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STEREOSPECIFIC SYNTHESIS OF *trans*-1,4-DIPHOSPHACYCLO- HEXANES

Yasuhiro Morisaki,* Hiroaki Imoto, Ryosuke Kato, Yuko Ouchi, and
Yoshiki Chujo*

Department of Polymer Chemistry, Graduate School of Engineering, Kyoto
University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan; E-mail:
ymo@chujo.synchem.kyoto-u.ac.jp, chujo@chujo.synchem.kyoto-u.ac.jp

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 Evans⁴ 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 alkyl lithium 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 oligomers⁶ and polymers.⁷

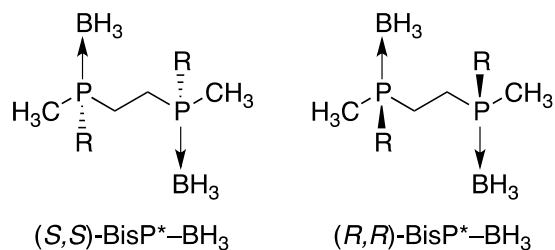
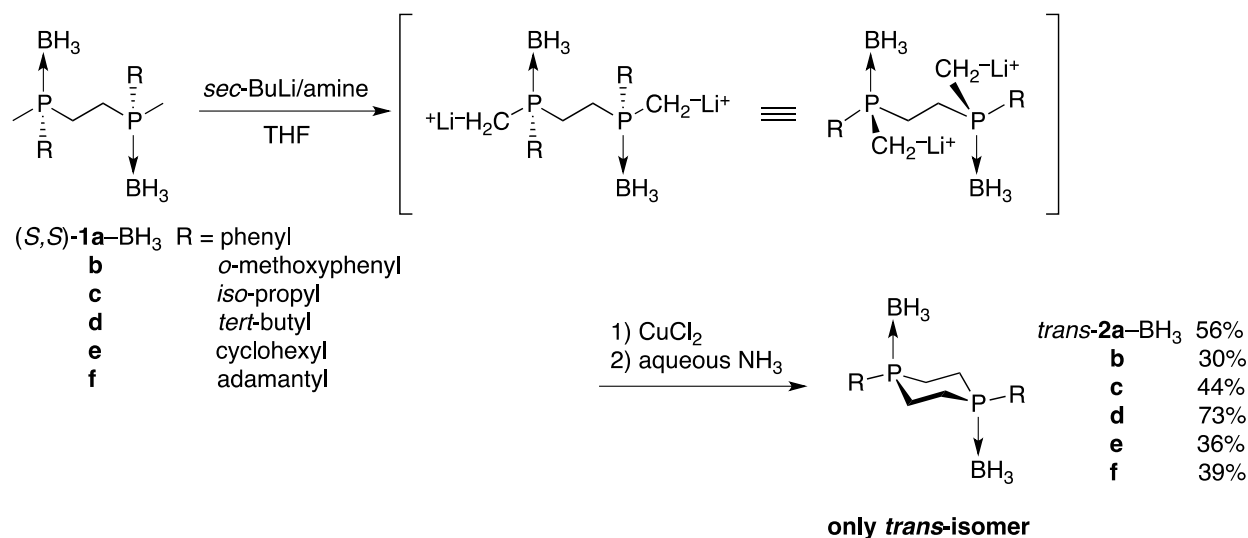


Figure 1. Structures of BisP*–BH₃ complexes

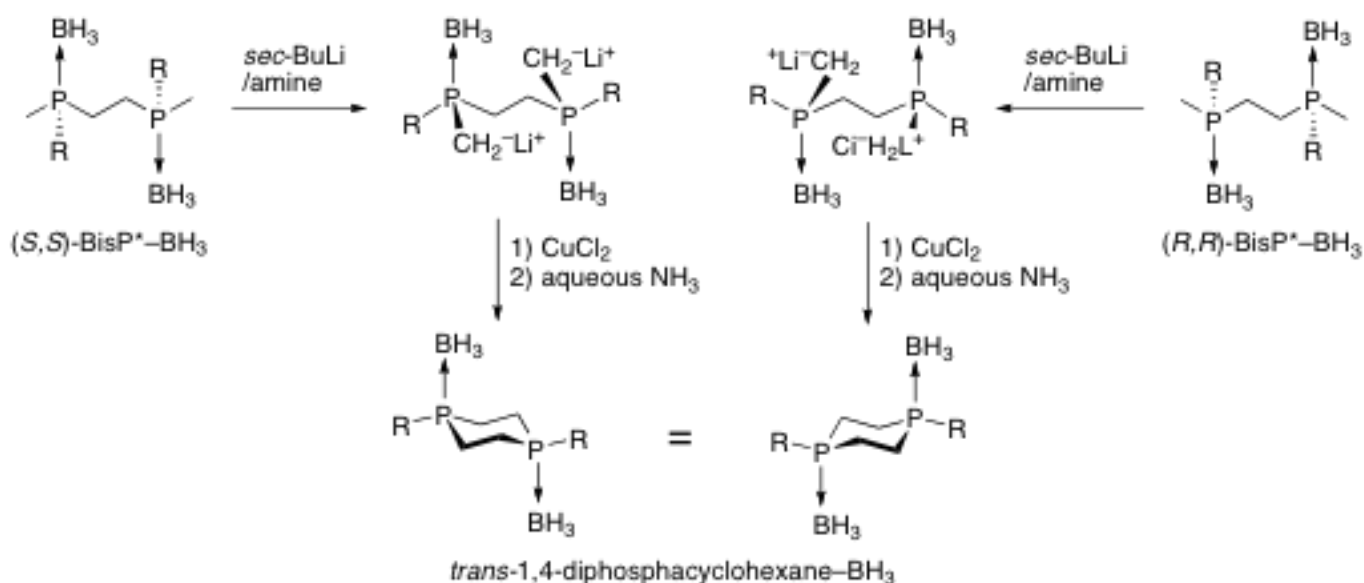
We found that intramolecular oxidative coupling of the lithiated BisP*–boranes afforded *trans*-diphosphacyclohexanes in a stereospecific manner,⁸ which is the rare example of the stereo-controlled synthesis of *cis*- or *trans*-diphosphacycloalkanes. Alder and coworkers succeeded in the stereoselective 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 coupling 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**–BH₃, as shown in Scheme 1. Treatment of (*S,S*)-**1a-f**–BH₃ with *sec*-BuLi and amine ligands such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and (–)-sparteine afforded a dilithiated intermediate. Transmetalation from Li to Cu using CuCl₂ and successive reductive elimination with aqueous NH₃ caused intramolecular oxidative coupling to provide the corresponding 1,4-diphosphacyclohexanes *trans*-**2a-f**–BH₃. The crude products were purified by SiO₂ 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 RMe₂P–BH₃ 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

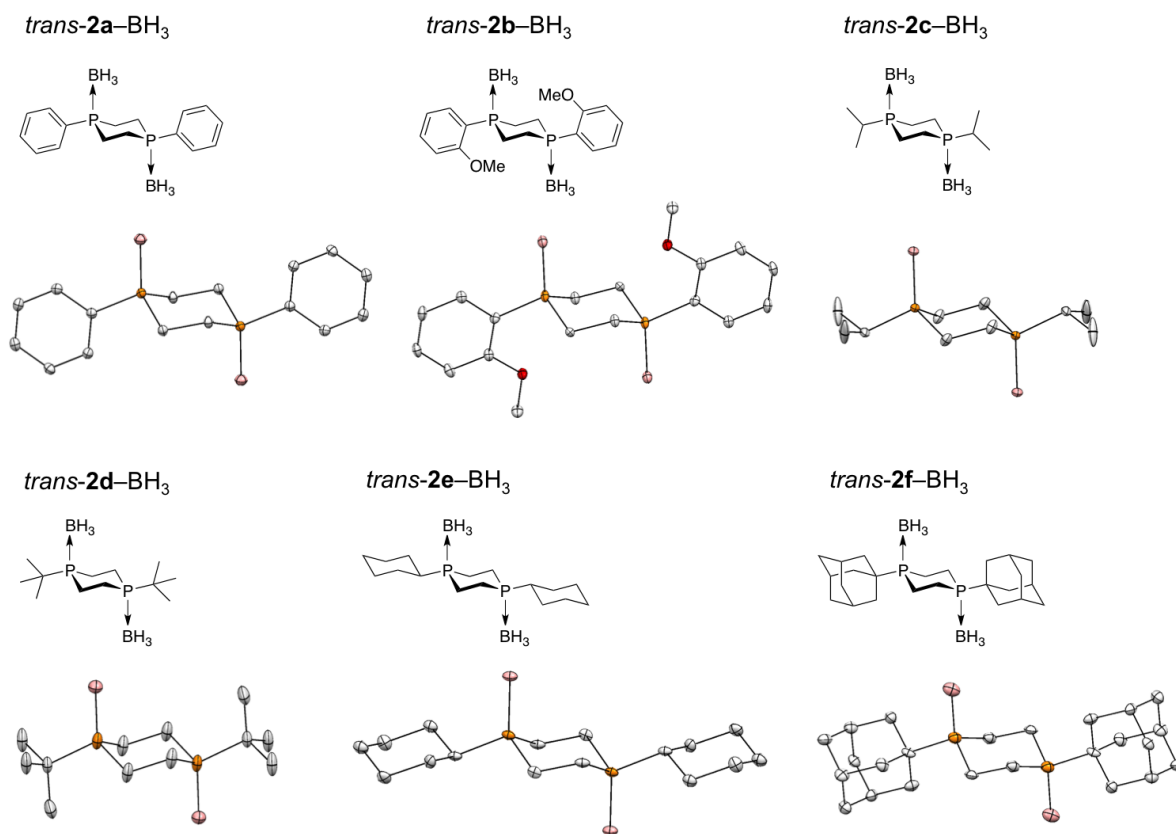
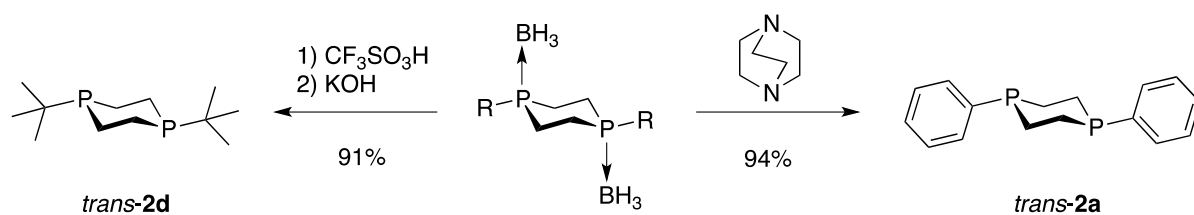


Figure 2. ORTEP drawings of *trans-2a-f*-BH₃. Thermal ellipsoids are shown at the 30% probability level, and all hydrogen atoms are omitted for clarity

All the *trans-2a-f*-BH₃ compounds prepared were purified by recrystallization from hot toluene and hexane. Their structures were confirmed by ¹H, ¹³C, and ³¹P NMR, high-resolution mass analysis, elemental analysis, and X-ray crystallography. The ORTEP drawings of *trans-2a-f*-BH₃ 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*-BH₃ 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*-BH₃ 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*-BH₃ with excess CF₃SO₃H and then with KOH afforded *trans-2d* in 91% isolated yield.¹¹ On the other hand, boranes of *trans-2a*-BH₃ 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

^1H (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**–BH₃ (0.302 g, 1.0 mmol) in THF (10 mL) was added dropwise, and the mixture was stirred at –78 °C for 3 h. CuCl₂ (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 NH₃ (10 mL) was added, and the organic species were extracted with CH₂Cl₂ (3 × 10 mL). The combined extracts were washed with 5% aqueous NH₃, 2 N HCl, and brine, and then dried over MgSO₄. After evaporation of the solvent, the residue was purified by column chromatography on SiO₂ with hexane-CH₂Cl₂ (v/v = 1:1) and recrystallization from hot toluene-hexane to obtain *trans*-**2a**–BH₃ (167 mg, 0.56 mmol) as a colorless solid.

***trans*-2a–BH₃:** CCDC # 888064; 56% isolated yield; *R_f* = 0.83 (CH₂Cl₂ 100%, SiO₂); ¹H NMR (CDCl₃, 400 MHz) δ 0.87 (br q, *J*_{HB} = 108.4 Hz, –BH₃, 6H), 2.19 (dd, *J* = 10.5 Hz, *J*_{HP} = 21.4 Hz, –PCH₂–, 4H), 2.81 (m, –PCH₂–, 4H), 7.56 (m, –*Ar*, 6H) 7.88 (m, –*Ar*, 4H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 19.7 (d, *J*_{CP} = 33.7 Hz, –PCH₂–), 127.3–132.2 (m, –*Ar*) ppm; ³¹P{¹H}NMR (CDCl₃, 161.9 MHz) δ +6.3 ppm. HRMS (EI). Calcd for C₁₆H₂₄B₂P₂ [M]⁺: 300.1539. Found 300.1532. Anal. Calcd for C₁₆H₂₄B₂P₂: C, 64.07; H, 8.07. Found: C, 63.85; H, 7.97.

***trans*-2b–BH₃:** CCDC # 888063; 30% isolated yield; *R_f* = 0.5 (hexane/EtOAc: v/v = 4:1, SiO₂); ¹H NMR (CDCl₃, 400 MHz) δ 0.91 (br q, *J*_{HB} = 123.0 Hz, –BH₃, 6H), 2.04 (m, P–CH₂–, 4H), 3.43 (m, P–CH₂, 4H), 4.05 (s, –CH₃, 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; ¹³C NMR (CDCl₃, 100 MHz) δ 17.0 (d, *J*_{CP} = 34.6 Hz, –PCH₂–), 55.6 (s, –OCH₃), 110.7, 120.9, 134.1, 136.4, 136.5 and 162.0 (–*Ar*) ppm; ³¹P{¹H}NMR (CDCl₃, 161.9 MHz) δ +6.6 (*J*_{PB} = 60.5 Hz) ppm. HRMS (ESI). Calcd for C₁₈H₂₈B₂O₂P₂ [M+Na]⁺: 383.1643. Found 383.1638. Anal. Calcd for C₁₈H₂₈B₂O₂P₂: C, 60.06; H, 7.84. Found: C, 59.89; H, 8.11.

***trans*-2c–BH₃:** CCDC # 888062; 44% isolated yield; ¹H NMR (CDCl₃, 400 MHz) δ 0.39 (br q, *J*_{HB} = 100.6 Hz, –BH₃, 6H), 1.19 (q, *J* = 8.3 Hz, –(CH₃)₂, 12H), 1.88–2.03 (m, –PCH₂– and –CH(CH₃)₂, 6H), 2.24 (m, –PCH₂–, 4H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 14.8 (d, *J*_{CP} = 29.7 Hz, –PCH₂–), 16.1 (s, –CH(CH₃)₂), 24.2 (d, *J*_{CP} = 35.5 Hz, –PCH–) ppm; ³¹P{¹H}NMR (CDCl₃, 161.9 MHz) δ +18.1 (*J*_{PB} = 65.9 Hz) ppm. HRMS (ESI). Calcd for C₁₀H₂₈B₂P₂ [M+H]⁺: 233.1925. Found 233.1926.

***trans*-2d–BH₃:** CCDC # 888065; 73% isolated yield; *R_f* = 0.78 (CH₂Cl₂ 100%, SiO₂); ¹H NMR (CDCl₃, 400 MHz) δ 0.40 (br q, *J*_{HB} = 98.8 Hz, –BH₃, 6H), 1.19 (d, *J*_{HP} = 14.0 Hz, –Bu^t, 18H), 1.88 (dd, *J* = 9.7 Hz, *J*_{HP} = 20.8 Hz, –PCH₂–, 4H), 2.36 (t, *J* = 10.0 Hz, –PCH₂–, 4H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 12.9 (d, *J*_{CP} = 29.2 Hz, –PCH₂–), 24.8 (s, –PC(CH₃)₃), 27.2 (d, –PC(CH₃)₃, *J*_{CP} = 32.9 Hz) ppm; ³¹P{¹H}NMR (CDCl₃, 161.9 MHz) δ +26.6 ppm. HRMS (FAB). Calcd for C₁₂H₃₂B₂P₂ [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-BH₃: CCDC # 888061; 36% isolated yield; $R_f = 0.6$ (hexane/EtOAc: v/v = 4:1, SiO₂); ¹H NMR (CDCl₃, 400 MHz) δ 0.39 (br q, $J_{HB} = 101.0$ Hz, -BH₃, 6H), 1.29 (m, -C₆H₁₁, 12H), 1.61-2.02 (m, -PCH₂- and -C₆H₁₁, 14H), 2.24 (m, -PCH₂-, 4H), ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 14.7 (d, $J_{CP} = 23.1$ Hz, -PCH₂-), 25.7, 25.8, 26.3, 26.4, 33.9 and 34.2 (-C₆H₁₂) ppm; ³¹P{¹H}NMR (CDCl₃, 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-BH₃: CCDC # 888060; 39% isolated yield; $R_f = 0.30$ (CHCl₃/hexane: v/v = 1:1, SiO₂); ¹H NMR (CDCl₃, 400 MHz) δ 0.36 (br q, $J_{HB} = 106.4$ Hz, -BH₃, 6H), 1.69-1.84 (m, C-CH₂-C and P-CH₂, 28H), 2.04 (s, -CH-, 6H), 2.35 (m, -PCH₂-, 4H) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 11.3 (d, $J_{CP} = 29.7$ Hz, -PCH₂-), 27.6 (d, $J_{CP} = 9.1$ Hz, -P-C-), 30.2 (d, $J_{CP} = 34.6$ Hz, -PCH₂-), 35.7 and 36.5 (s, adamantyl) ppm; ³¹P{¹H}NMR (CDCl₃, 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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REFERENCES

- (a) R. E. Weston, *J. Am. Chem. Soc.*, 1954, **76**, 2645; (b) R. D. Baechler and K. Mislow, *J. Am. Chem. Soc.*, 1970, **92**, 3090.
- (a) K. M. Pietrusiewicz and M. Zablocka, *Chem. Rev.*, 1994, **94**, 1375; (b) M. J. Johansson and N. C. Kann, *Mini-Rev. Org. Chem.*, 2004, **1**, 233; (c) A. Grabulosa, J. Granell, and G. Muller, *Coord. Chem. Rev.*, 2007, **251**, 25.
- (a) Y. Yamanoi and T. Imamoto, *Rev. Heteroatom Chem.*, 1999, **20**, 227; (b) K. V. L. Crepy and T. Imamoto, *Top. Curr. Chem.*, 2003, **229**, 111; (c) K. V. L. Crepy and T. Imamoto, *Adv. Synth. Catal.*, 2003, **345**, 79; (d) T. Imamoto, *J. Synth. Org. Chem. Jpn.*, 2007, **65**, 1060.
- A. R. Muci, K. R. Campos, and D. A. Evans, *J. Am. Chem. Soc.*, 1995, **117**, 9075.
- T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, and K.

- Yamaguchi, *J. Am. Chem. Soc.*, 1998, **120**, 1635.
6. Y. Morisaki, Y. Ouchi, K. Naka, and Y. Chujo, *Chem. Asian J.*, 2007, **2**, 1166.
 7. (a) Y. Morisaki, K. Suzuki, H. Imoto, and Y. Chujo, *Macromol. Rapid Commun.*, 2010, **31**, 1719; (b) H. Imoto, Y. Morisaki, and Y. Chujo, *Chem. Commun.*, 2010, **46**, 7542; (c) Y. Morisaki, K. Suzuki, H. Imoto, and Y. Chujo, *Macromol. Chem. Phys.*, 2011, **212**, 2603.
 8. Y. Morisaki, H. Imoto, Y. Ouchi, Y. Nagata, and Y. Chujo, *Org. Lett.*, 2008, **10**, 1489.
 9. (a) R. W. Alder and D. Read, *Coord. Chem. Rev.*, 1998, **176**, 113; (b) R. W. Alder, C. Ganter, C. J. Harris, and A. G. Orpen, *J. Chem. Soc., Chem. Commun.*, 1992, 1170; (c) R. W. Alder, D. D. Ellis, J. K. Hogg, A. Martín, A. G. Orpen, and P. N. Taylor, *Chem. Commun.*, 1996, 537; (d) R. W. Alder, C. Ganter, M. Gil, R. Gleiter, C. J. Harris, S. E. Harris, H. Lange, A. G. Orpen, and P. N. J. Taylor, *Chem. Soc., Perkin Trans. 1*, 1998, 1643.
 10. V. H. Gessner, S. Dilsky, and C. Strohmann, *Chem. Commun.*, 2010, **46**, 4719.
 11. (a) L. McKinstry and T. Livinghouse, *Tetrahedron Lett.*, 1994, **35**, 9319; (b) L. McKinstry and T. Livinghouse, *Tetrahedron*, 1994, **50**, 6145.
 12. A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, and F. J. Timmers, *Organometallics*, 1996, **15**, 1518.
 13. I. D. Gridnev, Y. Yamanoi, N. Higashi, H. Tsuruta, M. Yasutake, and T. Imamoto, *Adv. Synth. Catal.*, 2001, **343**, 118.