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STEREOSPECIFIC SYNTHESIS OF *trans*-1,4-DIPHOSPHACYCLOHEXANES

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Abstract — Stereospecific synthesis of *trans*-1,4-diphosphacyclohexanes via intramolecular oxidative coupling of P-stereogenic bisphosphine borane complexes is reported. Regardless of the enantiopurity of the starting materials, only *trans*-isomers were formed. The synthesis and characterization of the obtained products are described in detail herein.

Phosphines (trivalent organophosphorus compounds; PR_3; R = organic moiety), similar to tertiary amines (NR_3), have a trigonal pyramidal structure with the phosphorus atom at the apex; however, the inversion energy of PR_3 is much higher because of the increased *s* character resulting from the unshared electron pair on phosphorus.[1] Therefore, the phosphorus atom behaves as a chiral center in the same manner as a chiral carbon atom, and optically active phosphines are conformationally stable. From this structural viewpoint, a large number of optically active P-stereogenic phosphines have been synthesized;[2] in particular, optically active P-stereogenic bisphosphines have been widely used as chiral ligands for transition-metal-catalyzed asymmetric reactions.[3] One such bisphosphine with a methyl substituent at each phosphorus atom, BisP* (Figure 1), was synthesized with relatively high enantiomeric excess (*ee*%) by Evans[4] and Imamoto.[5] In this study, we investigated the reactivity of BisP*–borane complexes and the feasibility of using BisP* as chiral building blocks for a variety of P-stereogenic compounds.

Lithiation of the methyl group of BisP* by alkyllithium reagents proceeds smoothly because of the strong electron-withdrawing character of the coordinated borane. Actually, the BisP*–boranes can also be prepared by the lithiation of methylphosphine boranes or methylphosphine sulfides.[4,5] Lithiation of BisP*–boranes and successive oxidative coupling affords various optically active P-stereogenic oligomers[6] and polymers.[7]

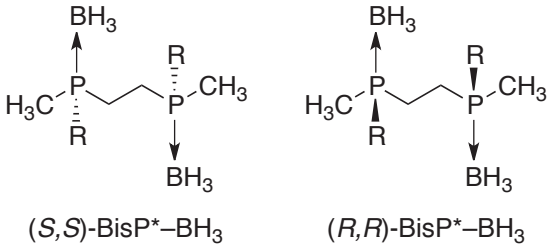
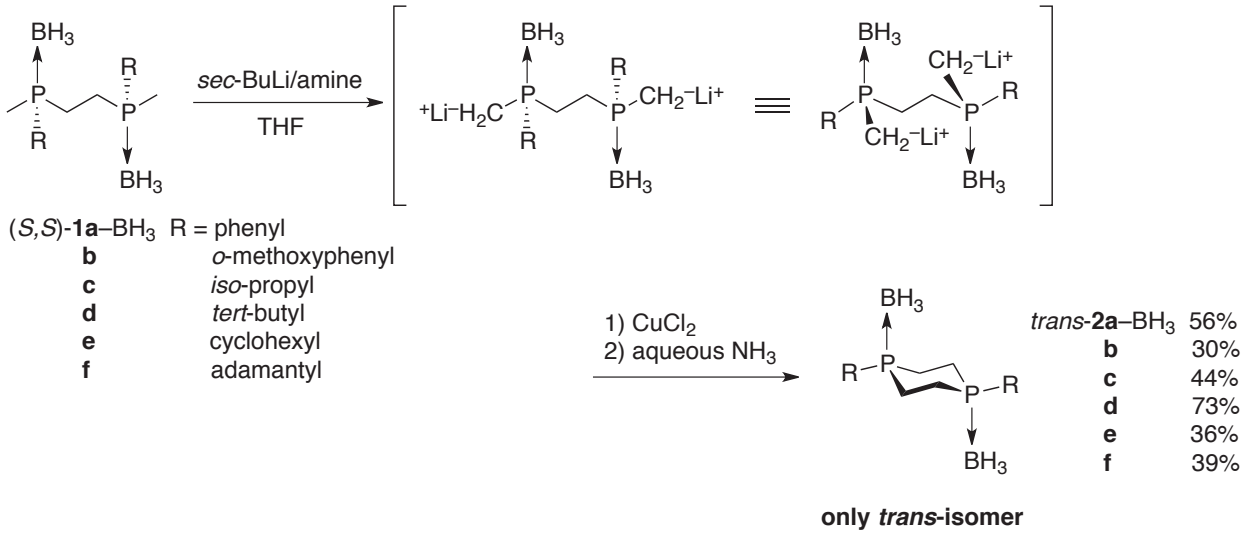


Figure 1. Structures of BisP*–BH_3 complexes

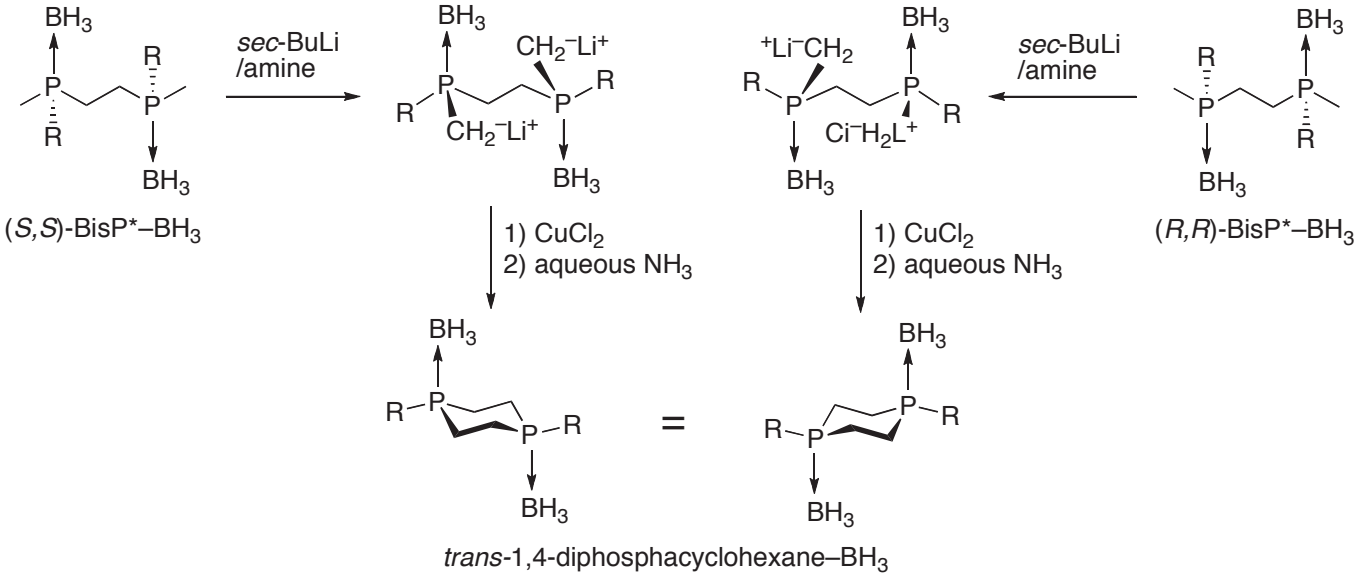
We found that intramolecular oxidative coupling of the lithiated BisP*–boranes afforded *trans*-diphosphacyclohexanes in a stereospecific manner,[8] which is the rare example of the stereo-controlled synthesis of *cis*- or *trans*-diphosphacycloalkanes. Alder and coworkers succeeded in the stereoselective synthesis of a series of *cis*-diphosphacycloalkanes by the ring-opening reaction of the corresponding bicyclic compounds.[9] Recently, Strohmann and coworkers reported the synthesis of *trans*-1,4-diphenyl-1,4-diphosphacyclohexane by the direct dilithiation of prochiral dimethylphenylphosphine borane and its one-pot oxidative cou pling reaction.[10] Our synthetic route is attractive in that the only *trans*-isomer can be obtained from BisP*–borane, regardless of the enantiopurity of the starting material. For the purpose of establishing the synthetic method for the stereospecific synthesis of *trans*-1,4-diphosphacyclohexanes, we carried out the synthesis of *trans*-1,4-diphosphacyclohexanes from several optically active BisP*–boranes and characterized the products in detail.

The synthesis of *trans*-1,4-diphosphacyclohexanes commenced with optically active BisP*–boranes (*S*,*S*)-**1a-f**–BH_3, as shown in Scheme 1. Treatment of (*S*,*S*)-**1a-f**–BH_3 with *sec*-BuLi and amine ligands such as *N*,*N*,*N*´,*N*´-tetramethylethylenediamine (TMEDA) and (–)-sparteine afforded a dilithiated intermediate. Transmetallation from Li to Cu using $CuCl_2$ and successive reductive elimination with aqueous NH_3 caused intramolecular oxidative coupling to provide the corresponding 1,4-diphosphacyclohexanes *trans*-**2a-f**–BH_3. The crude products were purified by SiO_2 column chromatography and recrystallized from hot toluene and hexane to give the desired products in moderate-to-good isolated yields. In this reaction, cyclization proceeded dominantly without polymeric compounds even in dilute solution, and the main by-product was the starting material.



Scheme 1

The stereochemistry of the obtained 1,4-diphosphacyclohexanes was completely "*trans*"; the reaction afforded only *trans*-isomers, because the reaction proceeded stereospecifically due to the use of enantiopure (*S,S*)-BisP*–boranes. In this stereospecific reaction, we do not need take care of the enantiopurity of the starting BisP*–boranes; in other words, BisP*–boranes with poor *ee%* as well as even *racemi*-BisP*–boranes provide only the *trans*-1,4-diphosphacyclohexanes, as shown in Scheme 2. (*S,S*)-BisP*–boranes could be readily obtained with high *ee%* by the intermolecular oxidative dimerization of $RMe_2P–BH_3$ using *sec*-BuLi and a chiral amine ligand such as (–)-sparteine; however, *meso*-BisP*–boranes formed in the reaction had to be removed from the reaction mixture since they would stereospecifically yield *cis*-1,4-diphosphacyclohexanes. Oxidative coupling of the mixture of *rac*- and *meso*-BisP*–boranes afforded equimolar amounts of *trans*- and *cis*-1,4-diphosphacyclohexane boranes, which could be separated by column chromatography, as shown in Scheme S1 (Supporting Information).



Scheme 2

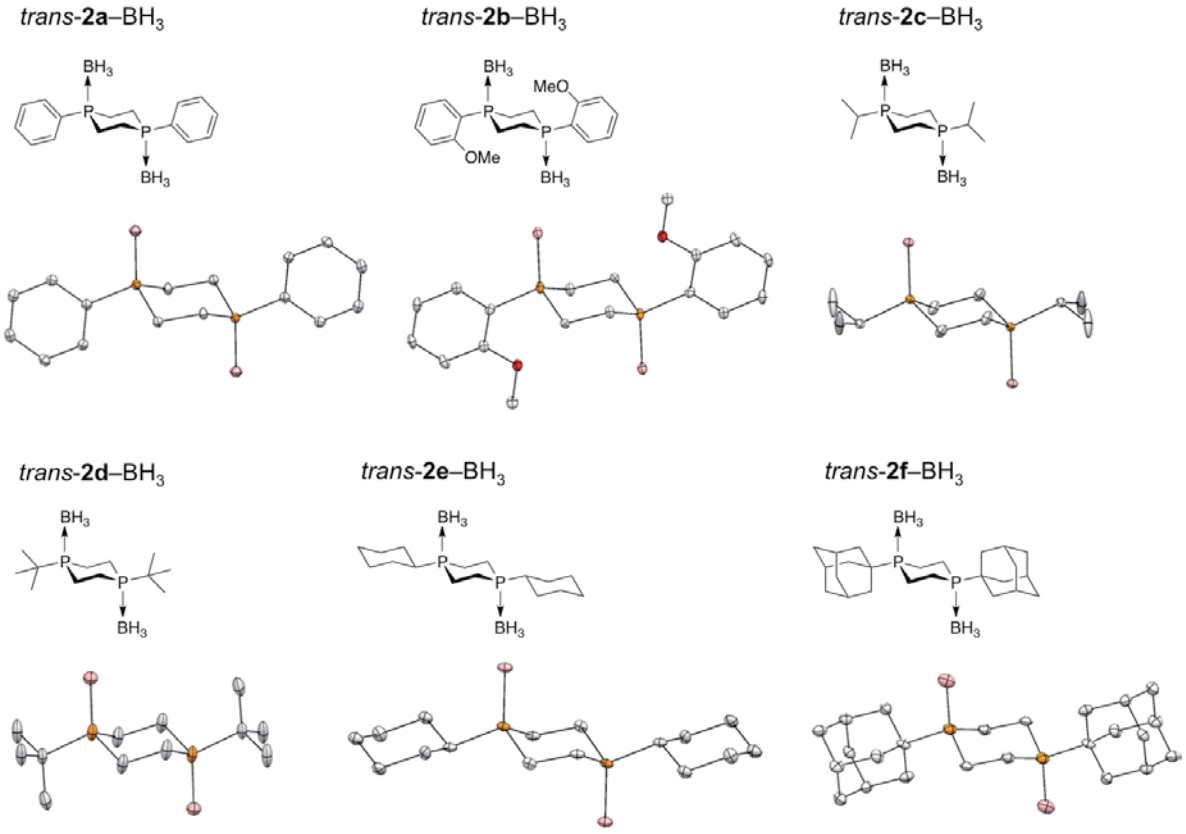
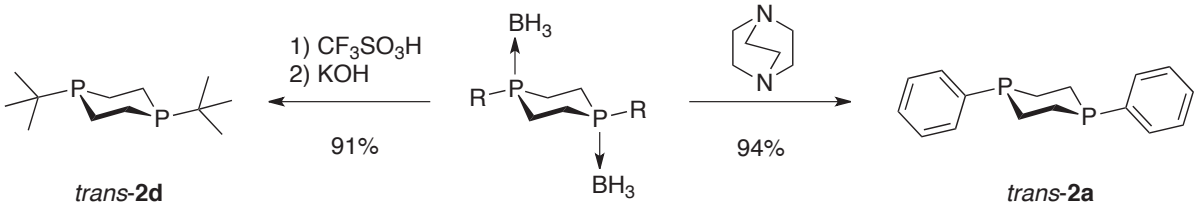


Figure 2. ORTEP drawings of *trans*-**2a-f**–BH_3. Thermal ellipsoids are shown at the 30% probability level, and all hydrogen atoms are omitted for clarity

All the *trans*-**2a-f**–BH_3 compounds prepared were purified by recrystallization from hot toluene and hexane. Their structures were confirmed by ^{1}H, ^{13}C, and ^{31}P NMR, high-resonance mass analysis, elemental analysis, and X-ray crystallography. The ORTEP drawings of *trans*-**2a-f**–BH_3 are shown in Figure 2, and the crystallographic data are listed in Tables S1–S6 (Supporting Information). X-Ray crystallographic analysis revealed that *trans*-**2a-f**–BH_3 adopted a chair conformation with equatorial alkyl (and aryl) substituents and axial boranes in the crystal state.

We confirmed that the coordinated boranes could be removed from the *trans*-1,4-diphosphacyclohexane-borane complexes to obtain *trans*-1,4-diphosphacyclohexanes. Scheme 3 shows the removal of boranes of *trans*-**2a**– and **2d**–BH_3 as representative examples of aryl- and alkyl-substituted compounds, respectively. Generally, the removal of boranes of trialkylphosphine requires a relatively severe reaction conditions because of the strong phosphorus–boron coordination bond. Treatment of *trans*-**2d**–BH_3 with excess CF_3SO_3H and then with KOH afforded *trans*-**2d** in 91% isolated yield.[11] On the other hand, boranes of *trans*-**2a**–BH_3 were readily removed by the reaction with an organic base such as 1,4-diazabicyclo[2.2.2]octane (DABCO) to afford the corresponding bisphosphine *trans*-**2a** in 94% isolated yield.



Scheme 3

In conclusion, we demonstrated that *trans*-1,4-diphosphacyclohexanes can be stereospecifically prepared via the intramolecular oxidative coupling of optically active bisphosphine BisP*–boranes. Only *trans*-1,4-diphosphacyclohexane skeletons were formed, regardless of the enantiopurity of the BisP*–boranes. We showed the generality of our original synthetic method for the formation of *trans*-1,4-diphosphacyclohexanes with various substituents. Enantiopure BisP*s have been employed only as chiral ligands for transition metal-catalyzed asymmetric reactions; the results of this study reveal an entirely new set of applications of BisP* as chiral building blocks for a variety of P-stereogenic phosphorus compounds.

EXPERIMENTAL

^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a JEOL EX400 or AL400 instrument. Samples were analyzed in $CDCl_3$, and the chemical shift values were expressed relative to Me_4Si as an internal standard. ^{31}P NMR spectra were recorded on a JEOL EX400 spectrometer at 161.9 MHz, and samples were analyzed in $CDCl_3$ using H_3PO_4 as an external standard. Mass analysis was performed at technical support office at Department of Synthetic Chemistry and Biological Chemistry, Kyoto University; high-resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX102A spectrometer for EI, JEOL JMS-HX110A for FAB, and Thermo Scientific EXACTIVE for ESI. Analytical thin layer chromatography (TLC) was performed with silica gel 60 Merck F254 plates. Column chromatography was performed with Wakogel C-300 SiO_2. Elemental analysis was performed at the Microanalytical Center of Kyoto University.

Materials. THF was purchased and purified by passage through purification column under Ar pressure.[12] Dehydrated grade solvents of toluene and $CHCl_3$ were purchased and used without further purification. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) and (–)-sparteine were purchased and distilled from KOH under Ar atmosphere. *sec*-BuLi (1.0 M in cyclohexane and n-hexane solution), 1,4-diazabicyclo[2.2.2]octane (DABCO), $CuCl_2$, aqueous NH_3 (28%) were purchased and used without purification. All (*S*,*S*)-BisP* borane complexes — (*S*,*S*)-**1a**–BH_3,[4] (*S*,*S*)-**1b**–BH_3,[4] (*S*,*S*)-**1c**–BH_3,[13] (*S*,*S*)-**1d**–BH_3,[5] (*S*,*S*)-**1e**–BH_3,[5] and (*S*,*S*)-**1f**–BH_3[5] — were prepared by the literature's procedures.

Reactions were performed under Ar atmosphere using standard Schlenk techniques.

Synthesis. Typical procedure is as follows. A solution of (–)-sparteine (0.55 mL, 2.5 mmol) as a ligand in THF (10 mL) was cooled to –78 °C. To this solution, *sec*-BuLi (1.0 M in cyclohexane and *n*-hexane solution, 2.5 mL, 2.5 mmol) was added by a syringe. After 15 min, a solution of (*S*,*S*)-**1a**–BH_3 (0.302 g, 1.0 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at –78 °C for 3 h. $CuCl_2$ (0.270 g, 2.0 mmol) was added in one portion with vigorous stirring, and the mixture was allowed to slowly warm to room temperature. After 15 h, aqueous NH_3 (10 mL) was added, and the organic species were extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were washed with 5% aqueous NH_3, 2 N HCl, and brine, and then dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography on SiO_2 with hexane-CH_2Cl_2 (v/v = 1:1) and recrystallization from hot toluene-hexane to obtain *trans*-**2a**–BH_3 (167 mg, 0.56 mmol) as a colorless solid.

***trans*-2a–BH_3:** CCDC # 888064; 56% isolated yield; R_f = 0.83 (CH_2Cl_2 100%, SiO_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (br q, J_{HB} = 108.4Hz, -B*H*$_3$, 6H), 2.19 (dd, J = 10.5 Hz, J_{HP} = 21.4 Hz, -PC*H*$_2$-, 4H), 2.81 (m, -PC*H*$_2$-, 4H), 7.56 (m, -*Ar*, 6H) 7.88 (m, -*Ar*, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.7 (d, J_{CP} = 33.7 Hz, -P*C*H$_2$-), 127.3-132.2 (m, -*Ar*) ppm; ^{31}P{^{1}H}NMR ($CDCl_3$, 161.9 MHz) δ +6.3 ppm. HRMS (EI). Calcd for $C_{16}H_{24}B_2P_2$ [M]$^+$: 300.1539. Found 300.1532. Anal. Calcd for $C_{16}H_{24}B_2P_2$: C, 64.07; H, 8.07. Found: C, 63.85; H, 7.97.

***trans*-2b–BH_3:** CCDC # 888063; 30% isolated yield; R_f = 0.5 (hexane/EtOAc: v/v = 4:1, SiO_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (br q, J_{HB} = 123.0 Hz, -B*H*$_3$, 6H), 2.04 (m, P-C*H*$_2$-, 4H), 3.43 (m, P-C*H*$_2$, 4H), 4.05 (s, -C*H*$_3$, 6H), 6.99 (d, J = 8.6 Hz, -*Ar*, 2H), 7.10 (t, J = 7.3 Hz, -*Ar*, 2H), 7.56 (t, J = 7.3 Hz, -*Ar*, 2H), 8.00 (q, J = 4.8 Hz, -*Ar*, 2H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.0 (d, J_{CP} = 34.6 Hz, -P*C*H$_2$-), 55.6 (s, -O*C*H$_3$), 110.7, 120.9, 134.1, 136.4, 136.5 and 162.0 (-*Ar*) ppm; ^{31}P{^{1}H}NMR ($CDCl_3$, 161.9 MHz) δ +6.6 (J_{PB} = 60.5 Hz) ppm. HRMS (ESI). Calcd for $C_{18}H_{28}B_2O_2P_2$ [M+Na]$^+$: 383.1643. Found 383.1638. Anal. Calcd for $C_{18}H_{28}B_2O_2P_2$: C, 60.06; H, 7.84. Found: C, 59.89; H, 8.11.

***trans*-2c–BH_3:** CCDC # 888062; 44% isolated yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.39 (br q, J_{HB} = 100.6 Hz, -B*H*$_3$, 6H), 1.19 (q, J = 8.3 Hz, -(C*H*$_3$)$_2$, 12H), 1.88-2.03 (m, -PC*H*$_2$- and -C*H*(CH$_3$)$_2$, 6H), 2.24 (m, -PC*H*$_2$-, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (d, J_{CP} = 29.7 Hz, -P*C*H$_2$-), 16.1 (s, -CH(*C*H$_3$)$_2$), 24.2 (d, J_{CP} = 35.5 Hz, -P*C*H-) ppm; ^{31}P{^{1}H}NMR ($CDCl_3$, 161.9 MHz) δ +18.1 (J_{PB} = 65.9 Hz) ppm. HRMS (ESI). Calcd for $C_{10}H_{28}B_2P_2$ [M+H]$^+$: 233.1925. Found 233.1926.

***trans*-2d–BH_3:** CCDC # 888065; 73% isolated yield; R_f = 0.78 (CH_2Cl_2 100%, SiO_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.40 (br q, J_{HB} = 98.8Hz, -B*H*$_3$, 6H), 1.19 (d, J_{HP} = 14.0 Hz, -Bu^t, 18H), 1.88 (dd, J = 9.7 Hz, J_{HP} =20.8Hz, -PC*H*$_2$-, 4H), 2.36 (t, J = 10.0Hz, -PC*H*$_2$-, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.9 (d, J_{CP} = 29.2 Hz, -P*C*H$_2$-), 24.8 (s, -PC(*C*H$_3$)$_3$), 27.2 (d, -P*C*(CH$_3$)$_3$, J_{CP} = 32.9 Hz) ppm; ^{31}P{^{1}H}NMR ($CDCl_3$, 161.9 MHz) δ +26.6 ppm. HRMS (FAB). Calcd for $C_{12}H_{32}B_2P_2$ [M-H]$^+$: 259.2087. Found

259.2086. Anal. Calcd for $C_{12}H_{32}B_2P_2$: C, 55.44; H, 12.41. Found: C, 55.45; H, 12.63.

***trans*-2e–BH_3:** CCDC # 888061; 36% isolated yield; R_f = 0.6 (hexane/EtOAc: v/v = 4:1, SiO_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.39 (br q, J_{HB} = 101.0 Hz, -B*H*$_3$, 6H), 1.29 (m, -C_6H_{11}, 12H), 1.61-2.02 (m, -PC*H*$_2$- and -C_6H_{11}, 14H), 2.24 (m, -PC*H*$_2$-, 4H), ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.7 (d, J_{CP} = 23.1 Hz, -P*C*H$_2$-), 25.7, 25.8, 26.3, 26.4, 33.9 and 34.2 (-*C*$_6$H$_{12}$) ppm; ^{31}P{^{1}H}NMR ($CDCl_3$, 161.9 MHz) δ +14.1 (J_{PB} = 60.5 Hz) ppm. HRMS (ESI). Calcd for $C_{16}H_{36}B_2P_2$ [M+Na]$^+$: 335.2371. Found 335.2364. Anal. Calcd for $C_{16}H_{36}B_2P_2$: C, 61.59; H, 11.63. Found: C, 61.30; H, 11.63.

***trans*-2f–BH_3:** CCDC # 888060; 39% isolated yield; R_f = 0.30 ($CHCl_3$/hexane: v/v = 1:1, SiO_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.36 (br q, J_{HB} = 106.4 Hz, -B*H*$_3$, 6H), 1.69-1.84 (m, C-C*H*$_2$-C and P-C*H*$_2$, 28H), 2.04 (s, -C*H*-, 6H), 2.35 (m, -PC*H*$_2$-, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.3 (d, J_{CP} = 29.7 Hz, -P*C*H$_2$-), 27.6 (d, J_{CP} = 9.1 Hz, -P-*C*-), 30.2 (d, J_{CP} = 34.6 Hz, -P*C*H$_2$-), 35.7 and 36.5 (s, adamantyl) ppm; ^{31}P{^{1}H}NMR ($CDCl_3$, 161.9 MHz) δ +19.6 (J_{PB} = 76.8 Hz) ppm. Anal. Calcd for $C_{24}H_{44}B_2P_2$: C, 69.26; H, 10.66. Found: C, 68.99; H, 10.74.

Synthetic details, spectral data, NMR spectra, and X-ray crystallographic data are shown in Supporting Information.

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