohexene, hept-1-ene, hept-2-ene, hept-3-ene, oct-1-ene, oct-2-ene, cyclooctene, non-1-ene, non-4-ene, dec-1-ene, dec-3-ene, buta-1,3-diene, penta-1,4-diene, cyclopenta-1,4-diene, hex-1,4,diene, cyclohexa-1,3-diene,
 10 cyclohexa-1,4-diene, cyclohepta-1,3-diene, cyclohepta-1,3,5-triene and cycloocta-1,3,5,7-tetraene, each of which may be optionally substituted. Preferably the straight chain branched or cyclic alkene contains between 2 and 20 carbon atoms.

- In this specification "optionally substituted" means that a group may or may not be further
 15 substituted with one or more groups selected from alkyl, alkenyl, alkynyl, aryl, halo, haloalkyl, haloalkenyl, haloalkynyl, haloaryl, hydroxy, alkoxy, alkenyloxy, aryloxy, aryloxyalkyl, benzyloxy, haloalkoxy, haloalkenyloxy, haloaryloxy, isocyano, cyano, formyl, carboxyl, nitro, nitroalkyl, nitroalkenyl, nitroalkynyl, nitroaryl, nitroheterocyclyl, amino, alkylamino, dialkylamino, alkenylamino, alkynylamino, arylamino, diarylamino,
 20 benzylamino, imino, alkylimino, alkenylimino, alkynylimino, arylimino, benzylimino, dibenzylamino, acyl, alkenylacyl, alkynylacyl, arylacyl, acylamino, diacylamino, acyloxy, alkylsulphonyloxy, arylsulphenyloxy, heterocyclyl, heterocycloxy, heterocyclamino, haloheterocyclyl, alkylsulphenyl, arylsulphenyl, carboalkoxy, carboaryloxy mercapto, alkylthio, benzylthio, acylthio, sulphonamido, sulfanyl, sulfo and phosphorus-containing
 25 groups.

The term "fused aliphatic or aromatic ring" as used herein in relation to divalent groups A, A and A² means that one or more of the bonds connecting the X moieties of the compounds of formulae I, II or III is part of an aliphatic or aromatic ring system.

As used herein the term "divalent group" refers to any group having two valencies available for bonding with another chemical moiety. Examples of suitable divalent groups include alkylene, alkenylene, cycloalkylene and the like.

- 5 The term "acyl" as used herein refers to carbamoyl, aliphatic acyl group and acyl group is referred to as heterocyclic acyl, preferably C₁₋₂₀ acyl. Examples of acyl include carbamoyl; straight chain or branched alkanoyl such as formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl and icosanoyl; alkoxy carbonyl such as methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl and heptyloxycarbonyl; cycloalkyl carbonyl such as cyclopropyl carbonyl, cyclobutyl carbonyl, cyclopentyl carbonyl and cyclohexyl carbonyl; alkylsulfonyl such as methylsulfonyl and ethylsulfonyl; alkoxy sulfonyl such as methoxysulfonyl and ethoxysulfonyl; aroyl such as benzoyl, toluoyl and naphthoyl; aralkanoyl such as phenylalkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutyl, phenylpentanoyl and phenylhexanoyl) and naphthylalkanoyl (e.g. naphthylacetyl, naphthylpropanoyl and naphthylbutanoyl); aralkenoyl such as phenylalkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl and phenylhexenoyl and naphthylalkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl and naphthylpentenoyl); aralkoxy carbonyl such as phenylalkoxy carbonyl (e.g. benzyloxy carbonyl); aryloxy carbonyl such as phenoxy carbonyl and naphthoxy carbonyl; aryloxyalkanoyl such as phenoxyacetyl and phenoxypropionyl; arylcarbamoyl such as phenylcarbamoyl; arylthiocarbamoyl such as phenylthiocarbamoyl; arylglyoxyloyl such as phenylglyoxyloyl and naphthylglyoxyloyl; arylsulfonyl such as phenylsulfonyl and naphthylsulfonyl; heterocyclic carbonyl; heterocyclicalkanoyl such as thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl and tetrazolylacetyl; heterocyclicalkenoyl such as heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl and heterocyclichexenoyl; and heterocyclicglyoxyloyl such as thiazolylglyoxyloyl and

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thienylglyoxyloyl.

The diboron derivatives may be made following the method of Brotherton et al. [R.J. Brotherton, A.L. McCloskey, L.L. Peterson and H. Steinberg, *J. Amer. Chem. Soc.* **82**, 6242 (1960); R.J. Brotherton, A.L. McCloskey, J.L. Boone and H.M. Manasevit, *J. Amer. Chem. Soc.* **82**, 6245 (1960)]. In this process $B(NMe_2)_3$, obtained by reaction of BCl_3 with $NHMe_2$, is converted to $BrB(NMe_2)_2$ by reaction with a stoichiometric amount of BBr_3 . Reduction in refluxing toluene with sodium metal gives the diboron compound $[B(NMe_2)_2]_2$ which, after purification by distillation, can be reacted with the alcohol (for example, pinacol or neopentandiol) in the presence of a stoichiometric amount (four equivalents) of HCl to give the desired ester product.

With many alcohols this reaction is unsatisfactory, the reaction being slow and complete removal of the amine being difficult unless anhydrous mineral acid (four equivalents) are added to the reaction.

An aspect of the present invention is the discovery that esters of tetrahydroxydiboron can be readily synthesised in near quantitative yield by the reaction of diboronic acid (tetrahydroxydiboron) with alcohols (including diols and polyols) and this reaction does not require the presence of acids. Furthermore, it has been found that the reaction of tetrahydroxydiboron with certain diols can be carried out with advantage in the presence of simple monoalcohols such as methanol or ethanol without these monoalcohols being incorporated in the final reaction products. These reactions, in the presence of monoalcohols, show that tetrahydroxydiboron esters of these monoalcohols readily undergo transesterification with diols that can form ring structures on a boron atom. The transesterification represents a further procedure for the production of esters of tetrahydroxydiboron. These reactions can be performed in a variety of solvents or mixtures thereof.

Accordingly in a further aspect of the present invention there is provided a process for the

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preparation of a diboronic acid ester comprising contacting diboronic acid with a suitable monoalcohol, diol or polyol for a time and under conditions such that the diboronic acid reacts with the diol or polyol to produce the diboron derivative.

5 Unlike the literature procedure, the process according to this aspect of the present invention lends itself readily to the synthesis of tetrahydroxydiboron esters with acid sensitive alcohols. The synthesis of tetrahydroxydiboron esters with alcohols possessing basic functionalities are difficult using the known literature method since the products obtained are partially or fully protonated on their basic functionalities. The process
10 according to this aspect of the present invention does not have this inherent problem.

In the prior art procedure the side product, the acid salt of the amine, must be removed to obtain pure product. A major advantage of the present process is that product obtained is sufficiently pure that it can generally be used without the need for further purification.

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The diboron derivatives according to the present invention are useful in the preparation of organic boronic acid derivatives, and by selection of appropriate substituents and reactants, it is possible to use the diboron derivatives to form organic boronic acid derivatives which are useful in organic coupling reactions.

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The organic boronic acid derivatives are generally prepared by reaction of a diboron derivative of this invention and an organic compound in the presence of a Group VIII metal catalyst. In order to participate in such a reaction the organic compound should possess a boron reactive site.

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The boron reactive site may be a halogen or halogen-like substituent on the organic compound, a carbon to carbon double or triple bond, or leaving group located in an allylic position.

30 In the case of halogen or halogen-like substituents, and allylic leaving groups, the diboron

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derivative displaces the group in a substitution reaction to form an organic boronic acid derivative. In the case of reaction with double and triple carbon-to-carbon bonds in the presence of platinum and like catalysts, the diboron compound tends to undergo an addition reaction across the double or triple bond to form products in which the boron
5 esters are located on adjacent carbon atoms.

The terms "halogen-like substituent" and "pseudo-halide" refer to any substituent which, if present on an organic compound, may react with a diboron derivative in the presence of a Group VIII metal catalyst and base to give an organic boronic acid derivative. Preferred
10 halogen substituents include I and Br. Cl may also be used although Cl is generally less reactive to substitution by the diboron compound. The reactivity of chloro substituted organic compounds can be increased by selection of appropriate ligands on the Group VIII metal catalyst. Examples of halogen-like substituents include triflates and mesylates, diazonium salts, phosphates and those described in Palladium Reagents & Catalysts
15 (Innovations in Organic Synthesis by J. Tsuji, John Wiley & Sons, 1995, ISBN 0-471-95483-7).

As used herein, the term "leaving group" refers to a chemical group which is capable of being displaced by a boronic acid residue. Suitable leaving groups are apparent to those
20 skilled in the art and include halogen and halogen-like substituents.

The temperature at which the preparation of the diboronic acid esters is conducted will depend on a number of factors including the desired rate of reaction, solubility and reactivity of the reactants in the selected solvent, boiling point of the solvent, etc. The
25 temperature of the reaction will generally be in the range of -100 to 200°C. In a preferred embodiment the process is performed at a temperature between 0 and 80°, more preferably between 15 and 40°C.

Chiral diboronic acid derivatives may be prepared from chiral starting materials or
30 intermediates under conditions in which the chirality is preserved or they may also be

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prepared via the racemate in which case a separation step will be required. Separation of the enantiomers may be achieved conventionally using conventional chromatographic methods including chiral chromatography, enzymatic resolution, or using a resolving agent. The individual chiral forms are also part of the present invention.

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Diboron derivatives containing a chiral centre, if there is an enantiomeric excess of one isomer, are particularly useful in the preparation of enantiomers of chiral compounds. In this regard it is possible to react a diboron compound having one or more chiral centers, and an enantiomeric excess of one enantiomer, with an organic compound having a boron
10 reactive site to produce an organic boronic acid ester derivative in which the chirality is preserved. The chiral organic boronic acid derivative may then be reacted with another organic compound to produce a new chiral centre, the stereochemistry of which is induced by the stereochemistry of the chiral organic boronic acid derivative. Suitable organic compounds with which to react the chiral organic boronic acid derivative include
15 aldehydes and unsymmetrical ketones, as reaction at the carbonyl produces a new chiral center. It is also possible to couple sterically hindered aromatic rings via an aromatic boronic acid derivative intermediate to produce chiral biaryl compounds in which the helical sense is maintained through restricted rotation about the bond linking the aromatic rings (also referred to as atropism).

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In a particularly preferred embodiment of the invention a diboron derivative is prepared by reacting a suitable diboron reactant with a chiral diol, examples include pinanediol, diisopropyl tartrate, and sugars, such as mannose or galactose and like sugars containing cis-hydroxy groups or other hydroxy groups suitably orientated to couple with boron. The
25 chiral diboron derivatives may then be reacted with suitable organic compounds having boron reactive sites to produce chiral organic boronic acid derivatives. These may be reacted in a stereospecific manner with an organic compound, with the formation of a new chiral center.

30 It is also possible to activate the boron to boron bond by selecting an R^1 to R^4 , A, A^1 , or

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A² substituent which is capable of further co-ordinating with one of the boron atoms. Such groups would include an electron rich substituent or atom which is capable of feeding electron density onto the boron atom. Examples of electron rich atoms include oxygen, nitrogen and sulphur.

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A difficulty with using the known pinacol ester of diboronic acid to produce organic boronic acids is that it is difficult to cleave the pinacol ester to give the corresponding organic boronic acid. Other esters of this invention have been found to hydrolyse more readily than the pinacol ester. Esters containing an aromatic ring on the carbon α to the X
10 moiety are surprisingly easy to cleave to the corresponding boronic acid. Benzyl ester derivatives are particularly useful for this purpose.

It is also possible to select substituents to improve the solubility of the diboron derivative in a particular solvent in which a subsequent reaction is to be carried out. Water solubility
15 of the diboron compound can be increased by introducing polar groups, such as hydroxy groups, into the R¹ to R⁴, A, A¹ and A² substituents. Similarly it is possible to select substituents which increase the solubility of the diboron compound in the desired organic solvent.

20 Many of the boronic acid ester derivatives prepared from the novel diboronic acid derivatives according to the present invention are also novel and represent a further aspect of the present invention.

These organic boronic acid derivatives may be reacted with organic compounds having
25 one or more boron reactive sites to produce coupled products, as described above. These coupling reactions are generally conducted in the presence of a group VIII metal catalyst and a suitable base.

The process and compounds according to the invention are also useful for the preparation
30 of reactive intermediates which are capable of taking part in further reactions or

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rearrangements. These reactive intermediates may be the organic boronic acid derivative or the coupled products. For example, organic boronic acid derivatives may take part in one or more of the palladium catalysed reactions of organoboron compounds described by Miyaura and Suzuki in Chem. Rev. 1995, 95 2457-2483. Examples of other types of
5 reactions in which the diboron derivatives of the present invention are useful are described in copending applications PCT/AU98/00245 and PCT/AU98/00476.

The invention will now be described with reference to the following examples which illustrate some preferred embodiments of the invention. It is to be understood that the
10 particularity of the following description is not to supersede the generality of the preceding description of the invention.

EXAMPLES

15 GENERAL PROCEDURES

General procedure A

Two equivalents of diol is added to a solution of tetrakis(dimethylamino)diboron in dry diethyl ether under nitrogen. The reaction mixture is stirred magnetically and cooled in an ice-bath before adding a dry ethereal solution of hydrogen chloride (4 equivalents) over 1h.
20 After stirring overnight at room temperature the reaction mixture is filtered and the solid collected is extracted with hot benzene (2X) to remove the dimethylamine hydrochloride salt. The ether filtrate and the benzene extracts are taken to dryness under vacuum. The resultant products are then combined, recrystallised from benzene/petroleum spirit (60-80°C) and dried under high vacuum.

25

General Procedure B

Two equivalents of diol is added to diboronic acid in benzene and the reaction mixture heated under reflux for 24 hours using a Dean-Stark apparatus. The benzene solution is separated from the water formed, dried and taken to dryness under vacuum to give the
30 diboronic ester. The addition of monoalcohols such as ethanol or methanol can be used to

- 17 -

enhance this procedure.

General Procedure C

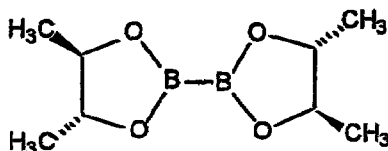
Two equivalents of diol is added to diboronic acid in tetrahydrofuran. A dehydrating agent such as anhydrous sodium sulphate is added and the reaction mixture stirred at room temperature overnight. The solution is then filtered and the filtrate taken to dryness under vacuum to yield the diboronic ester. The addition of monoalcohols such as methanol and ethanol can be used to enhance the procedure. The presence of a dehydrating agent is not always necessary for satisfactory yields.

10

Example 1

(4R,4'R,5R,5'R)-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane

15



This diboronic ester is prepared following general procedure A using

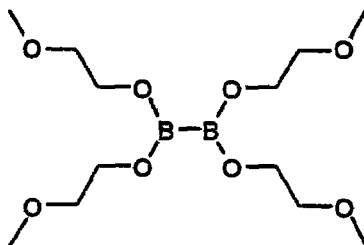
(2R,3R)-(-)-2,3-butanediol. ¹H-nmr (CDCl₃, 200MHz): δ 1.22 (6H, multiplet; CHCH₃)

20 and 4.00 (2H, multiplet; CHCH₃).

Example 2

1,1,2,2-Tetrakis(2-methoxyethoxy)diborane

25

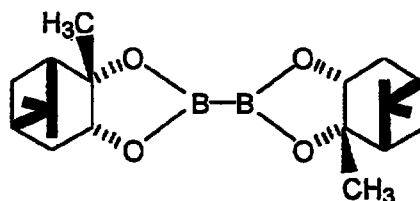


30

This diboronic ester is prepared following general procedure A using

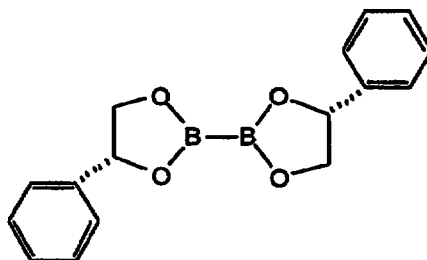
- 18 -

2-methoxy-ethanol. ^1H -nmr (CDCl_3 , 200MHz): δ 3.36 (3H, singlet; CH_3), 3.42-3.51 (2H, multiplet; BOCH_2) and 3.62-3.71 (2H, multiplet; CH_2O).

Example 3**5 Bis((1S,2S,3R,5S)-(+)-pinanediolato)diboron(B-B)**

10

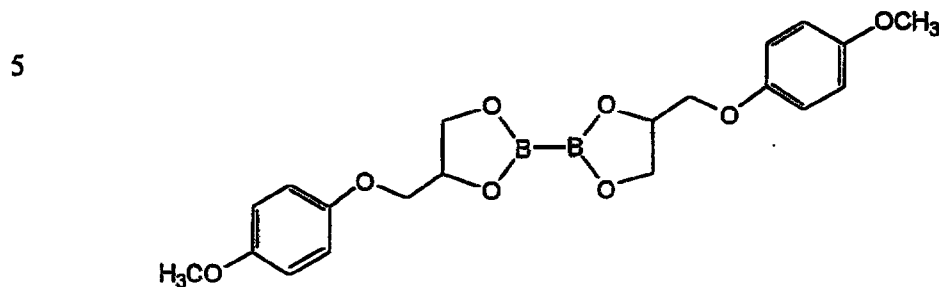
This diboronic ester is prepared following general procedure A using (1S,2S,3R,5S)-(+)-pinanediol. Yield 98%. ^1H -nmr (CDCl_3 , 200MHz): δ 0.77 (singlet, 3H; C_3CH_3), 1.01-1.13 (doublet, 2H; C_2CH), 1.20 (3H, singlet; C_5CH_3), 1.87-1.91 (2H, multiplet; C_2CH_2),
 15 1.92-2.31 (3H, multiplet; CH_2CO and CHCO) and 4.15-4.26 (1H, multiplet; C_2CHO).

Example 4**(4R,4'R)-Diphenyl-2,2'-bi-1,3,2-dioxaborolane**

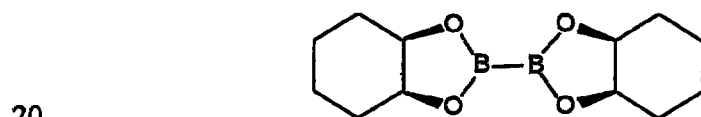
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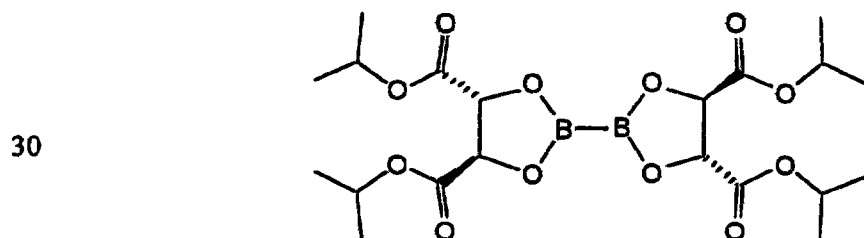
This diboronic ester is prepared following general procedure A using (R)-(-)-1-phenyl-1,2-ethanediol. Yield, 88%. ^1H -nmr (CDCl_3 , 200MHz): δ 3.90-4.01 (1H, triplet; CH_2C), 4.42-4.57 (1H, triplet; CH_2C) and 7.10-7.31 (5H, multiplet; ArH). ^{13}C -nmr (CDCl_3 , 200MHz): δ 72.73 (1C; $\underline{\text{CH}_2}$), 78.78 (1C; $\underline{\text{CPh}}$) 125.71 (2C; $m\text{-C}$), 128.17 (1C; $p\text{-C}$),
 30 128.70 (2C; $o\text{-C}$) and 140.65 (1C; $\underline{\text{C-O}}$).

Example 5**4,4'-Bi-[(4-methoxyphenoxy)methyl]-2,2'-bi-1,3,2-dioxaborolane**

This diboronic ester is prepared following general procedure A using 3-(4-methoxyphenoxy)-1,2-propanediol. Yield, 70%. ^{13}C -nmr (D_6 -DMSO, 200MHz): δ 55.27, 66.50, 70.00, 70.74, 74.80, 114.51, 115.45, 152.30 and 153.60.

Example 6**2,2'-Bi-(3aR,7aS)hexahydro-1,3,2-benzodioxaborole**

This diboronic ester is prepared following general procedure A using *cis*-1,2-cyclohexanediol. Yield, 65%. ^1H -nmr (CDCl_3 , 200MHz): δ 1.20-2.00 (multiplet, 8H; CH_2) and 4.30 (multiplet, 2H; CH).

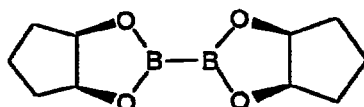
Example 7**Tetraisopropyl (4R,4'R,5R,5'R)-2,2'-bi-1,3,2-dioxaborolane-4,4'5,5'-tetracarboxylate**

- 20 -

This diboronic ester is prepared following general procedure A using diisopropyl L-tartrate. Yield, quantitative. ¹H-nmr (CDCl₃, 200MHz): δ 1.10-1.30 (multiplet, 28H; CHCH₃ and CH₃) and 4.30 (singlet, 4H; OCH).

5 Example 8

(3aR,3'aR,6aS,6'aS)-Di-(tetrahydro-3aH-cyclopenta[d])-2,2'-bi-1,3,2-dioxaborolane



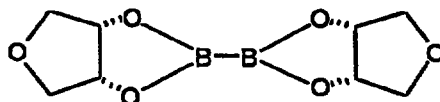
10

This diboronic ester is prepared following general procedure A using *cis*-1,2-cyclopentanediol. Yield, 78%. ¹H-nmr (CDCl₃, 200MHz): δ 1.40-1.61 (multiplet, 4H; OCHCH₂), 1.75-2.00 (multiplet, 2H; CH₂CH₂CH₂) and 4.80 (multiplet, 2H; OCH).

15

Example 9

(3R,6S,3'R,6'S)-Di-(tetrahydrofuro[3,4-d])-2,2'-bi-1,3,2-dioxaborolane



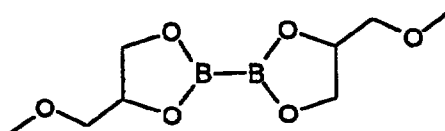
20

This diboronic ester is prepared following general procedure A using 1,4-anhydroerythritol. Yield, 78%. ¹H-nmr (CDCl₃, 200MHz): δ 3.40-3.50 (multiplet, 2H; OCHH), 4.00-4.14 (multiplet, 2H; CHH) and 4.90 (multiplet, 2H; OCH).

25

Example 10

4,4'-Bis(methoxymethyl)-2,2'-bi-1,3,2-dioxaborolane



30

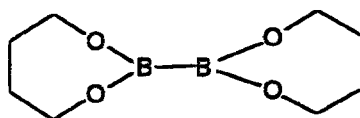
This diboronic ester is prepared following general procedure A using

- 21 -

3-methoxy-1,2-propanediol. Yield, 96%. ^1H -nmr (CDCl_3 , 200MHz): δ 3.23 (singlet, 6H; OCH_3), 3.30-3.40 (multiplet, 4H; CH_2OCHH), 3.80-3.95 (multiplet, 2H; CH_2OCHH), 4.10-4.20 (triplet, 2H; CH_2OB) and 4.40-4.50 (multiplet, 2H; OCH).

5 Example 11

2,2'-Bi-1,3,2-dioxaborepane

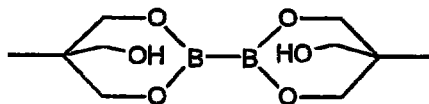


10

This diboronic ester is prepared following general procedure A using 1,4-butanediol. ^1H -nmr (D_6 -DMSO, 200 MHz): δ 1.36-1.42 (multiplet, 4H; $\text{CH}_2\text{CH}_2\text{CH}_2$) and 3.36 (multiplet, 4H; CH_2O).

15 Example 12

5,5'-Dihydroxymethyl-5,5'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane



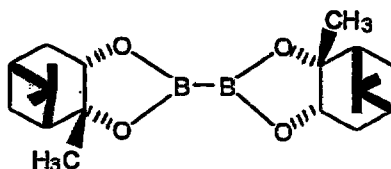
20

This diboronic ester is prepared following general procedure C using 1,1,1-tris(hydroxymethyl)ethane. Yield, 90%. ^1H -nmr (d_6 -dmso; 200MHz): δ 0.79 (singlet, 6H; 2 x CH_3), 3.21-3.75 (multiplet, 12H; 6 x CH_2O) and 4.76 (triplet, 2H; 2 x OH). F.W.: calc. for $\text{C}_{10}\text{H}_{22}\text{B}_2\text{O}_6$ = 257.89, found m/z 259 ($\text{M}+1$).

25

Example 13

Bis(1R,2R,3S,5R-(-)-pinanediolato)diboron(B-B)



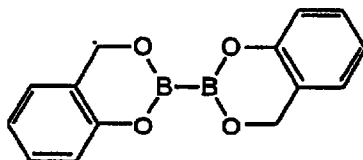
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- 22 -

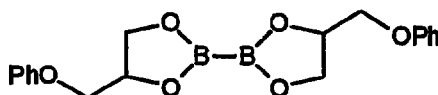
This diboronic ester is prepared following general procedure A using 1R,2R,3S,5R-(-)-pinanediol. Yield, 77%. ¹H-nmr (CDCl₃, 200MHz): δ 0.84 (singlet, 6H; 2 x C₃CH₃), 1.08-1.14 (doublet, 2H; 2 x C₂CH), 1.28 (singlet, 6H; 2 x C₃CH₃), 1.39 (singlet, 6H; 2 x CH₃CO), 1.87-1.97 (multiplet, 4H; 2 x C₂CH₂), 2.04-2.37 (multiplet, 6H; 2 x CH₂CO and 2 x CHCO) and 4.24-4.29 (multiplet, 2H; 2 x C₂CHO). F.W.: calc. for C₂₀H₃₂B₂O₄ = 358.09, found m/z 359 (M+1).

Example 14**2,2'-Bi-4H-1,3,2-benzodioxaborinine**

10



15 This diboronic ester is prepared following general procedure C using 2-hydroxybenzyl alcohol. Yield, 77%. ¹H-nmr (CDCl₃, 200MHz): δ 5.12 (singlet, 4H; 2 x ArCH₂), 6.91-7.26 (multiplet, 8H; 2 x ArH). F.W.: calc. for C₁₄H₁₂B₂O₄ = 265.87, found m/z 267 (M+1).

Example 15**4,4'-Bi-(phenoxyethyl)-2,2'-1,3,2-dioxaborolane**

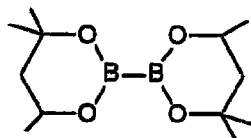
25

This diboronic ester is prepared following general procedure A using 3-phenoxy-1,2-propanediol. Yield, 71%. ¹H-nmr (CDCl₃, 200MHz): δ 3.96-4.41 (multiplet, 8H; 4 x CH₂O), 4.74-4.86 (multiplet, 2H; 2 x OCH) and 6.86-7.34 (multiplet, 10H; 2 x OArH). F.W.: calc. for C₁₈H₂₀B₂O₆ = 353.97, found m/z 355 (M+1).

- 23 -

Example 16**4,4,4',4',6,6'-Hexamethyl-2,2'-bi-1,3,2-dioxaborinane**

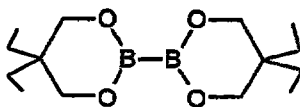
5



This diboronic ester is prepared following general procedure A using 2-methyl-2,4-pentanediol. Yield, 71%. ¹H-nmr (CDCl₃, 200MHz): δ 1.18-1.32 (multiplet, 18H; 6 x CH₃), 1.44-1.56 (multiplet, 2H; 2 x HCHC), 1.69-1.78 (multiplet, 2H; 2 x HCHC) and 4.07-4.22 (multiplet, 2H; 2 x OCH). F.W.: calc. for C₁₂H₂₄B₂O₄ = 253.94, found m/z 255 (M+1).

Example 17**5,5,5',5'-Tetraethyl-2,2'-bi-1,3,2-dioxaborinane**

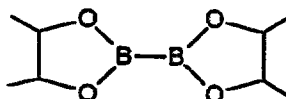
15



20 This diboronic ester is prepared following general procedure A using 2,2-diethyl-1,3-propanediol. Yield, 79%. H-nmr (CDCl₃, 200MHz): δ 0.75-0.82 (triplet, 12H; 4 x CH₃), 1.25-1.37 (quartet, 8H; 4 x CH₂CH₃) and 3.69 (singlet, 8H; 4 x CH₂O). F.W.: calc. for C₁₄H₂₈B₂O₄ = 282.00, found m/z 283 (M+1).

Example 18**4,4',5,5'-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane**

25



30

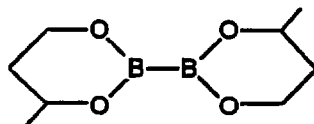
This diboronic ester is prepared following general procedure A using 2,3-butanediol. ¹H-nmr (CDCl₃, 200MHz): δ 1.10-1.28 (multiplet, 12H; 4 x CH₃) and 4.42-4.52 (multiplet,

- 24 -

4H; 4 x CH).

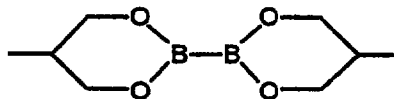
Example 19**4,4'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane**

5



This diboronic ester is prepared following general procedure A using 1,3-butanediol.

- 10 Yield, 94%. ¹H-nmr (CDCl₃, 200MHz): δ 1.21-1.25 (doublet, 6H; 2 x CH₃), 1.56-1.94 (multiplet, 4H; 2 x CH₂CH₂CH) and 3.81-4.14 (multiplet, 6H; 2 x OCH₂ and 2 x OCH). F.W.: calc. for C₈H₁₆B₂O₄ = 197.83, found m/z 199 (M+1).

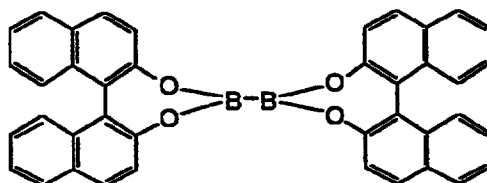
Example 20**15 5,5'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane**

This diboronic ester is prepared following general procedure A using 2-methyl-1,3-

- 20 propanediol. Yield, 96%. ¹H-nmr (CDCl₃, 200MHz): δ 0.80-0.84 (doublet, 6H; 2 x CH₃), 1.97-2.17 (multiplet, 2H; 2 x CHCH₃), 3.43-3.57 (triplet, 4H; 4 x HCHCCH₃) and 3.87-3.95 (multiplet, 4H; 4 x HCHCCH₃). F.W.: calc. for C₈H₁₆B₂O₄ = 197.83, found m/z 199 (M+1).

25 Example 21**Bi-(dinaphtho[2,1-d:1,2-f])-2,2'-bi-1,3,2-dioxaborepine**

30

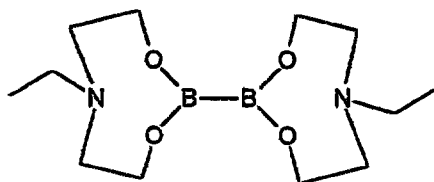


- 25 -

This diboronic ester is prepared following general procedure A using 1,1'-bis-2-naphthol. ¹H-nmr (CDCl₃, 200MHz): δ 6.90-6.95 (multiplet, 2H; ArH), 7.12-7.34 (multiplet, 6H; ArH) and 7.83-7.99 (multiplet, 2H; ArH).

5 Example 22

6,6'-Diethyl-2,2'-bi-1,3,6,2-dioxazaborocane



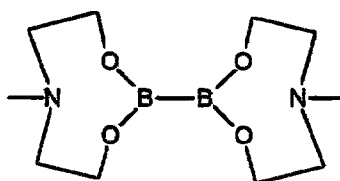
10

This diboronic ester is prepared following a similar method to that described in general procedure C using N-ethyldiethanolamine, but this time adding the sodium sulphate in the initial stages of the reaction and heating the mixture under reflux. ¹H-nmr (200MHz; CDCl₃): δ 1.15-1.23 (triplet, 6H; 2 x CH₃), 2.88-2.91 (multiplet, 12H; 6 x CH₂N) and 3.83-3.85 (multiplet, 8H; 4 x OCH₂).

15

Example 23

6,6'-Dimethyl-2,2'-bi-1,3,6,2-dioxazaborocane



20

25

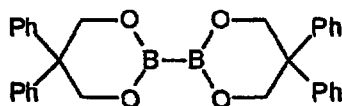
This diboronic ester is prepared following general procedure B using N-methyldiethanolamine. ¹H-nmr (200MHz; CDCl₃): δ 2.51 (triplet, 6H; CH₃), 2.79-3.35 (multiplet, 8H; 4 x CH₂N) and 3.76-3.94 (multiplet, 8H; 4 x CH₂O).

30

- 26 -

Example 24**5,5,5',5'-Tetraphenyl-2,2'-bi-1,3,2-dioxaborinane**

5

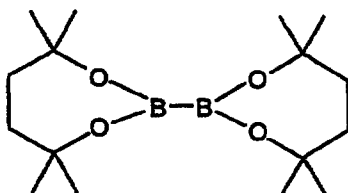


This diboronic ester is prepared following general procedure A using 2,2-diphenyl-1,3-propanediol. ¹H-nmr (CDCl₃, 200MHz): δ 4.48 (singlet, 8H; CH₂O) and 7.13-7.31 (multiplet, 20H; ArH).

10

Example 25**4,4,4',4',7,7,7',7'-Octamethyl-2,2'-bi-1,3,2dioxaborepane**

15

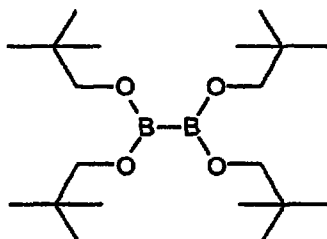


This diboronic ester is prepared following general procedure A using 2,5-dimethyl-2,5-hexanediol. ¹H-nmr (CDCl₃, 200MHz): δ 1.27 (singlet, 24H; CH₃) and 1.77 (singlet, 8H; CH₂).

20

Example 26**1,1,2,2-Tetrakis(neopentyloxy)diborane**

25



30 This diboronic ester is prepared following general procedure A using neopentylalcohol.

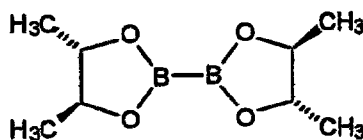
- 27 -

¹H-nmr (CDCl₃, 200MHz): δ 0.93 (singlet, 36H; CH₃) and 3.62 (singlet, 8H; CH₂).

F.W.: calc. for C₂₀H₄₄B₂O₄ = 370.19, found (GCMS) m/z=371 (M+1).

Example 27

5 (4S,4'S,5S,5'S)-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane

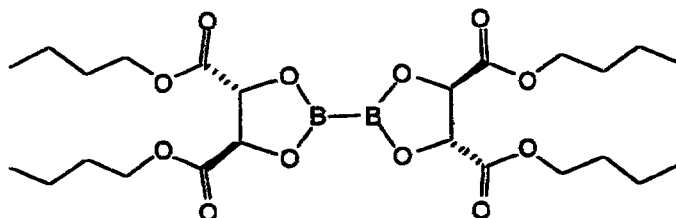


- 10 This diboronic ester is prepared following general procedure A using (2S,3S)-(+)-2,3-butanediol. Yield, quantitative. ¹H-nmr (CDCl₃, 200MHz): δ 1.30 (singlet, 6H, CH₃), 1.33 (singlet, 6H, CH₃) and 3.99 (multiplet, 4H; CH). F.W.: calc. for C₈H₁₆B₂O₄ = 197.83, found (GCMS) m/z=199 (M+1).

15 Example 28

Tetrabutyl (4R,4'R,5R,5'R)-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxylate

20



This diboronic ester is prepared following general procedure A using dibutyl L-tartrate.

Yield, 93%. ¹H-nmr (CDCl₃, 200MHz): δ 0.89-0.98 (multiplet, 12H; CH₃), 1.27-1.47

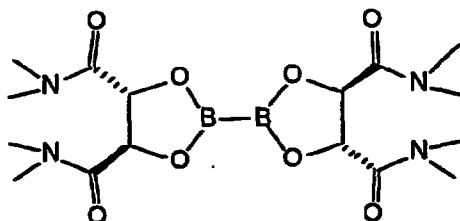
- 25 (multiplet, 8H; CH₂CH₂), 1.58-1.72 (multiplet, 8H; CH₂CH₂CH₂), 4.15-4.25 (multiplet, 8H; CH₂O) and 4.92 (singlet, 4H; CHCO₂). The desired compound was detected by GCMS.

30

Example 29

(4R,4'R,5R,5'R)-N⁴,N^{4'},N⁵,N^{5'},N⁶,N^{6'},N⁷,N^{7'}-Octamethyl-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxamide

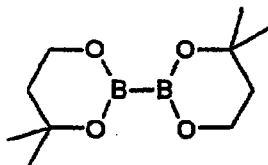
5



- 10 This diboronic ester is prepared following general procedure A using N,N,N',N'-tetramethyl L-tartaramide. Yield, 74%. ¹H-nmr (CDCl₃, 200MHz): δ 2.90 (singlet, 12H; NCH₃), 3.14 (singlet, 12H; NCH₃) and 5.54 (singlet, 4H; CHC=O).

Example 30

- 15 **4,4,4',4'-Tetramethyl-2,2'-bi-1,3,2-dioxaborinane**
Synthesis of



20

- The diol 2-methyl-2,4-dihydroxybutane (1.04 g, 1 mmol) was reacted with diboronic acid (0.45 g, 0.5 mmol) in 25 ml dry THF at room temp. (procedure C without dehydrating agent). The diboronic acid rapidly dissolved to give a colourless, clear solution. The gc
25 on a small aliquot of the reaction solution, diluted with ethyl acetate, showed only two peaks of area ratio 2 : 98. The weak peak corresponded to the retention time of the diol. On removing the solvent from the reaction solution under reduced pressure the product ester was obtained as a white solid. ¹H nmr (CDCl₃) δ 1.30 (s, 12H), 1.78 (t, J = 5.8 Hz, 4H), 3.98 (t, J = 5.8 Hz, 4H).

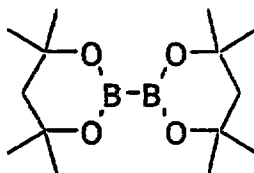
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Example 31**4,4,4',4',6,6,6',6'-Octamethyl-2,2'-bi-1,3,2-dioxaborinane**

Synthesis of

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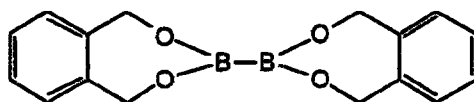
The diol 2,4-dimethyl-2,4-dihydroxypentane (1.32 g, 1 mmol) was reacted with diboronic acid (0.45 g, 0.5 mmol) in 25 ml dry THF at room temp. (procedure C without
10 dehydrating agent). The diboronic acid dissolved to give a colourless, clear solution. The gc on a small aliquot of the reaction solution, diluted with ethyl acetate, showed only two peaks of area ratio 4 : 95. The weak peak corresponded to the retention time of the diol. On removing the solvent from the reaction solution under reduced pressure the product ester was obtained as a white solid. ¹H nmr (D₆-DMSO) δ 1.25 (s, 24H), 1.77 (s, 4H).

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Example 32**3,3'-Bi-1,5-dihydro-2,4,3-benzodioxaborepine**

Synthesis of

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The diol 1,2-benzenedimethanol (1.38 g, 1 mmol) was reacted with diboronic acid (0.45 g, 0.5 mmol) in 25 ml dry THF at room temp. (procedure C without dehydrating agent). After most of the diboronic acid had dissolved, the reaction was warmed to 50-55°C. for
25 several hours and then filtered to give a clear, colourless solution. The solvent was removed from the compound under reduced pressure and a white, soft compound was obtained. ¹H nmr (CDCl₃) gave three broad peaks at δ 4.74, 4.89, 5.01 and a sharp singlet at 5.10 (total 8H), and two multiplets at 7.22 and 7.28 (total 8H). The broad peaks sharpened on cooling the CDCl₃ solution and are possibly due to isomers of the
30 desired compound.

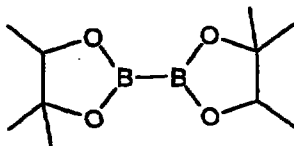
- 30 -

The formation of the ester, at room temp., is considerably faster in ethanol than in THF, all the diboronic acid (0.45 g, 0.5 mmol) reacting with the diol 1,2-benzenedimethanol (1.38 g, 1 mmol) within several minutes following solvent addition (25 ml) to give a clear, colourless solution. This was stirred at room temperature before removal of the solvent under reduced pressure. A white, hard solid was obtained, free from ethanol (^1H nmr) after pumping on the material for several hours at 10^{-7} to 10^{-6} mmHg and temperature around 40°C . ^1H nmr (CDCl_3) δ 4.73(s), 5.09(s) (intensity ratio 1 : 4.3, total 8H), and 7.23 and 7.32 (total 8H). The peaks at δ 4.73 and 7.31 are weak and may be due to an isomer of the product in which the ligands bridge the two boron atoms.

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Example 33**4,4,4',4',5,5'-Hexamethyl-2,2'-bi-1,3,2-dioxaborolane**

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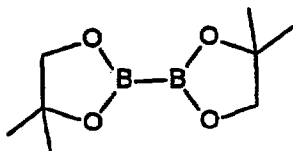


This diboronic ester is prepared following general procedure A using 2-methyl-2,3-butanediol. ^1H -nmr (CDCl_3 , 200MHz): δ 0.75-1.18 (multiplet, CH_3 and CH). F.W.: calc. for $\text{C}_{10}\text{H}_{20}\text{B}_2\text{O}_4$ = 225.89, found (GCMS) m/z =226 ($M+1$).

20

Example 34**4,4,4',4'-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane**

25



This diboronic ester is prepared following general procedure A using 2-methylpropane-1,2-diol. ^1H -nmr (CDCl_3 , 200MHz): δ 1.22 (singlet, 12H; CH_3) and 3.73 (singlet, 4H; CH_2). F.W.: calc. for $\text{C}_8\text{H}_{16}\text{B}_2\text{O}_4$ = 197.83, found (GCMS) m/z = 198 ($M+1$).

30

TABLE 1

IUPAC Nomenclature:

Compound	Compound Name
Example 1	(4R,4'R,5R,5'R)-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane.
5 Example 2	1,1,2,2-Tetrakis(2-methoxyethoxy)diborane.
Example 3	Bis((1S,2S,3R,5S)-(+)-pinanediolato)diboron(B-B).
Example 4	(4R,4'R)-Diphenyl-2,2'-bi-1,3,2-dioxaborolane.
Example 5	4,4'-Bi-[(4-methoxyphenoxy)methyl]-2,2'-bi-1,3,2-dioxaborolane.
Example 6	2,2'-Bi-(3aR,7aS)hexahydro-1,3,2-benzodioxaborole.
10 Example 7	Tetraisopropyl (4R,4'R,5R,5'R)-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxylate.
Example 8	(3aR,3'aR,6aS,6'aS)-Di-(tetrahydro-3aH-cyclopenta[d])-2,2'-bi-1,3,2-dioxaborolane.
Example 9	(3R,6S,3'R,6'S)-Di-(tetrahydrofuro[3,4-d])-2,2'-bi-1,3,2-dioxaborolane.
Example 10	4,4'-Bis(methoxymethyl)-2,2'-bi-1,3,2-dioxaborolane.
Example 11	2,2'-Bi-1,3,2-dioxaborepane.
15 Example 12	5,5'-Dihydroxymethyl-5,5'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane.
Example 13	Bis(1R,2R,3S,5R-(-)-pinanediolato)diboron(B-B).
Example 14	2,2'-Bi-4H-1,3,2-benzodioxaborinine.
Example 15	4,4'-Bi-(phoxymethyl)-2,2'-1,3,2-dioxaborolane.
Example 16	4,4,4',4',6,6'-Hexamethyl-2,2'-bi-1,3,2-dioxaborinane.
20 Example 17	5,5,5',5'-Tetraethyl-2,2'-bi-1,3,2-dioxaborinane.
Example 18	4,4',5,5'-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane.
Example 19	4,4'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane.
Example 20	5,5'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane.
Example 21	Bi-(dinaphtho[2,1-d:1,2-f])-2,2'-bi-1,3,2-dioxaborepine.
25 Example 22	6,6'-Diethyl-2,2'-bi-1,3,6,2-dioxazaborocane.

Compound	Compound Name
Example 23	6,6'-Dimethyl-2,2'-bi-1,3,6,2-dioxazaborocane.
Example 24	5,5,5',5'-Tetraphenyl-2,2'-bi-1,3,2-dioxaborinane.
Example 25	4,4,4',4',7,7,7',7'-Octamethyl-2,2'-bi-1,3,2-dioxaborepane.
Example 26	1,1,2,2-Tetrakis(neopentyloxy)diborane.
5 Example 27	(4S,4'S,5S,5'S)-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane.
Example 28	Tetrabutyl (4R,4'R,5R,5'R)-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxylate.
Example 29	(4R,4'R,5R,5'R)-N ⁴ ,N ⁴ ,N ⁴ ,N ⁴ ,N ⁵ ,N ⁵ ,N ⁵ ,N ⁵ -Octamethyl-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxamide.
Example 30	4,4,4',4'-Tetramethyl-2,2'-bi-1,3,2-dioxaborinane.
Example 31	4,4,4',4',6,6,6',6'-Octamethyl-2,2'-bi-1,3,2-dioxaborinane.
10 Example 32	3,3'-Bi-1,5-dihydro-2,4,3-benzodioxaborepine.
Example 33	4,4,4',4',5,5'-Hexamethyl-2,2'-bi-1,3,2-dioxaborolane.
Example 34	4,4,4',4'-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane.

15 Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

20 Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in the specification, individually or collectively, and any and all combinations of any two or

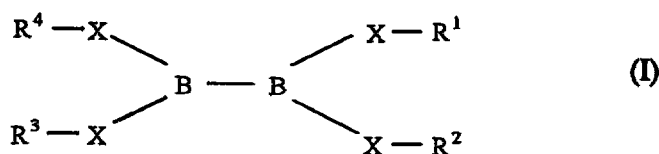
25 more of said steps or features.

THE CLAIMS:

1. A diboron derivative of formula (I)



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where R^1 , R^2 , R^3 and R^4 are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, and a group of the formula $-(\text{R}^5\text{Q})_m\text{R}^6$ where Q is selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer from 1 to 3, the or each R^5 is independently an optionally substituted $\text{C}_1\text{-C}_3$ alkylene, R^6 is $\text{C}_1\text{-C}_3$ alkyl or hydrogen and R^7 is hydrogen or $\text{C}_1\text{-C}_{12}$ alkyl; and

15

each X is independently selected from O, $\text{S}(\text{O})_n$ and NR^7 , where n is an integer of 0 to 3 and R^7 is hydrogen or $\text{C}_1\text{-C}_{12}$ alkyl, or one or more of $-\text{NR}^1\text{R}^7$, $-\text{NR}^2\text{R}^7$, $-\text{NR}^3\text{R}^7$ and $-\text{NR}^4\text{R}^7$ represent an optionally substituted 5 or 6 membered heterocyclyl group,

20

provided that when each X is O and R^1 to R^4 are identical, R^1 to R^4 are not unsubstituted straight chain alkyl, phenyl or naphthyl, isopropyl, or phenyl substituted with alkyl; when each X is $\text{N}(\text{C}_1\text{-C}_6 \text{ alkyl})$, R^1 to R^4 are not $\text{C}_1\text{-C}_6$ alkyl and $-\text{NR}^1\text{R}^7$, $-\text{NR}^2\text{R}^7$, $-\text{NR}^3\text{R}^7$ and $-\text{NR}^4\text{R}^7$ are not unsubstituted piperidyl or unsubstituted pyrrolidinyl; when each X is NH, R^1 to R^4 are not $\text{C}_1\text{-C}_6$ alkyl or unsubstituted phenyl; and when $-\text{XR}^1$ is $-\text{OCH}_3$, $-\text{XR}^2$ is $-\text{N}(\text{CH}_3)_2$ and $-\text{XR}^4$ is $-\text{N}(\text{CH}_3)_2$, $-\text{XR}^3$ is not OCH_3 .

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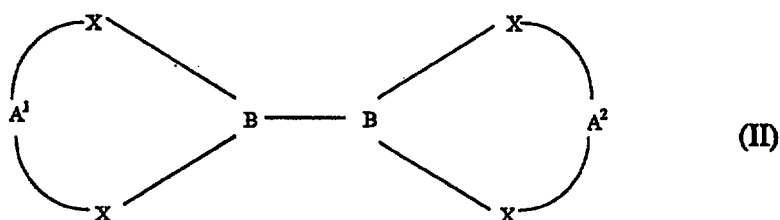
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2. A diboron derivative of formula (II)



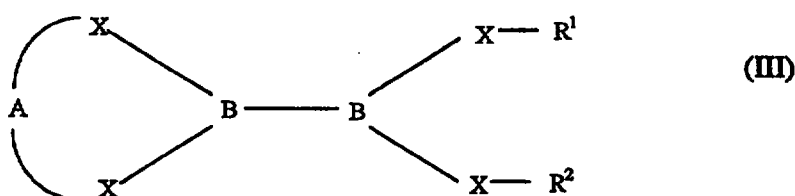
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10 where X is independently selected from O, S(O)_n and NR⁷ where n is an integer from 0 to 2, R⁷ is hydrogen or C₁-C₁₂ alkyl, and A¹ and A² are divalent groups which may be the same or different, provided that when each X is O, A¹ and A² are not unsubstituted C₁-C₃ alkylene, 1,1,2,2-tetramethylethylene, 2,2-dimethylpropylene, 1,2-dialkoxycarbonylethylene, 1,2-diphenylethylene, 1-phenylethylene, unsubstituted phenylene or phenylene mono- or di-substituted with C₁-C₄ alkyl; and when each X is S or NMe, both of A¹ and A² are not ethylene.

3. A diboron derivative of formula (III)

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25 where R¹ and R² are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, a group of the formula -(R⁵Q)_mR⁶ where Q is selected from O, S, NR⁷, optionally substituted arylene and optionally substituted cycloalkylene, m is an integer selected from 1 to 3, the or each R⁵ is independently

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an optionally substituted C_1-C_3 alkylene, R^6 is hydrogen or C_1-C_3 alkyl, and R^7 is hydrogen or C_1-C_{12} alkyl;

5 each X is independently selected from O, $S(O)_n$ and NR^7 , where n is an integer of 0 to 3 and R^7 is hydrogen or C_1-C_{12} alkyl, or one or both of $-NR^1R^7$ and $-NR^2R^7$ represent an optionally substituted 5 or 6 membered heterocyclyl group; and

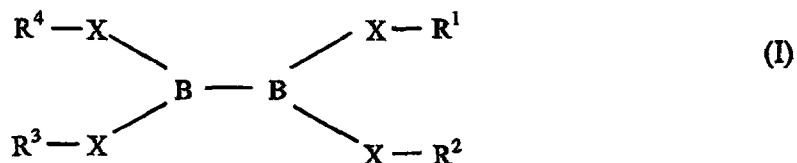
A is a divalent group;

10 provided that when R^1 and R^2 are Me and each X is NMe then A is not unsubstituted ethylene.

4. A diboron derivative of formula (I)

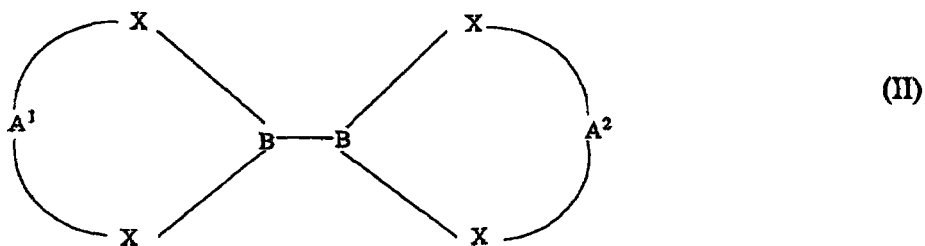


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20 or a diboron derivative of formula (II)

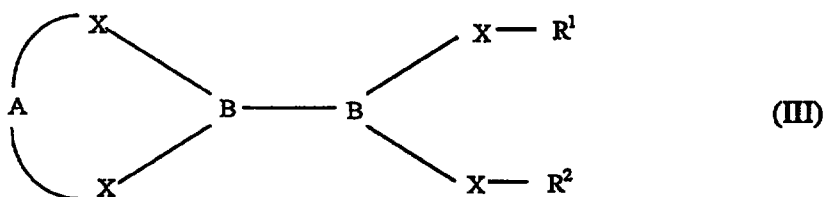
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30



or a diboron derivative of formula (III)



where R^1 , R^2 , R^3 and R^4 are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR^7 , optionally substituted arylene and optionally substituted cycloalkylene, m is an integer selected from 1 to 3, the or and each R^5 is independently an optionally substituted C_1 - C_3 alkylene, R^6 is C_1 - C_3 alkyl or hydrogen, and R^7 is hydrogen or C_1 - C_{12} alkyl;

each X is independently selected from O, $S(O)_n$ and NR^7 , where n is an integer from 0 to 3, R^7 is hydrogen or C_1 - C_{12} alkyl, or one or more of $-NR^1R^7$, $-NR^2R^7$, $-NR^3R^7$ and $-NR^4R^7$ represent an optionally substituted 5 or 6 membered heterocyclyl group,

and A , A^1 and A^2 are divalent groups which may or may not be different, wherein said derivative has one or more chiral centres and there is an enantiomeric excess of one form.

5. A diboron derivative of any one of claims 1 to 4 wherein X is O.

6. A diboron derivative of claim 2 wherein A^1 and A^2 are independently selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted alkylarylene, optionally substituted cycloalkylene, optionally substituted cycloalkenylene, or a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O,

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S, NR⁷, optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, R⁵ and R⁶ are independently an optionally substituted C₁-C₃ alkylene, and R⁷ is hydrogen or C₁-C₁₂ alkyl.

- 5 7. A diboron derivative according to claim 3 wherein A is independently selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted arylene, optionally substituted cycloalkylene, optionally substituted cycloalkenylene, or a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR⁷, optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, R⁵ and R⁶ are independently an optionally substituted C₁-C₃ alkylene, and R⁷ is hydrogen or C₁-C₁₂ alkyl.
- 10
8. A diboron derivative according to claim 4 wherein A, A¹ and A² are independently selected from optionally substituted alkylene, optionally substituted alkenylene, optionally substituted alkynylene, optionally substituted arylene, optionally substituted alkylarylene, optionally substituted cycloalkylene, optionally substituted cycloalkenylene, or a group of the formula $-(R^5Q)_mR^6$ where Q is selected from O, S, NR⁷, optionally substituted arylene and optionally substituted cycloalkylene, m is an integer of 1 to 3, R⁵ and R⁶ are independently an optionally substituted C₁-C₃ alkylene, and R⁷ is hydrogen or C₁-C₁₂ alkyl.
- 15
9. A diboron derivative according to any one of claims 6 to 8 wherein at least one of A, A¹ and A² includes a fused aliphatic or aromatic ring or ring system.
- 20
- 25 10. A diboron derivative according to any one of claims 1 to 4 wherein at least one of R¹ to R⁴, A, A¹ and A² is capable of further coordinating with one of the boron atoms.



- 30 11. A diboron derivative according to claim 10 wherein said at least one of R¹ to R⁴,



A, A¹ and A² includes an electron rich substituent or atom capable of feeding electron density onto the boron atom.

12. A diboron derivative according to claim 4 wherein the enantiomeric excess is greater than 80%.
13. A diboron derivative according to claim 12 wherein the enantiomeric excess is greater than 90%.
14. A process for the preparation of a diboronic acid ester comprising contacting diboronic acid with a suitable monoalcohol, diol or polyol, for a time and under conditions such that the diboronic acid reacts with the monoalcohol, diol or polyol to form the diboronic acid ester.
15. A process according to claim 14 wherein the reaction is conducted in a solvent comprising a monoalcohol.
16. A process according to claim 15 wherein the monoalcohol is a lower alkanol.
17. A process according to claim 16 wherein at least four equivalents of monoalcohol are used and the derivative formed is reacted with a second alcohol by transesterification.
18. A process according to claim 16 wherein the lower alkanol is methanol or ethanol.
19. A process according to claim 14 performed in the absence of a catalyst.
20. A process for the preparation of a diboron derivative according to claim 4 wherein X is O comprising reacting a suitable diboron reactant with a chiral alcohol.

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21. A process for the preparation of a chiral organic boronic acid ester derivative comprising contacting a diboron derivative of claim 4 with an organic compound having a boron reactive site for a time and under conditions such that the chiral boronic acid ester derivative is formed.
- 5
22. A process for the preparation of chiral compounds comprising reacting a chiral organic boronic acid ester prepared according to the process of claim 21 with an aldehyde or an unsymmetric ketone.
- 10 23. A diboron derivative in all its isomeric forms selected from:
- Tetramethyl-2,2'-bi-1,3,2-dioxaborolane.;
- 1,1,2,2-Tetrakis(2-methoxyethoxy)diborane;
- Bis(pinanediolato)diboron(B-B);
- 15 Diphenyl-2,2'-bi-1,3,2-dioxaborolane.;
- 4,4'-Bi-[(4-methoxyphenoxy)methyl]-2,2'-bi-1,3,2-dioxaborolane;
- 2,2'-Bi-hexahydro-1,3,2-benzodioxaborole;
- Tetraisopropyl-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxylate;
- Di-(tetrahydro-3aH-cyclopenta[d])-2,2'-bi-1,3,2- dioxaborolane;
- 20 Di-(tetrahydrofuro[3,4-d])-2,2'-bi-1,3,2-dioxaborolane;
- 4,4'-Bi-(methoxymethyl)-2,2'-bi-1,3,2-dioxaborolane;
- 2,2'-Bi-1,3,2-dioxaborepane;
- 5,5'-Dihydroxymethyl-5,5'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane;
- Bis(pinanediolato)diboron(B-B);
- 25 2,2'-Bi-4H-1,3,2-benzodioxaborinine ;
- 4,4'-Bi-(phenoxymethyl)-2,2'-1,3,2-dioxaborolane;
- 4,4,4',4',6,6'-Hexamethyl-2,2'-bi-1,3,2-dioxaborinane;
- 5,5,5',5'-Tetraethyl-2,2'-bi-1,3,2-dioxaborinane;
- 4,4',5,5'-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane;
- 30 4,4'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane;



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- 5,5'-Dimethyl-2,2'-bi-1,3,2-dioxaborinane;
 Bi-(dinaphtho[2,1-*d*:1,2-*f*])-2,2'-bi-1,3,2-dioxaborepine;
 6,6'-Diethyl-2,2'-bi-1,3,6,2-dioxazaborocane;
 6,6'-Dimethyl-2,2'-bi-1,3,6,2-dioxazaborocane;
 5 5,5,5',5'-Tetraphenyl-2,2'-bi-1,3,2-dioxaborinane;
 4,4,4',4',7,7,7',7'-Octamethyl-2,2'-bi-1,3,2-dioxaborepane;
 1,1,2,2-Tetrakis(neopentyloxy)diborane;
 Tetramethyl-2,2'-bi-1,3,2-dioxaborolane;
 Tetrabutyl-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-tetracarboxylate;
 10 N⁴,N⁴,N⁴,N⁴,N⁵,N⁵,N⁵,N⁵-Octamethyl-2,2'-bi-1,3,2-dioxaborolane-4,4',5,5'-
 tetracarboxamide;
 4,4,4',4'-Tetramethyl-2,2'-bi-1,3,2-dioxaborinane;
 4,4,4',4',6,6,6',6'-Octamethyl-2,2'-bi-1,3,2-dioxaborinane;
 3,3'-Bi-1,5-dihydro-2,4,3-benzodioxaborepine;
 15 4,4,4',4',5,5'-Hexamethyl-2,2'-bi-1,3,2-dioxaborolane; or
 4,4,4',4'-Tetramethyl-2,2'-bi-1,3,2-dioxaborolane.

