

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 November 2009 (05.11.2009)

(10) International Publication Number
WO 2009/133045 A1

(51) International Patent Classification:

C07F 5/00 (2006.01) **C07B 37/00** (2006.01)
C07F 5/02 (2006.01)

(21) International Application Number:

PCT/EP2009/055018

(22) International Filing Date:

27 April 2009 (27.04.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/048,407 28 April 2008 (28.04.2008) US

(71) Applicant (for all designated States except US): **BASF SE** [DE/DE]; 67056 Ludwigshafen (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **Burkhardt, Elizabeth** [US/US]; 1025 Lakemont Drive, Bridgeville, PA 15017 (US). **PICHLMAIR, Stefan** [AT/US]; 100 7th Street, Apt. 808, Pittsburgh, PA 15222 (US).

(74) Common Representative: **BASF SE**; 67056 Ludwigshafen (DE).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: NEW BORANE-AMINE COMPLEXES AND THEIR APPLICATION IN SUZUKI-TYPE CROSS -COUPLING REACTIONS

(57) Abstract: The invention relates to new amine complexes of B-organyl-9-borabicyclo[3.3.1]nonanes and to solutions of said complexes. Furthermore, the invention relates to a method of using trialkylborane-amine complexes in Suzuki-type cross-coupling reactions and to a process to form new carbon-carbon bonds in a Suzuki-type cross-coupling reaction with a triorganoborane, which is carried out in the presence of an amine.



WO 2009/133045 A1

New borane-amine complexes and their application in Suzuki-type cross-coupling reactions

Field of the Invention

5

The invention relates to new amine complexes of B-organyl-9-borabicyclo[3.3.1]nonanes and to solutions of said complexes. Furthermore, the invention relates to a method of using trialkylborane-amine complexes in Suzuki-type cross-coupling reactions and to a process to form new carbon-carbon bonds in a Suzuki-type cross-coupling reaction with a triorganoborane, which is carried out in the presence of an amine.

10

Background of the Invention

15 The transition metal-catalyzed cross-coupling reaction between organic electrophiles and organoboron derivatives to form new carbon-carbon bonds is known as Suzuki-type cross-coupling reaction (Miyaura, N.; Suzuki, A., Chem. Rev. 95, pages 2457 to 2483 (1995)). For example, triorganoboranes can be used as sources for a nucleophilic organic moiety that will be coupled to an organic electrophile in this Suzuki-type cross-coupling reactions. Readily available B-organyl-9-borabicyclo[3.3.1]nonanes (B-organyl-9-BBN's) are especially useful reagents in said cross-coupling reactions since the exocyclic alkyl group is coupled preferentially over the bicyclic 9-borabicyclo[3.3.1]nonane skeleton (Miyaura, N.; Suzuki, A. et al., J. Am. Chem. Soc. 111, pages 314 to 321 (1989); Netherton, M. R. et al., J. Am. Chem. Soc. 123, pages 10099 to 10100 (2001)).

25

Hydroboration of alkenes or alkynes with 9-borabicyclo[3.3.1]nonane (9-BBN) provides easy access to many B-organyl-9-borabicyclo[3.3.1]nonanes. In favourable cases formation of the B-organyl-9-BBN via hydroboration of an appropriate alkene and the subsequent Suzuki-type cross-coupling reaction with an organic electrophile can be conducted as one-pot synthesis with the two steps run consecutively in the same reaction vessel (e. g. Rodriguez, A. et al., Org. Biomol. Chem. 1, pages 973 to 977 (2003)).

30

Owing to its dimeric structure 9-BBN forms a pyrophoric solid with only poor solubility in typical organic solvents (Soderquist, J. A.; Brown, H. C., J. Org. Chem. 46, pages 4599 to 4600 (1981)). These properties may hamper the large scale application of 9-BBN and so alternatives are desirable.

35

It is known that the 9-BBN dimer can be split by addition of certain Lewis bases and that in some cases stable 9-BBN-Lewis base complexes are formed (Brown, H. C. et al., J. Am. Chem. Soc. 104, pages 7148 to 7155 (1982); Gazzetta Chimica Italiana 117, pages 517 to 523 (1987)). However, the 9-BBN-pyridine complex (Brown, H. C., J. Org. Chem. 45, pages 846 to 849 (1980)) shows only a relatively poor ability to act as a hy-

40

droborating agent (Brown, H. C. et al., Inorg. Chem. 16, pages 3090 to 3094 (1977)). Recently, new dialkylborane-amine complexes have been developed that are more suitable for hydroboration reactions and therefore give access to the corresponding trialkylborane-amine complexes or mixtures (WO 2008/055859).

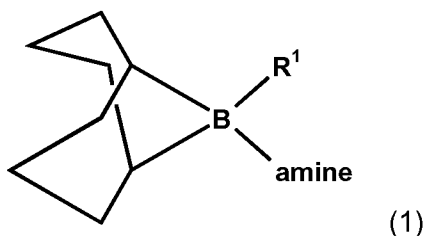
5

It was an object of the present invention to develop new trialkylborane-amine complexes and solutions thereof. It was another object of the present invention to provide a new method of using trialkylborane-amine complexes in Suzuki-type cross-coupling reactions. It was still another object of the present invention to develop a process to form new carbon-carbon bonds in a Suzuki-type cross-coupling reaction, which is carried out in the presence of an amine.

10

Summary of the Invention

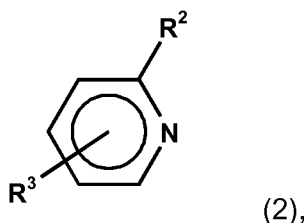
15 Accordingly, new B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes of the formula (1) have been found,



20 wherein

R¹ is an organyl comprising at least one carbon atom that is directly bound to the boron atom, and

amine is a substituted pyridine of the formula (2)



25

wherein

R² is C₁ - C₁₀ alkyl, C₁ - C₈ alkoxy or C₁ - C₈-alkoxy-C₁ - C₁₀ alkyl, and

R³ is hydrogen or a C₁ - C₁₀ alkyl, C₁ - C₈ alkoxy or C₁ - C₈-alkoxy-C₁ - C₁₀ alkyl group, or an alkylamine of the formula (3)

30



wherein

R^4 is hydrogen or $C_1 - C_{10}$ alkyl, and
 R^5 is $C_1 - C_{10}$ alkyl.

Another embodiment of the present invention are solutions comprising at least one of
 5 the new B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes of the formula (1) and
 at least one solvent.

Still another embodiment of the present invention is a new method of using B-organyl-
 9-BBN-amine complexes of the formula (1) in Suzuki-type cross-coupling reactions to
 10 form new carbon-carbon bonds.

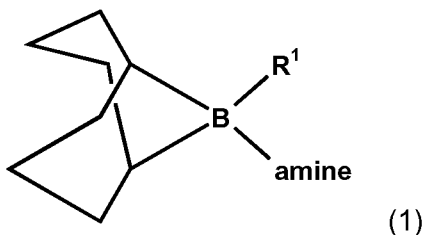
Furthermore, a process has been found to form new carbon-carbon bonds comprising
 a Suzuki-type cross-coupling reaction with a triorganoborane, which is carried out in
 the presence of an amine.

15

Detailed Description of the Invention

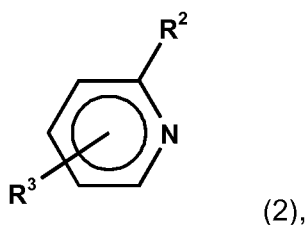
The new B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes of the present inven-
 tion have chemical structures according to the general formula (1),

20



wherein

R^1 is an organyl comprising at least one carbon atom that is directly bound to the boron
 25 atom, and
 amine is a substituted pyridine of the formula (2)



30

wherein

R^2 is $C_1 - C_{10}$ alkyl, $C_1 - C_8$ alkoxy or $C_1 - C_8$ -alkoxy- $C_1 - C_{10}$ alkyl, and
 R^3 is hydrogen or a $C_1 - C_{10}$ alkyl, $C_1 - C_8$ alkoxy or $C_1 - C_8$ -alkoxy- $C_1 - C_{10}$ alkyl group,
 or an alkylamine of the formula (3)



wherein

R^4 is hydrogen or $C_1 - C_{10}$ alkyl, and

R^5 is $C_1 - C_{10}$ alkyl.

5

In a preferred embodiment of the present invention the new B-organyl-9-BBN-amine complexes have chemical structures according to the general formula (1), wherein the amine is a substituted pyridine of the formula (2).

- 10 As used in connection with the present invention, the term "organyl" denotes an organic group comprising at least one carbon atom, that may contain heteroatoms like hydrogen, oxygen, nitrogen, sulphur, phosphorus, fluorine, chlorine, bromine, iodine, boron, silicon, selenium, tin or transition metals like iron, nickel, zinc, platinum, etc. The organyl can have any linear or cyclic, branched or unbranched, mono- or polycyclic,
- 15 carbo- or heterocyclic, saturated or unsaturated molecular structure and may comprise protected or unprotected functional groups. Furthermore, the organyl may be linked to or part of an oligomer or polymer with a molecular weight up to one million Dalton.

- Preferred organyl groups are $C_1 - C_{24}$ alkyl, $C_3 - C_{16}$ cycloalkyl, substituted alkyl, $C_2 - C_{22}$ alkenyl, $C_5 - C_{15}$ cycloalkenyl and $C_2 - C_{22}$ alkynyl groups.
- 20

- As used in connection with the present invention, the term " $C_1 - C_{24}$ alkyl" denotes a branched or an unbranched saturated hydrocarbon group comprising between 1 and 24 carbon atoms; examples are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl, 4-methylpentyl, 1-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-methylhexyl, 1-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethylpentyl, 4,4-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 1,2,3-trimethylbutyl, 1,1,2-trimethylbutyl, 1,1,3-trimethylbutyl, octyl, 6-methylheptyl, 1-methylheptyl, 1,1,3,3-tetramethylbutyl, nonyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-methyloctyl, 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, 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 isopinocampheyl. Preferred are the alkyl groups ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, amyl, isoamyl, sec-amyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, hexyl and octyl.
- 35

40

The term " $C_3 - C_{16}$ cycloalkyl" denotes a saturated hydrocarbon group comprising between 3 and 16 carbon atoms including a mono- or polycyclic structural moiety. Exam-

ples are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl. Preferred are the cycloalkyl groups cyclopropyl, cyclopentyl and cyclohexyl.

- 5 The term "substituted alkyl" denotes an alkyl group in which at least one hydrogen atom is replaced by a halide atom like fluorine, chlorine, bromine or iodine, a C₁ - C₂₀ alkoxy group, an ester group, a trialkylsilyl group, a C₆ - C₁₄ aryl group, or a C₃ - C₁₄ heteroaryl group.
- 10 The term "C₁ - C₂₀ alkoxy" stands for a group derived from an aliphatic monoalcohol with between 1 and 20 carbon atoms.

- The term "C₆ - C₁₄ aryl" denotes an unsaturated hydrocarbon group comprising between 6 and 14 carbon atoms including at least one aromatic ring system like phenyl or
- 15 naphthyl or any other aromatic ring system.

- The term "C₃ - C₁₄ heteroaryl" denotes a mono- or polycyclic aromatic ring system comprising between 3 and 14 ring atoms, in which at least one of the ring carbon atoms is replaced by a heteroatom like nitrogen, oxygen or sulfur. Examples are pyridyl, pyranyl,
- 20 thiopyranyl, chinolinyl, isochinolinyl, acridyl, pyridazinyl, pyrimidyl, pyrazinyl, phenazinyl, triazinyl, pyrrolyl, furanyl, thiophenyl, indolyl, isoindolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl and triazolyl.

- The term "C₂ - C₂₂ alkenyl" denotes a straight chain or branched unsaturated hydrocarbon group comprising between 2 and 22 carbon atoms including at least one carbon-carbon double bond. Examples are vinyl, allyl, 1-methylvinyl, butenyl, isobutenyl, 3-methyl-2-butenyl, 1-pentenyl, 1-hexenyl, 3-hexenyl, 2,5-dimethylhex-4-en-3-yl, 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 and 1,4-hexadienyl. Preferred are the
- 25 alkenyl groups vinyl, allyl, butenyl, isobutenyl, 1,3-butadienyl and 2,5-dimethylhex-4-en-3-yl.
- 30

- The term "C₅ - C₁₅ cycloalkenyl" denotes an unsaturated hydrocarbon group comprising between 5 and 15 carbon atoms including at least one carbon-carbon double bond and
- 35 a mono- or polycyclic structural moiety. Examples are cyclopentenyl, 1-methylcyclopentenyl, cyclohexenyl, cyclooctenyl, 1,3-cyclopentadienyl, 1,3-cyclohexadienyl, 1,4-cyclohexadienyl, 1,3-cycloheptadienyl, 1,3,5-cycloheptatrienyl and 1,3,5,7-cyclooctatetraenyl.

- 40 The term "C₂ - C₂₂ alkynyl" denotes a straight chain or branched unsaturated hydrocarbon group comprising between 2 and 22 carbon atoms including at least one carbon-

carbon triple bond. Examples of alkynyl groups include ethynyl, 2-propynyl and 2- or 3-butynyl.

According to the invention, the substituted pyridine of the formula (2) can be, for example, 2-picoline, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine, 5-ethyl-2-methylpyridine, 4-ethyl-2-methylpyridine, 3-ethyl-2-methylpyridine, 2,5-diethylpyridine, 5-propyl-2-methylpyridine, 4-propyl-2-methylpyridine, 5-isopropyl-2-methylpyridine, 5-*t*-butyl-2-methylpyridine, 5-*n*-hexyl-2-methylpyridine, 4-isobutyl-2-methylpyridine or 2,4-dipropylpyridine. Preferred pyridines of the formula (2) are 2-picoline, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine and 5-ethyl-2-methylpyridine.

In a preferred embodiment of the present invention the new B-organyl-9-BBN-amine complexes have chemical structures according to the general formula (1), wherein R¹ is an organyl that is directly bound to the boron atom via two methylene groups and (1) exhibits a moiety of the formula >BCH₂CH₂-, i. e. R¹ is -CH₂CH₃ or -CH₂CH₂-organyl. These preferred derivatives of (1) can, for example, be synthesized via hydroboration of terminal alkenes with 9-BBN or 9-BBN-amine complexes, owing to the well-known anti-Markovnikov regioselectivity of such hydroborations. Examples for these preferred B-organyl-9-BBN-amine complexes (1) have chemical structures according to the general formula (1), wherein R¹ is ethyl, propyl, butyl, pentyl, hexyl and octyl.

In cases where the organyl R¹ is substituted at the -BCH₂CH₂- moiety the R¹ group becomes more bulky and complexation between the amine and the triorganoborane might be hampered. In some cases a mixture of the new B-organyl-9-BBN-amine complex and the uncomplexed B-organyl-9-BBN is observed, in other cases there is no complexation at all. However, compositions comprising any amine and a B-organyl-9-BBN derivative can very often be used for further reactions independent from complex formation (see below).

In another preferred embodiment of the present invention the new B-organyl-9-BBN-amine complexes have chemical structures according to the general formula (1), wherein the amine is a compound according to the formula (2), wherein R³ is hydrogen or C₁ – C₄-alkyl.

Most preferred is an embodiment of the present invention where the new B-organyl-9-BBN-amine complexes have chemical structures according to the general formula (1), wherein R¹ is -CH₂CH₃ or -CH₂CH₂-organyl and the amine is 2-picoline, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine or 5-ethyl-2-methylpyridine.

The ¹¹B NMR spectra of the new B-organyl-9-BBN-amine complexes of the formula (1) generally show a broad singlet with a chemical shift δ between +10 to +35 ppm, indicating strong coordination between the amine and the trialkylborane moieties in solution.

For example, the B-octyl-9-borabicyclo[3.3.1]nonane-2-picoline complex shows a ^{11}B NMR resonance at $\delta = 26.6$ ppm (cf. example 1).

The new B-organyl-9-BBN-amine complexes (1) can, for example, be obtained via hydroboration of an unsaturated compound like an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex (e. g. 9-BBN-THF or 9-BBN-dimethyl sulfide) followed by adding the respective amine of the formula (2) or (3) to the resulting B-organyl-9-BBN derivative. Alternatively, the hydroboration of an alkene or alkyne can be conducted directly with a complex of 9-BBN and an amine of the formula (2) or (3).

Another embodiment of the present invention is therefore a process to synthesize new B-organyl-9-BBN-amine complexes of the formula (1), comprising the step of hydroborating an alkene or an alkyne with a complex of 9-BBN and an amine of the formula (2) or (3) or hydroborating an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex followed by adding an amine of the formula (2) or (3).

If necessary, the hydroboration of alkenes or alkynes with 9-BBN or a complex of 9-BBN can be carried out in solution in the presence of at least one solvent. Preferably, complexes of 9-BBN and an amine of the formula (2) or (3) are reacted with alkenes or alkynes in organic solvents. Owing to the generally higher solubility of these 9-BBN-amine complexes in organic solvents compared to 9-BBN this allows for working at higher concentrations, thereby permitting higher loadings of reactors and avoids the difficulties connected with the handling of 9-BBN as a pyrophoric solid. The initial products of this synthetic route are therefore solutions of the new B-organyl-9-BBN-amine complexes (1). These solutions can either be directly employed for further reactions or the new B-organyl-9-BBN-amine complexes (1) can be isolated in pure form by evaporation of the solvent. The preferred method for removal of the solvent is evaporation under reduced pressure to decrease the boiling point of the solvent.

Another embodiment of the present invention is therefore a solution comprising at least one B-organyl-9-BBN-amine complexes of the formula (1) and at least one solvent. Suitable solvents for the solutions of the present invention are those in which the B-organyl-9-BBN-amine complexes have a high solubility. Examples are ethers like diethyl ether, tetrahydrofuran or 2-methyltetrahydrofuran, sulfides like dimethyl sulfide or 1,6-thioxane and hydrocarbons like pentane, hexane(s), heptane(s), cyclohexane, toluene or xylenes. Preferred solvents for the solutions comprising at least one B-organyl-9-BBN-amine complex of the formula (1) are tetrahydrofuran, 2-methyltetrahydrofuran, dimethyl sulfide, 1,6-thioxane, toluene, hexane(s), heptane(s) or cyclohexane, most preferred are tetrahydrofuran, 2-methyltetrahydrofuran, toluene, hexane(s), heptane(s) or cyclohexane.

The solutions of the present invention generally contain the new B-organyl-9-BBN-amine complexes of the formula (1) in concentrations between 0.05 and 5 mol/l, preferably between 0.1 and 5 mol/l, more preferably between 0.5 and 3 mol/l.

- 5 Another embodiment of the present invention is a process to synthesize a solution comprising at least one of the new B-organyl-9-BBN-amine complexes of the formula (1) and at least one solvent, comprising the steps of hydroborating an alkene or an alkyne with a complex of 9-BBN and an amine of the formula (2) or (3) or hydroborating an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex followed by adding
10 an amine of the formula (2) or (3) in at least one solvent.

- Still another embodiment of the present invention is a process to synthesize the new B-organyl-9-BBN-amine complexes of the formula (1), comprising the steps of hydroborating an alkene or an alkyne with a complex of 9-BBN and an amine of the formula (2)
15 or (3) or hydroborating an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex followed by adding an amine of the formula (2) or (3) in at least one solvent and isolating the complex from the formed solution. Preferably the isolation is done by evaporation of the solvent.

- 20 The present invention further provides a new method of using the new B-organyl-9-BBN-amine complexes of the formula (1) in Suzuki-type cross-coupling reactions to form new carbon-carbon bonds. The direct use of the new B-organyl-9-BBN-amine complexes of the formula (1) in Suzuki-type cross-coupling reactions without the need to separate the trialkylborane from the amine is highly desirable for development of
25 cost effective processes.

- Moreover, it was found that in Suzuki-type cross coupling reactions with trialkylboranes as nucleophile the presence of an amine does not interfere with the catalytic cycle. It turned out to be irrelevant whether there is a complex formed between the trialkylborane and the amine or not or if there is a dynamic equilibrium between the complex and the separated trialkylborane and amine species. This is of great value since trialkylboranes are easily prepared via hydroboration of alkenes and alkynes with dialkylborane-amine complexes, which are much easier to handle and have a much higher solubility than the corresponding dialkylboranes without any amine. Therefore, the crude product
30 of the reaction between a dialkylborane-amine complex and an alkene or alkyne can be used directly in a Suzuki-type cross-coupling reaction.

- Therefore, a further aspect of the present invention is a process to form new carbon-carbon bonds comprising a Suzuki-type cross-coupling reaction with a triorganoborane,
40 which is carried out in the presence of an amine.

Another embodiment of the present invention is a process to form new carbon-carbon bonds comprising the steps of hydroborating an alkene or alkyne with a diorganoborane-amine complex and using the resulting mixture of a triorganoborane and the amine in a Suzuki-type cross-coupling reaction.

5

In one embodiment of the present invention the triorganoborane in these processes is a B-organyl-9-BBN derivative, e. g. B-octyl-9-BBN. In another embodiment of present invention the amine in these processes is a substituted pyridine of the formula (2) or an alkylamine of the formula (3) as defined above.

10

Examples

The following examples illustrate the present invention without limitation of the same. All reactions were performed under dry and oxygen free conditions.

15

Example 1:

Hydroboration of 1-octene with 9-BBN-2-picoline complex

20

29.5 g of a 43.1 wt% solution of 9-BBN-2-picoline complex in THF (60 mmol) were diluted with 6.5 ml of anhydrous THF and cooled to 0°C. 6.73 g of 1-octene (60 mmol) were added slowly and the mixture was stirred at room temperature for three hours. After that analysis of the reaction mixture by ¹¹B NMR spectroscopy revealed that no 9-BBN-2-picoline complex ($\delta = -1.6$ ppm) was left and a major peak at 26.6 ppm was visible assigned to B-octyl-9-BBN-2-picoline complex. This prepared 1.02 M stock solution of B-octyl-9-BBN-2-picoline complex in THF was used for the following Suzuki experiments.

25

Example 2:

Hydroboration of methyl-10-undecenoate with 9-BBN-2-picoline complex

30

2.5 g of a 43.1 wt% solution of 9-BBN-2-picoline complex in THF (5 mmol) were diluted with 10 ml of anhydrous THF. Then 1.12 ml of methyl-10-undecenoate (5 mmol) were added dropwise and the mixture was stirred at room temperature for three hours. After that analysis of the reaction mixture by ¹¹B NMR spectroscopy revealed that no 9-BBN-2-picoline complex ($\delta = -1.6$ ppm) was left and a major peak at $\delta = 29.6$ ppm was visible, assigned to B-(11-methylundecanoate)-9-BBN-2-picoline complex.

35

Example 3:

Hydroboration of isoprene with 9-BBN-2-picoline complex

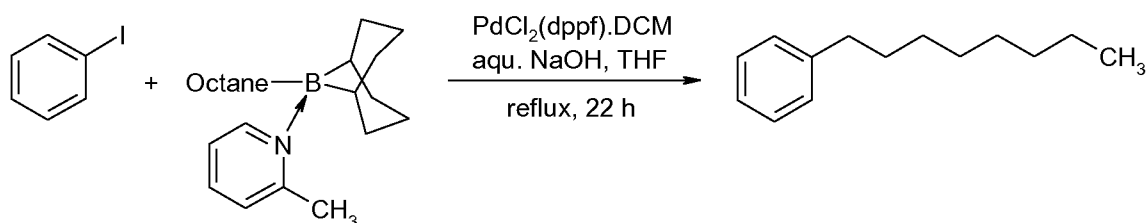
40

2.69 g of a 40 wt% solution of 9-BBN-2-picoline complex in THF (5 mmol) were diluted with 10 ml of anhydrous THF. Then 0.5 ml of isoprene (5 mmol) were added and the

mixture was stirred at room temperature for 24 hours. After that analysis of the reaction mixture by ^{11}B NMR spectroscopy revealed that no 9-BBN-2-picoline complex ($\delta = -1.6$ ppm) was left. Two resonances were observed at $\delta = 76.1$ ppm and 18.1 ppm assigned to the complexed and uncomplexed product (1 : 0.71 = triorganylborane-2-picoline : triorganylborane). The proton spectra showed the formation of two isomers caused by addition to either of the double bonds of isoprene

Example 4:

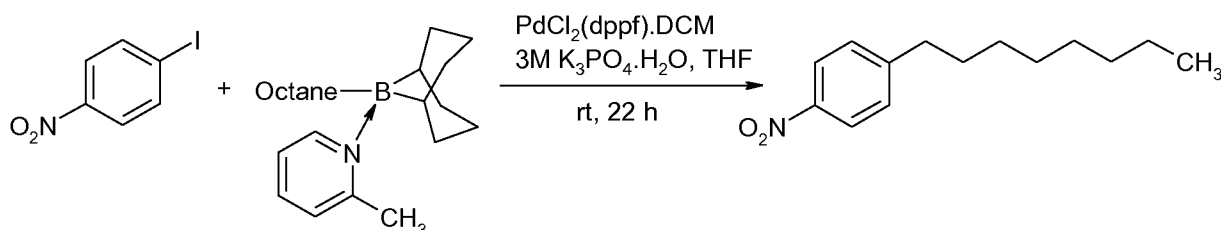
Suzuki coupling of iodobenzene and B-octyl-9-BBN-2-picoline complex ($\text{sp}^2\text{-sp}^3$)



123 mg (0.15 mmol) of $\text{PdCl}_2(\text{dppf}) \cdot \text{DCM}$ complex ([1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)-complex with dichloromethane), 12 ml distilled THF and 1.02 g (5 mmol) iodobenzene were mixed. Then, 7.53 g of a 16 wt% solution of B-octyl-9-BBN-2-picoline complex in THF were added followed by 5 ml of a 3 M aqueous sodium hydroxide (NaOH) solution, which resulted in a dark brown reaction mixture. The mixture was heated to reflux for 22 hours. Then it was cooled to room temperature, hexane (20 ml) was added and the mixture was quenched with hydrogen peroxide (30w%, 2 ml). Stirring was continued for 10 minutes until the gas evolution ceased. The aqueous layer was separated from the organic layer, extracted with hexane (1 x 20 ml) and the combined organic layers were dried over sodium sulfate (Na_2SO_4), filtered and evaporated to dryness. The crude product (1.83 g) was purified by column chromatography on silica gel (pure hexane) to give 558 mg (59%) of pure 1-octylbenzene as a colorless oil.

Example 5:

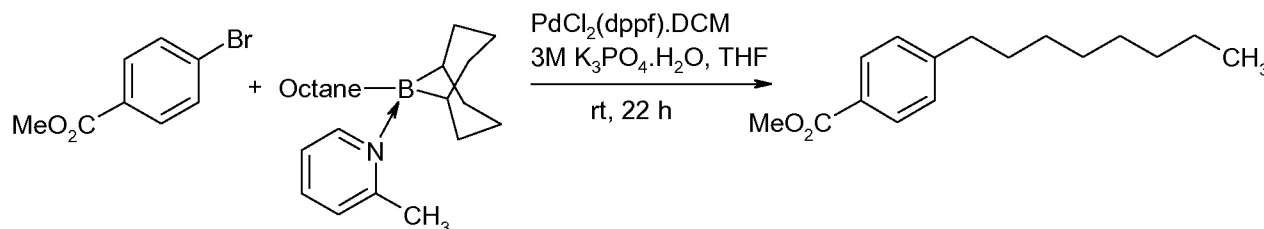
Suzuki Coupling of 1-iodo-4-nitrobenzene and B-octyl-9-BBN-2-picoline complex ($\text{sp}^2\text{-sp}^3$)



204 mg (0.25 mmol) of $\text{PdCl}_2(\text{dppf})\cdot\text{DCM}$ complex, 14.6 ml distilled THF and 1.245 g (5 mmol) 1-iodo-4-nitrobenzene were mixed. Then 5.39 ml of a 1.02 M solution of B-octyl-9-BBN-2-picoline complex was added followed by 3.33 ml of a 3 M aqueous potassium phosphate (K_3PO_4) solution, which resulted in a black reaction mixture. The mixture was stirred for 21 h, then hexane (20 ml), followed by water (5 ml) and hydrogen peroxide (H_2O_2 , 30w%, 2 ml) were added. Stirring was continued for 10 minutes until the gas evolution ceased. The black mixture was filtered over a pad of celite, the aqueous layer was separated from the organic layer and extracted with diethyl ether (2 x 15 ml). The combined organic layers were dried over sodium sulfate (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (pure hexane) to result in 0.70 g (60 %) of 1-nitro-4-octylbenzene as a colorless oil.

Example 6:

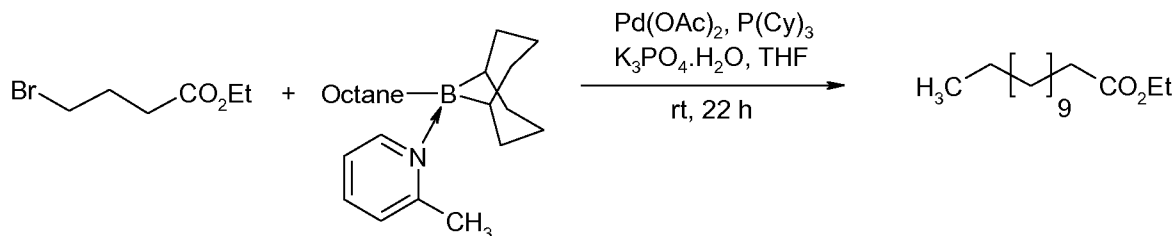
Suzuki Coupling of methyl-4-bromobenzoate and B-octyl-9-BBN-2-picoline complex ($\text{sp}^2\text{-sp}^3$)



204 mg (0.25 mmol) of $\text{PdCl}_2(\text{dppf})\cdot\text{DCM}$ complex, 14.6 ml distilled THF and 1.08 g (5 mmol) methyl-4-bromobenzoate were mixed. Then 5.39 ml of a 1.02 M solution of B-octyl-9-BBN-2-picoline complex was added followed by 3.33 ml of a 3 M aqueous potassium phosphate (K_3PO_4) solution, which resulted in a black reaction mixture. The mixture was stirred for 23 h, then hexane (20 ml), followed by water (5 ml) and hydrogen peroxide (H_2O_2 , 30w%, 2 ml) were added. Stirring was continued for 10 minutes until the gas evolution ceased. The aqueous layer was separated from the organic layer and extracted with diethyl ether (2 x 15 ml). The combined organic layers were dried over sodium sulfate (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (gradient elution: pure hexane to hexane : ethyl acetate = 97 : 3) to result in 1.24 g (99 %) of methyl-4-octylbenzoate as a colorless oil.

Example 7:

Suzuki coupling of ethyl-4-bromobutanoate and B-octyl-9-BBN-2-picoline complex ($\text{sp}^3\text{-sp}^3$)



5 1.38 g (6 mmol) of solid potassium phosphate ($\text{K}_3\text{PO}_4 \cdot \text{H}_2\text{O}$), 50 mg (0.2 mmol) of Palladium-(II)-acetate ($\text{Pd}(\text{OAc})_2$) and 112 mg (0.4 mmol) of tricyclohexylphosphine ($\text{P}(\text{Cy})_3$) were mixed. The mixture was purged with nitrogen for 15 minutes and then 5.88 ml of a 1.02 M solution of B-octyl-9-BBN-2-picoline complex (6 mmol) in THF was added to the solids. The mixture was diluted with 5.9 ml anhydrous THF and treated
10 with ethyl-4-brombutanoate (975 mg, 5.0 mmol). The black suspension was stirred for 22 h at room temperature, than hydrogen peroxide (H_2O_2 , 30w%, 2 ml) was added and stirring was continued for another 10 minutes. After that, diethyl ether (20 ml), followed by water (5 ml) was added. The aqueous layer was separated from the organic layer and extracted twice with diethyl ether (2 x 15 ml). The combined organic layers were
15 dried over sodium sulfate (Na_2SO_4), filtered and evaporated to dryness. The crude product was purified by column chromatography on silica gel (pure hexane) to result in 870 mg (73 %) of ethyl dodecanoate as a colorless oil.

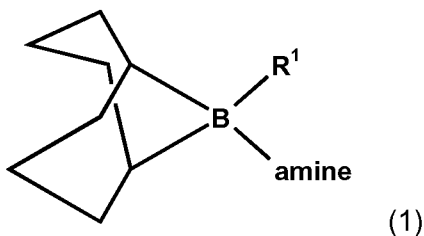
20 All the references described above are incorporated by reference in its entirety for all useful purposes.

While there are shown and described certain specific structures embodying the invention, it will be manifest to those skilled in the art that various modifications and rearrangements of the parts may be made without departing from the spirit and scope of the underlying inventive concept and the same is not limited to the particular forms herein shown and described.

Claims:

1. B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes with chemical structures according to the general formula (1),

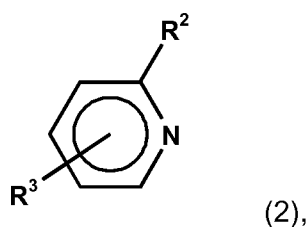
5



wherein

- R¹ is an organyl comprising at least one carbon atom that is directly bound to the boron atom, and
- amine is a substituted pyridine of the formula (2)

10



15

wherein

- R² is C₁ - C₁₀ alkyl, C₁ - C₈ alkoxy or C₁ - C₈-alkoxy-C₁ - C₁₀ alkyl, and
 - R³ is hydrogen or a C₁ - C₁₀ alkyl, C₁ - C₈ alkoxy or C₁ - C₈-alkoxy-C₁ - C₁₀ alkyl group,
- or an alkylamine of the formula (3)

20



wherein

- R⁴ is hydrogen or C₁ - C₁₀ alkyl, and
- R⁵ is C₁ - C₁₀ alkyl.

25

2. B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes according to claim 1, wherein the amine is a substituted pyridine of the formula (2).
3. B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes according to claim 1, wherein the amine is 2-picoline, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine or 5-ethyl-2-methylpyridine.
4. B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes according to claim 1, wherein R¹ is -CH₂CH₃ or -CH₂CH₂-organyl.

30

5. B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes according to claim 1, wherein R¹ is C₁ - C₂₄ alkyl, C₃ - C₁₆ cycloalkyl, substituted alkyl, C₂ - C₂₂ alkenyl, C₅ - C₁₅ cycloalkenyl or C₂ - C₂₂ alkynyl.
5
6. B-organyl-9-borabicyclo[3.3.1]nonane-amine complexes according to claim 1, wherein R¹ is -CH₂CH₃ or -CH₂CH₂-organyl and the amine is 2-picoline, 2,3-lutidine, 2,4-lutidine, 2,5-lutidine or 5-ethyl-2-methylpyridine.
- 10 7. A solution comprising at least one B-organyl-9-BBN-amine complex of the formula (1) and at least one solvent.
8. A solution according to claim 7, wherein the solvent is selected from the group, consisting of tetrahydrofuran, 2-methyltetrahydrofuran, dimethyl sulfide, 1,6-
15 thioxane, toluene, hexane(s), heptane(s) and cyclohexane.
9. A process to synthesize a solution comprising at least one B-organyl-9-BBN-amine complex of the formula (1) and at least one solvent, comprising the steps of hydroborating an alkene or an alkyne with a complex of 9-BBN and an amine of the
20 formula (2) or (3) or hydroborating an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex followed by adding an amine of the formula (2) or (3) in at least one solvent.
10. A process to synthesize a B-organyl-9-BBN-amine complex of the formula (1),
25 comprising the step of hydroborating an alkene or an alkyne with a complex of 9-BBN and an amine of the formula (2) or (3) or hydroborating an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex followed by adding an amine of the formula (2) or (3).
- 30 11. A process to synthesize a B-organyl-9-BBN-amine complex of the formula (1), comprising the steps of hydroborating an alkene or an alkyne with a complex of 9-BBN and an amine of the formula (2) or (3) or hydroborating an alkene or an alkyne with 9-BBN or a 9-BBN-Lewis base complex followed by adding an amine of the formula (2) or (3) in at least one solvent and isolating the complex from the
35 formed solution.
12. Method of using B-organyl-9-BBN-amine complexes of the formula (1) in Suzuki-type cross-coupling reactions to form new carbon-carbon bonds.

13. Process to form new carbon-carbon bonds comprising a Suzuki-type cross-coupling reaction with a triorganoborane, which is carried out in the presence of an amine.
- 5
14. Process according to claim 13, wherein the triorganoborane is a B-organyl-9-BBN derivative.
- 10
15. Process according to claim 13, wherein the amine is a substituted pyridine of the formula (2) or an alkylamine of the formula (3).
- 15
16. Process to form new carbon-carbon bonds comprising the steps of hydroborating an alkene or alkyne with a diorganoborane-amine complex and using the resulting mixture of a triorganoborane and the amine in a Suzuki-type cross-coupling reaction.
17. Process according to claim 16, wherein the triorganoborane is a B-organyl-9-BBN derivative.
- 20
18. Process according to claim 16, wherein the amine is a substituted pyridine of the formula (2) or an alkylamine of the formula (3).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/055018

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07F5/00 C07F5/02 C07B37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07F C07B

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WRACKMEYER, BERND ET AL: "Reactivity of bicyclic N-pyrrolylboranes" JOURNAL OF ORGANOMETALLIC CHEMISTRY , 545-546, 297-308 CODEN: JORCAI; ISSN: 0022-328X, 1997, XP002532879 Scheme 2	1-6
X	COLE, THOMAS E. ET AL: "Migration of 1-alkenyl groups from zirconium to boron compounds" ORGANOMETALLICS , 10(10), 3777-81 CODEN: ORGND7; ISSN: 0276-7333, 1991, XP002532880 Table I	1-6
	----- -/--	



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone.
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

19 June 2009

Date of mailing of the international search report

10/09/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040.
Fax: (+31-70) 340-3016

Authorized officer

Rinkel, Bert

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/055018

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BROWN, HERBERT C. ET AL: "Molecular addition compounds. 8. Carbon-13 and boron-11 NMR examination of .beta.-substituted derivatives of 9-borabicyclo[3.3.1]nonane and their pyridine complexes" JOURNAL OF ORGANIC CHEMISTRY , 45(5), 846-9 CODEN: JOCEAH; ISSN: 0022-3263, 1980, XP002532881 the whole document -----	1-6
X	MIDLAND, M. MARK ET AL: "Chiral trialkylborane reducing agents. Preparation of 1-deuterio primary alcohols of high enantiomeric purity" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 101(9), 2352-5 CODEN: JACSAT; ISSN: 0002-7863; 1979, XP002532882 Table II, entry 11 -----	1-6
X	RAMSEY, BRIAN G. ET AL: "A comparison of modified CNDO/2 calculations and the photoelectron, NMR and UV spectroscopic properties of boron-substituted monophenylboranes" JOURNAL OF ORGANOMETALLIC CHEMISTRY , 141(3), 257-73 CODEN: JORCAI; ISSN: 0022-328X, 1977, XP002532883 Table 4 -----	1-6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2009/055018

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

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

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

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

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

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

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

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see additional sheets

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6

Compounds of formula (1)

2. claims: 7,8

Solution comprising a compound of formula (1)

3. claim: 9

Process to prepare a solution comprising a compound of formula (1)

4. claims: 10,11

Process to prepare a compound of formula (1)

5. claim: 12

Use of a compound of formula (1)

6. claims: 13-15

Process to form a carbon-carbon bond

7. claims: 16-18

Process to form a carbon-carbon bond
