Phosphorus derivatives of carboranes as ligands for Pd-catalyzed cross-coupling reactions

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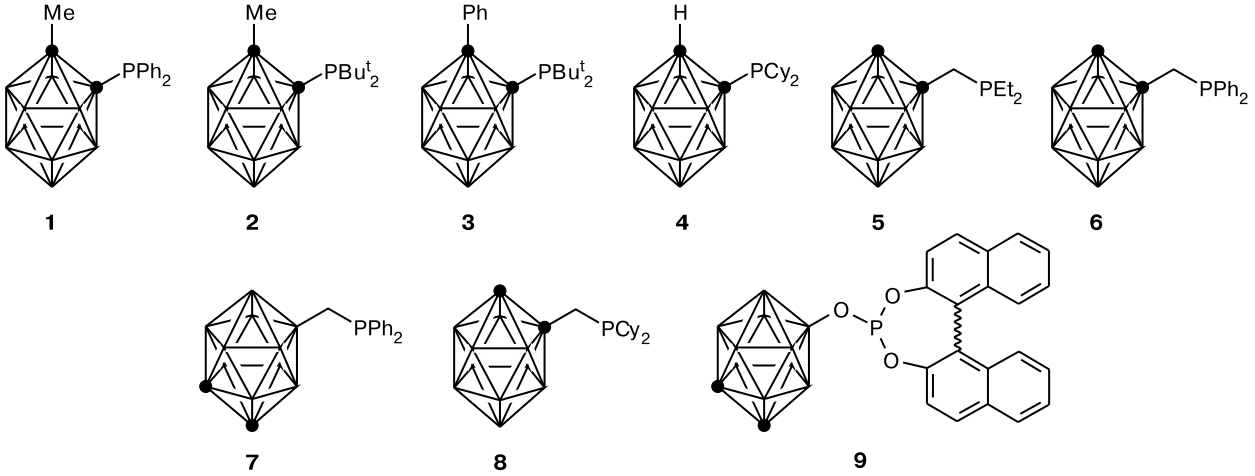
Carborane-containing phosphine ligands having different steric and electronic properties were synthesized. Testing of these ligands in the Pd-catalyzed Suzuki—Miyaura reaction showed higher catalytic activity for sterically congested phosphine ligands with acceptor carborane substituents.

Key words: carboranes, cross-coupling, phenylboronic acid, aryl halides, phosphines, phosphites.

The Suzuki—Miyaura reaction (Pd-catalyzed cross-coupling of aryl halides with boronic acids) is a convenient approach to selective formation of carbon—carbon bonds, in particular, to the synthesis of biaryls widely used for the preparation of biologically active agents and polymeric materials for nonlinear optics.[1,2]

It is known that the activity of metal complex catalyst is considerably affected by correct selection of a ligand having appropriate steric and electronic characteristics. For cross-coupling reactions, sterically hindered phosphines such as Bu^t_3P, Cy_3P, and Ad_2PBu^n are most effective ligands.[3] Promising objects for the development of a new generation of metal complex catalysts are icosahedral carboranes ($C_2B_{10}H_{12}$) with high steric requirements (the effective van der Waals radius is 5 Å) and extensive possibilities for modification of the carborane cage by introducing additional substituents to carbon and boron atoms, which allows fine tuning of the electronic and steric parameters of the ligands.[4—6] In addition, the electronic properties of the carboranyl group vary considerably depending on the position of carbon and boron atoms in the carborane fragment: thus the 9-*ortho*-carboranyl group is a strong electron-donating substituent ($\sigma_i = -0.23$),[7] whereas the 1-*ortho*-carboranyl group is a strong electron-withdrawing substituent ($\sigma_i = +0.38$).[8] Thus, phosphorus derivatives of carboranes provide the unique possibility of fine tuning of steric and electronic features of a catalytic system and study of the structure—activity relationship for Pd-catalyzed cross-coupling processes. Hence, of considerable interest is development of methods for the synthesis of sterically congested carborane-containing ligands having different electronic characteristics and study of the effect of this type of ligand on the activity of cross-coupling reactions.



Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2262—2265, November, 2008.

In this paper we report for the first time the results of testing of a series of new and known carborane-containing phosphine and phosphite ligands **1—9** in the Pd-catalyzed reaction of aryl halides with phenylboronic acid and identify a series of aspects influencing the efficiency of these ligands in this reaction.

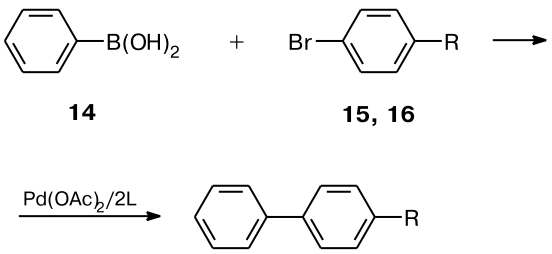
Results and Discussion

Carborane-containing phosphines **1, 5, 6** (see Refs 9—10) and phosphites **9** (see Ref. 11) were obtained by previously developed methods. For investigating the effect of the steric factor of the ligands on the activity of the metal complex catalysts, we also synthesized a series of sterically more congested phosphine ligands **2—4** in which the phosphorus atom was bound directly to the carborane cage. In addition, in order to elucidate the effect of electronic properties of carborane-containing ligands on the catalyst activity, we prepared new phosphine ligands containing both electron-donating 9-*ortho*-carborane fragment (**7**) and electron-donating sterically congested dicyclohexyl phosphorus center at the electron-withdrawing 1-*ortho*-carboranyl substituent.

Two methods were developed for preparing previously unknown (*o*-carboran-9-ylmethyl)diphenylphosphine **7** (Scheme 1): the first one comprised synthesis of *o*-carboran-9-ylmethyl bromide (**12**), its transformation into (*o*-carboran-9-ylmethyl)diphenylphosphine (**13**) by the Arbuzov reaction, and subsequent reduction with $HSiCl_3$ to give the target phosphine **7**; the second route was based on direct transformation of *o*-carboran-9-ylcarboxylic acid **10** into oxide **13** followed by reduction with trichlorosilane.

Ligands **1—9** were used in the Pd-catalyzed cross-coupling reactions of phenylboronic acid **14** (Scheme 2 and Tables 1, 2) with bromobenzene **15** and with 4-bromotoluene **16**.

Scheme 2



R = H (**15, 17**), Me (**16, 18**).

For bromobenzene used as the substrate, we showed that an increase in the bulk of the phosphorus center promotes the reaction. Indeed, in the case of ligands **1—4**, di-*tert*-butyl is the substituent of choice (see Table 1, entries *2*, *3*), while introduction of a bulky but electron-

Scheme 1

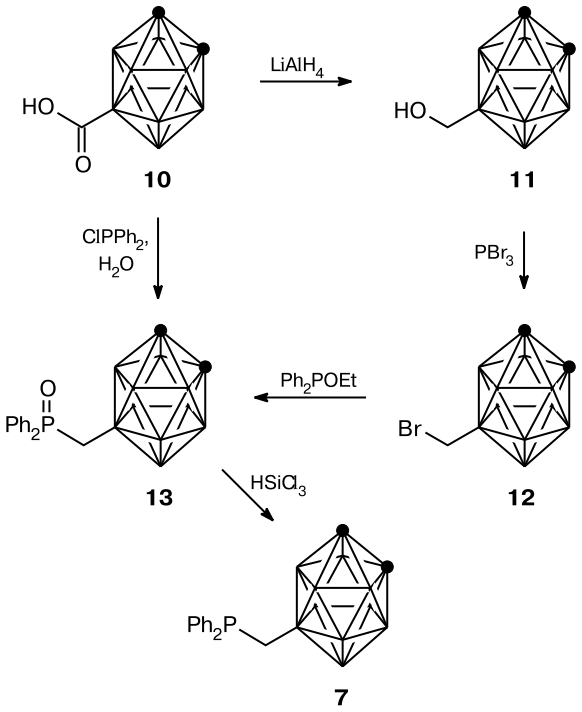


Table 1. Pd-Catalyzed cross-coupling of phenylboronic acid **14** with bromobenzene **15***

Entry	L	Bromobenzene conversion (%)	Entry	L	Bromobenzene conversion (%)
1	**1**	17	*6*	**6**	75
2	**2**	82	*7*	**7**	31
3	**3**	69	*8*	**8**	71
4	**4**	32	*9*	**9**	8
5	**5**	20			

* Conditions: 1.0 equiv. BrPh, 1.2 equiv. $PhB(OH)_2$, 2 equiv. Na_2CO_3, benzene—methanol—water (7 : 2 : 1), 40 °C, 3 h.

Table 2. Pd-Catalyzed cross-coupling of phenylboronic acid **14** with 4-bromotoluene **16***

Entry	L	4-Bromotoluene conversion (%)	Entry	L	4-Bromotoluene conversion (%)
1	**1**	18	*6*	**6**	93
2	**2**	68	*7*	**7**	41
3	**3**	34	*8*	**8**	75
4	**4**	32	*9*	**9**	66
5	**5**	18			

* Conditions: 1.0 equiv. 4-Br-Tol, 1.2 equiv. $PhB(OH)_2$, 2.5 equiv. K_3PO_4, toluene, 80 °C, 1.5 h.

withdrawing phenyl substituent into the carboranyl fragment (Fig. 1, ligand **3**) results in a decrease in the catalyst activity (see Table 1, entry *3*). For ligands **5—8**, the catalyst efficiency was found to be determined by not only steric but also, to a greater extent, electronic properties of the ligands. Thus phosphine ligand **6** containing an electron-withdrawing (σ_i = +0.38) 1-*ortho*-carboranyl fragment provides a higher degree of bromobenzene conversion (see Table 1, entry *6*) than isomeric ligand **7** containing electron-donating (σ_i = −0.23) 9-*ortho*-carboranyl fragment (see Table 1, entry *7*). An increase in the donor properties of the phosphorus center in ligands **5**, **8** also entails a decrease in the bromobenzene conversion compared to ligand **6** (see Table 1, entries *5*, *6*, and *8*). The steric bulk of the phosphorus center is still a fairly important aspect influencing the catalyst activity. The least sterically congested 1-(*ortho*-carboranylmethyl)-diethylphosphine ligand **5** showed the lowest conversion (see Table 1, entry *5*). Attempts at increasing the electron-withdrawing properties of the ligands by using phosphite **9** were useless due to catalyst destruction and palladium black deposition as a result of rigorous reaction conditions (Na_2CO_3, benzene—methanol—water).

The efficiency of carborane ligands in the Pd-catalyzed cross-coupling of phenylboronic acid with the less active substrate, bromotoluene,[3] was studied at 80 °C in toluene. The highest activity was found for (*o*-carboran-1-ylmethyl)diphenylphosphine (**6**, Table 2). The replacement of the electron-withdrawing 1-*ortho*-carboranyl group by donor 9-*ortho*-carboranyl group (ligand **7**, see Table 2, entries *6* and *7*) and replacement of the diphenylphosphine center by more electron-donating dicyclohexylphosphine fragment (ligand **8**) decreased substantially the conversion activity of the catalyst. Moreover, the least sterically congested ligand **5** showed a low efficiency, despite the presence of electron-withdrawing 1-*ortho*-carboranyl substituent. The trend for increasing the catalyst activity with increase in the steric effect of the phosphorus center of the ligand can also be followed among ligands **1—4** where higher degrees of conversion are provided by phosphines with the di-*tert*-butyl group (see Table 2, entries *1—4*). In addition, elimination of water and methanol from the reaction mixture allowed using the synthetically more accessible phosphite type ligand ensuring rather high conversion (ligand **9**, see Table 2, entry *9*).

Thus, for the first time the possibility of using phosphine and phosphite type carborane ligands in the Suzuki—Miyaura reaction was demonstrated. We showed that ligands with electron-withdrawing carboranyl substituents and sterically congested phosphorus center are the best choice for attaining high degrees of conversion. In addition, anhydrous reaction conditions allow one to use also phosphite ligands, which are synthetically more accessible than phosphine analogs. Moreover, known higher modularity and electron-withdrawing ability of phosphite type ligands may promote in the future the preparation of more active carboranyl ligands. Work along this line is in progress in our laboratories.

Experimental

^{31}P, ^{1}H, and ^{11}B NMR spectra were recorded on a Avance 400 instrument (161.98, 400.13, and 128.4 MHz) relative to 85% H_3PO_4 in D_2O, Me_4Si, and $BF_3 \cdot OEt_2$, respectively. Elemental analysis was carried out at the Laboratory of Organic Microanalysis of the A. N. Nesmeyanov Institute of Organoelement Compounds.

All reactions were carried out under dry argon in anhydrous solvents. 1-Diphenylphosphino-2-methyl-1,2-dicarba-*closo*-dodecaborane (**1**),[9] 1-diphenylphosphinomethyl-1,2-dicarba-*closo*-dodecaborane (**6**),[10] 1-diethylphosphinomethyl-1,2-dicarba-*closo*-dodecaborane (**5**),[10] 9-carboxy-1,2-dicarba-*closo*-dodecaborane (**10**),[12] and 9-hydroxymethyl-1,2-dicarba-*closo*-dodecaborane (**11**)[13] were prepared by known procedures. The following commercially available (Aldrich) chemicals were used: di-*tert*-butylchlorophosphine, dicyclohexylchlorophosphine, diphenylchlorophosphine, a 1.6 *M* solution of *n*-butyllithium in hexane, phosphorus tribromide, ethyl diphenylphosphinite, trichlorosilane, phenylboronic acid, bromobenzene, 4-bromotoluene, 4-phenyltoluene, and palladium acetate.

Synthesis of *o*-carboranylphosphines (2—4). A 1.6 *M* solution of *n*-butyllithium in hexane (6.9 mL, 11 mmol) was added with stirring to a solution of specified *ortho*-carborane (10 mmol) in anhydrous toluene (20 mL), and the mixture was stirred for 1 h. Then the specified chlorophosphine (11 mmol) in anhydrous toluene (10 mL) was added to the reaction mixture. The mixture was refluxed for 5 h, cooled, carefully quenched by water, and extracted with ether. After removal of the solvent, the residue was flash chromatographed on silica gel (elution with hexane).

1-Di-*tert*-butylphosphino-2-methyl-1,2-dicarba-*closo*-dodecaborane (2). The product was recrystallized from methanol. Yield 2.03 g (67%). M.p. 94—95 °C. Found (%): C, 43.51; H, 10.38; B, 35.76; P, 10.22. $C_{11}H_{31}B_{10}P$. Calculated (%): C, 43.68; H, 10.33; B, 35.75; P, 10.24. ^1H NMR ($CDCl_3$), δ: 1.42 (d, 18 H, $^3J_{HP}$ = 12.1 Hz, $C(CH_3)_3$); 2.15 (d, 3 H, $^4J_{HP}$ = 1.4 Hz, CH_3); 1.8—3.4 (m, 10 H, BH). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 74.6. ^{11}B NMR ($CDCl_3$), δ: −8.96 (m, 8 B); −4.93 (d, 1 B, J_{BH} = 148.4 Hz); 1.02 (d, 1 B, J_{BH} = 147.3 Hz).

1-Di-*tert*-butylphosphino-2-phenyl-1,2-dicarba-*closo*-dodecaborane (3). The product was recrystallized from methanol. Yield 2.73 g (75%). M.p. 143—144 °C. Found (%): C, 52.68; H, 9.24; B, 29.74; P, 8.51. $C_{16}H_{33}B_{10}P$. Calculated (%): C, 52.72; H, 9.12; B, 29.66; P, 8.50. ^1H NMR ($CDCl_3$), δ: 1.23 (d, 18 H, $^3J_{HP}$ = 11.8 Hz, $C(CH_3)_3$); 1.6—3.8 (m, 10 H, BH); 7.31 (t, 2 H, $^3J_{HH}$ = 7.9 Hz, *m*-CH_{Ph}); 7.39 (t, 1 H, $^3J_{HH}$ = 7.4 Hz, *p*-CH_{Ph}); 7.56 (d, 2 H, $^3J_{HH}$ = 8.2 Hz, *o*-CH_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 78.28. ^{11}B NMR ($CDCl_3$), δ: −8.80 (m, 8 B); −2.87 (d, 1 B, J_{BH} = 148.4 Hz); 1.91 (d, 1 B, J_{BH} = 147.3 Hz).

1-Dicyclohexylphosphino-1,2-dicarba-*closo*-dodecaborane (4). The product was recrystallized from heptane. Yield 2.93 g (86%). M.p. 130 °C. Found (%): C, 49.51; H, 9.74; B, 32.23; P, 8.94. $C_{14}H_{33}B_{10}P$. Calculated (%): C, 49.38; H, 9.77; B, 31.75; P, 9.10. ^1H NMR ($CDCl_3$), δ: 1.30 (m, 12 H, CH_2); 1.81 (m, 10 H, CH_2); 3.52 (s, 1 H, CH carborane); 1.5—3.4 (m, 10 H, BH).

$^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: 48.4. ^{11}B NMR ($CDCl_3$), δ: −11.84 (m, 6 B); −8.01 (d, 2 B, J_{BH} = 150.2 Hz); −1.63 (d, 2 B, J_{BH} = 149.0 Hz).

1-Dicyclohexylphosphinomethyl-1,2-dicarba-*closo*-dodecaborane (8). An ether solution (6.5 mmol) of 1-*o*-carboranylmethylmagnesium bromide was slowly added with stirring at 0 °C to a solution of dicyclohexylchlorophosphine (1.5 g, 6.45 mmol) in anhydrous ether (10 mL). The reaction mixture was stirred for 1 h at 20 °C, refluxed for 5 h, cooled, carefully quenched by water, and extracted with ether. After removal of the solvent, the residue was recrystallized from acetone. Yield 2.1 g (91%). M.p. 160 °C (acetone). Found (%): C, 50.70; H, 9.98; B, 30.12; P, 8.49. $C_{15}H_{35}B_{10}P$. Calculated (%): C, 50.82; H, 9.95; B, 30.49; P, 8.74. ^1H NMR ($CDCl_3$), δ: 1.0—1.3 (m, 12 H, CH_{2Cy}); 1.45—1.85 (m, 10 H, CH_{2Cy}); 2.28 (d, 2 H, CH_2, $^2J_{HP}$ = 3.0); 1.5—3.1 (m, 10 H, BH); 4.02 (s, 1 H, CH carborane). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: −0.3.

9-Bromomethyl-1,2-dicarba-*closo*-dodecaborane (12). A solution of PBr_3 (3.0 g, 11.1 mmol) in anhydrous benzene (10 mL) was added with stirring to a solution of 9-(hydroxymethyl)-*o*-carborane (**11**) (5.7 g, 32.7 mmol) in anhydrous benzene (60 mL). The mixture was stirred for 10 h, poured in water, and extracted with benzene. After removal of the solvent, the residue was distilled *in vacuo*. Yield 5.8 g (75%). B.p. 158 °C (1.5 Torr), m.p. 47 °C. Found (%): C, 15.66; H, 5.61; B, 45.68. $C_3H_{13}B_{10}Br$. Calculated (%): C, 15.19; H, 5.53; B, 45.59; Br, 33.69. ^1H NMR ($(CD_3)_2CO$), δ: 1.4—3.1 (m, 9 H, BH); 2.68 (s, 2 H, CH_2); 4.42 (s, 1 H, CH carborane); 4.48 (s, 1 H, CH carborane). ^{11}B NMR ($(CD_3)_2CO$), δ: −13.96 (m, 6 B); −9.07 (d, 2 B, J_{BH} = 150.2 Hz); −2.56 (d, 1 B, J_{BH} = 147.9 Hz); 5.46 (s, 1 B).

1,2-Dicarba-*closo*-dodecaborane-9-diphenylphosphinomethyl oxide (13). Method *A*. A mixture of 9-bromomethyl-*o*-carborane (**12**) (0.10 g, 0.42 mmol) and Ph_2POEt (0.3 mL) was heated for 5 h at 150 °C and evacuated for 1 h at 60 °C (1 Torr). The residue was dissolved in 5 mL of toluene with heating and cooled, and the precipitated crystals were filtered off and dried. The product was recrystallized from acetonitrile. Yield 0.14 g (95%). M.p. 240 °C (acetonitrile). Found (%): C, 50.34; H, 6.52; B, 30.30; P, 8.44. $C_{15}H_{23}B_{10}OP$. Calculated (%): C, 50.26; H, 6.47; B, 30.16; O, 4.46; P, 8.64.

Method *B*. Chlorodiphenylphosphine (10.55 g, 47.82 mmol) was added to a cooled (0 °C) mixture of 9-carboxy-*o*-carborane (**10**) (3.0 g, 15.94 mmol) and water (0.57 g, 31.87 mmol). The reaction mixture was heated for 3 h at 80 °C and for 80 h at 180 °C. After cooling, the glassy substance was triturated with toluene (20 mL) with heating to 80 °C. The precipitate was filtered off, washed with a 5% aqueous solution of Na_2CO_3, dried, and recrystallized from acetonitrile. Yield 4.0 g (70%).

9-Diphenylphosphinomethyl-1,2-dicarba-*closo*-dodecaborane (7). Trichlorosilane (3 mL) was added to a suspension of (*o*-carboran-9-ylmethyl)diphenylphosphine oxide (**13**) (0.20 g, 0.56 mmol) in toluene (10 mL). The reaction mixture was heated for 5 h at 100 °C until the white precipitate completely dissolved. After cooling, the mixture was concentrated *in vacuo*. The product was recrystallized from a heptane—toluene mixture. Yield 0.19 g (98%). M.p. 138 °C. Found (%): C, 52.31; H, 6.02; B, 31.76; P, 9.81. $C_{15}H_{23}B_{10}P$. Calculated (%): C, 52.61; H, 6.77; B, 31.57; P, 9.05. ^1H NMR ($CDCl_3$), δ: 1.3—3.1 (m, 9 H, BH); 1.57 (s, 2 H, CH_2); 3.40 (s, 1 H, CH carborane); 3.43 (s, 1 H, CH carborane); 7.26 (m, 6 H, CH_{Ph}); 7.44 (m, 4 H, CH_{Ph}). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ: −13.0. ^{11}B NMR ($CDCl_3$), δ: −14.34 (m, 6 B); −8.58 (d, 2 B, J_{BH} = 149.7 Hz); −1.69 (d, 1 B, J_{BH} = 147.9 Hz); 6.67 (s, 1 B).

Suzuki—Miyaura cross-coupling. The specified haloarene **15** or **16** (0.5 mmol), phenylboronic acid (73 mg, 0.6 mmol), and the specified base (Na_2CO_3, K_3PO_4) (1—1.5 mmol) were placed into a Schlenk flask. Then $Pd(OAc)_2$ (1 mg, 0.005 mmol) and specified ligand **1—9** (0.01 mmol) were added. The reactor was purged with argon and the specified solvent (5 mL) was added. The mixture was stirred for 1.5—3 h at 40—80 °C (see Table 1), cooled to 20 °C, diluted with hexane (10 mL), filtered through a silica gel layer, and analyzed by ^1H NMR spectroscopy.

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Received April 25, 2008;
in revised form July 4, 2008