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A new optically active secondary diphosphine—its use for the improved synthesis of (*R*,*R*)-1,2-bis(boranato(*tert*-butyl)methylphosphino)ethane

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Abstract—(*S*,*S*)-1,2-Bis(boranato(*tert*-butyl)phosphino)ethane has been synthesized efficiently and in excellent enantioselectivity. This secondary diphosphine serves as the starting material for an elegant preparation of (*R*,*R*)-1,2-bis(boranato(*tert*-butyl)methylphosphino)ethane, known as (*R*,*R*)-*t*-Bu-BisP*–borane.

Asymmetric catalysis is one of the most elegant ways for conferring chiral information to organic products.[1] However, although effective control of enantioselectivity has been demonstrated for a great number of optically active transition-metal complexes, both counter-enantiomers of the ligands are not always available. Yet, biological and physical functions are generated through precise molecular recognition and matching of chirality. For instance, (*S*,*S*)-1,2-bis(*tert*-butylmethylphosphino)ethane, known as (*S*,*S*)-*t*-Bu-BisP* (**1**),[2] is counted among the most successful ligands in highly selective asymmetric hydrogenation reactions,[3] while (*R*,*R*)-*t*-Bu-BisP* (**2**) is required for the effective introduction of an asymmetric center in the synthesis of some compounds exhibiting biological activity (Fig. 1).[4]

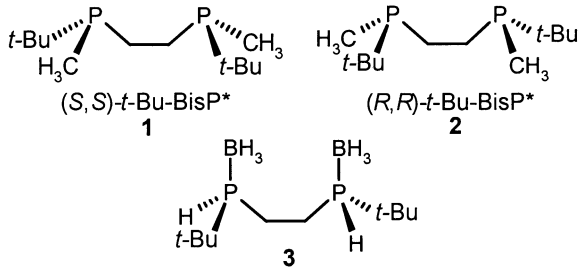

Figure 1.

We demonstrated that the synthesis of (*S*,*S*)-*t*-Bu-BisP* is reasonably easy.[2] The key step consists of the enantiodifferentiating deprotonation of one methyl group of prochiral *tert*-butyl(dimethyl)phosphine–borane using *s*-butyllithium in the presence of (−)-sparteine as the chiral inductor.[5] Unfortunately, the previously reported syntheses of (+)-sparteine are laborious,[6] meaning that it is practically impossible to produce the counter-enantiomer (*R*,*R*)-*t*-Bu-BisP* using the same methodology. Alternative routes suffer from both lengthy steps and a poor overall yield, or inapplicability to a large scale preparation.[7] Therefore, further research was deemed necessary for practical applications of this important enantiomer.

Here we wish to report the synthesis of a new C_2-symmetric, electron-rich, P-chirogenic secondary diphosphine–borane **3**, which constitutes a valuable synthetic intermediate for the construction of various diphosphines, as exemplified by the largely improved synthesis of (*R*,*R*)-*t*-Bu-BisP*.

The synthetic route to the newly designed secondary diphosphine–borane **3** is depicted in Scheme 1. Enantiomerically enriched (*R*)-*tert*-butyl(hydroxymethyl)-methylphosphine–borane (**4**) (91% ee)[8] was subjected to double deprotonation of both alcohol moiety and methyl group using two molar equivalents of *s*-BuLi, followed by copper promoted oxidative coupling reaction,[9] and purification by silica gel column chromatography to afford the desired diphosphine alcohol **5**[10] in isolated yield averaging 50%. Interestingly, this coupling was selective to the carbon–carbon bond formation, without impairment with the oxygen anions. The

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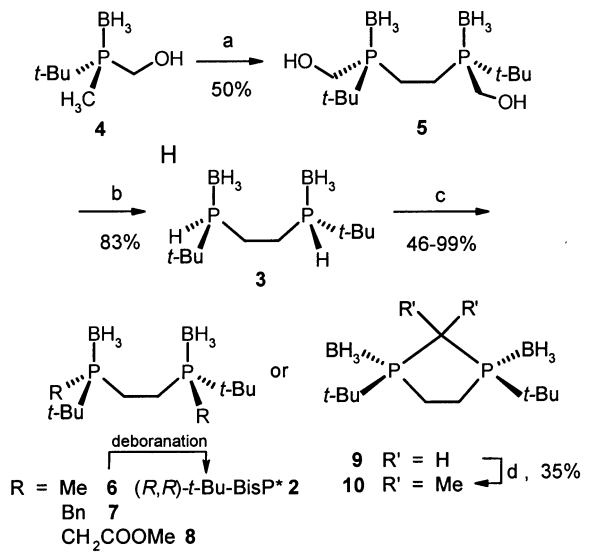

Scheme 1. *Reagents and conditions*: (a) (i) *s*-BuLi, THF, −78°C, 1 h, then −25°C, 4 h, (ii) $CuCl_2$, 2 h, 50%; (b) (i) $K_2S_2O_8$, KOH, H_2O, 0°C, then $RuCl_3 3H_2O$, (ii) **5**, acetone, 0°C, then rt, 2 h, 83%; (c) (i) *n*-BuLi, THF, −78°C, 30 min, (ii) nucleophile, −78°C, 30 min, then rt, 1 h, 46–99% (nucleophiles: MeI, BnCl, $ClCH_2COOMe$, CH_2Cl_2); (d) (i) *s*-BuLi, THF, 0°C, 4 h, (ii) MeI, 0°C to rt, 2 h, 35%.

pure substrate underwent a ruthenium-catalyzed oxidative one-carbon degradation in the presence of potassium persulfate and potassium hydroxide,[8] leading to (*S*,*S*)-1,2-bis(boranato(*tert*-butyl)phosphino)ethane (**3**)[11] in high isolated yield (79–85%), and with excellent optical purity even before recrystallization.[12]

We reasoned that it should be possible to prepare the borane complex of the counter-enantiomer (*R*,*R*)-*t*-Bu-BisP* (**2**) of (*S*,*S*)-*t*-Bu-BisP* (**1**) by treating secondary diphosphine–borane **3** with a small excess of *n*-BuLi at −78°C and MeI (Scheme 1). In less than 2 h, the desired (*R*,*R*)-*t*-Bu-BisP*–borane was produced as a virtually pure white solid in quantitative yield. The chiral HPLC of the crude sample indicated it to contain over 98% of (*R*,*R*)-*t*-Bu-BisP*–borane and a minor amount of (*S*,*S*)-*t*-Bu-BisP*–borane. No trace of *meso*-compound was detected by HPLC or NMR analysis,[13] probably because the oxidative coupling to yield **5** proceeded with enantiomeric enrichment owing to the electronic repulsion of the two alcolates in direct neighborhood in the case of the *meso*-compound. On the other hand, the recrystallized sample was enantiomerically pure (*R*,*R*)-*t*-Bu-BisP*–borane, physical properties of which were in all points identical to the (*S*,*S*)-enantiomer.[14] This new method for the synthesis of (*R*,*R*)-*t*-Bu-BisP* via the new intermediate **3** furnishes an attractive substitution for the other previously reported procedures.[7]

We further reacted the deprotonated secondary diphosphine **3** with two other electrophiles (benzyl bromide and methyl chloroacetate), producing **7**[15] and **8**,[16] respectively, in reasonable to good yields (83 and 46%, respectively). As pictured in Scheme 1, cyclic diphosphine **9**[17] was also successfully synthesized by deprotonation (*n*-BuLi at −78°C) of both acidic hydrogens on the phosphorus atoms and quenching with CH_2Cl_2 at the same temperature.[18] Isolated yields of pure (recrystallized) cyclic diphosphine **9** varied from 35 to 53% depending on the scale and the nature of the electrophile. Further double methylation on the methylene bridge was performed by treating **9** with more than two molar equivalents of *s*-BuLi and excess methyl iodide to afford compound **10** in 35% yield.[19] It is likely that deprotonation of the two hydrogen atoms and subsequent methylations occurred in a two-step mechanism.

The new class of monodentate cyclic diphosphine–boranes **9** and **10** is especially interesting. Their skeleton is attractive because of the rigidity of the five-membered ring formed and the opposite orientation of the lone pair of each phosphorus atoms after deboranation. Cleavage of the P–B bond using HBF_4 followed by treatment with saturated aqueous $NaHCO_3$,[20] was effectively performed, affording monodentate ligands bearing two chelating centers. When complexed with a suitable transition-metal, they are expected to be powerful ligands required for the realization of a high level of enantioselectivity in the type of asymmetric reactions where only one phosphine binding is possible.

In summary, a new optically active secondary diphosphine–borane has been successfully prepared via a short synthesis and in reasonable yield. It constitutes a valuable synthetic precursor, as exemplified by the preparation of (*R*,*R*)-*t*-Bu-BisP* and new cyclic monodentate diphosphines. Not only does this secondary diphosphine–borane serves as a simple key starting material, but also it presents potential catalytic applications on its own. This research is currently pursued in our laboratory, and will be communicated in due course.

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10. (*S*,*S*) - 1,2 - Bis(boranato((*tert* - butyl)hydroxymethyl)phosphino)ethane (**5**): White crystals, mp 136–138°C (EtOAc/hexane 2:7); R_f 0.46 (2:5 EtOAc/hexane); $[\alpha]_D^{27}=+3.6$ (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.47 (br. q, J_{HB} 95.9 Hz, 6 H), 1.21–1.25 (d, $^3J_{HP}$ 13.8 Hz, 18 H), 1.95–2.05 (m, 4 H), 2.29 (br. s, 2 H), 4.09 (s, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.1 (d, J_{CP} 28.7 Hz), 25.8, 28.3 (d, J_{CP} 31.2 Hz), 55.9 (d, J_{CP} 35.3 Hz); IR (KBr): 3480 (br), 2985, 2365, 1465, 1190, 1070, 1050 cm^{-1}; FAB MS (rel. int.): 293 (M^+, 85%), 289 (100), 279 (M^+-BH_3, 60), 223 (M^+-BH_3-t-Bu+H, 13), 154, 136, 57 (*t*-Bu, 90). Anal. calcd for $C_{12}H_{34}B_2O_2P_2$: C, 49.03; H, 11.66. Found: C, 49.16; H, 11.78%.
11. (*S*,*S*)-1,2-Bis(boranato(*tert*-butyl)phosphino)ethane (**3**): White fluffy needles, mp 96–98°C (EtOAc/hexane 1:10); R_f 0.37 (2:5 EtOAc/hexane); $[\alpha]_D^{27}=-82.8$ (*c* 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.61 (br. q, J_{HB} 92.9 Hz, 6 H), 1.25 (d, $^3J_{HP}$ 14.7 Hz, 18 H), 1.88–1.99 (m, 2 H), 2.09–2.15 (m, 2 H), 4.40 (d, J_{HP} 352.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2 (d, J_{CP} 30.3 Hz), 26.7, 27.1 (d, J_{CP} 34.5 Hz); IR (KBr): 2990, 2885, 1460, 1200, 1060 cm^{-1}; FAB MS (rel. int.): 233 (M^+, 75%), 231 (79), 219 (M^+-BH_3, 100), 207, 161, 136, 105, 57 (*t*-Bu, 67). Anal. calcd for $C_{10}H_{30}B_2P_2$: C, 51.35; H, 12.93. Found: C, 51.68; H, 13.08%.
12. HPLC analysis of crude (*R*,*R*)-*t*-Bu-BisP* (**2**) synthesized from **3** before recrystallization revealed 98% ee.
13. The regions corresponding to the methylene groups, ranging from 1.84 to 2.30 ppm (^{1}H NMR) or between 4.46 and 16.10 ppm (^{13}C NMR), are significantly different for the borane complexes of (*S*,*S*)-BisP* and *meso*-BisP*.
14. (*R*,*R*) - 1,2 - Bis(boranato(*tert* - butyl)methylphosphino)-ethane (**6**): White crystals, mp 168–170°C (EtOAc/hexane 2:5); R_f 0.23 (2:5 EtOAc/hexane); $[\alpha]_D^{28}=+8.8$ (*c* 0.99, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.42 (br. q, J_{HB} 88.7 Hz, 6 H), 1.18 (d, $^3J_{HP}$ 13.8 Hz, 18 H), 1.22 (d, $^2J_{HP}$ 9.4 Hz, 6 H), 1.57–1.66 (m, 2 H), 1.97–2.05 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.6 (d, J_{CP} 35.3 Hz), 15.9 (d, J_{CP} 30.3 Hz), 25.1, 27.1 (d, J_{CP} 33.6 Hz); IR (KBr): 2960, 2390, 2345, 1190, 1065 cm^{-1}; FAB MS (rel. int.): 261 (M^+, 89%), 259 (98), 247 (M^+-BH_3, 100), 235 (45), 189 (45), 154 (67), 57 (*t*-Bu, 34). Anal. calcd for $C_{12}H_{34}B_2P_2$: C, 55.02; H, 13.08. Found: C, 55.05; H, 13.15%. ee >99% (Daicel Chiracel OD-H, 0.5 mL/min, 25°C, 10% 2-propanol/hexane, (*R*,*R*) $t_1=10.2$ min (*S*,*S*) $t_2=14.2$ min). As expected, opposite sign of the $[\alpha]_D$ of (*S*,*S*)-*t*-Bu-BisP* was observed.
15. (*R*,*R*) - 1,2 - Bis(boranato(*tert* - butyl)benzylphosphino)-ethane (**7**): White needles, mp 142–143°C (EtOAc/hexane 1:9); R_f 0.53 (2:5 EtOAc/hexane); $[\alpha]_D^{22}=-31.7$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.42 (br. q, J_{HB} 53.1 Hz, 6 H), 1.08 (d, $^3J_{HP}$ 13.5 Hz, 18 H), 1.67–1.75 (m, 2 H), 2.78–2.95 (m, 4 H), 7.19–7.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14 (d, J_{CP} 29.5 Hz), 25.4, 28.7 (d, J_{CP} 27.1 Hz), 29 (d, J_{CP} 31.1 Hz), 127.1, 128.5, 130.1, 132.9; IR (KBr): 3040, 2980, 2360, 1500, 1460, 1370, 1060 cm^{-1}. HRMS (FAB) calcd for $C_{24}H_{42}B_2P_2$: 414.16. Found: 414.2952.
16. (*R*,*R*) - 1,2 - Bis(boranato(*tert* - butyl)(methylacetate)phosphino)ethane (**8**): White solid, mp 116–118°C (EtOAc/hexane 1:9); R_f 0.14 (2:5 EtOAc/hexane); $[\alpha]_D^{23}=+30.5$ (*c* 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.40 (br. q, J_{HB} 78.8 Hz, 6 H), 1.20–1.26 (m, 18 H), 1.99–2.08 (m, 2 H), 2.23–2.32 (m, 2 H), 2.78–2.79 (m, 4 H), 3.75 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (d, J_{CP} 28.7 Hz), 25.4, 27.7 (d, J_{CP} 21.3 Hz), 29.2 (d, J_{CP} 31.1 Hz), 52.5, 168.4–168.5 (m); IR (KBr): 2980, 2400, 1740, 1470, 1430, 1280, 1200, 1120 cm^{-1}. HRMS (FAB) calcd for $C_{16}H_{38}B_2P_2O_4$: 378.05. Found: 378.2271.
17. Compound **9**: White solid, mp 153–155°C (EtOAc/hexane 1:8); R_f 0.60 (2:5 EtOAc/hexane); $[\alpha]_D^{22}=-0.8$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.50 (br. q, J_{HB} 87 Hz, 6 H), 1.25 (d, $^3J_{HP}$ 14.7 Hz, 18 H), 1.82–1.87 (m, 2 H), 2.04–2.19 (m, 2 H), 2.28–2.32 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.71 (m), 18.68 (d, J_{CP} 32.8 Hz), 25.51, 28.35 (d, J_{CP} 28.7 Hz); IR (KBr): 2980, 2840, 2380, 1460, 1370, 1200, 1060 cm^{-1}. Anal. calcd for $C_{11}H_{30}B_2P_2$: C, 53.72; H, 12.30. Found: C, 53.71; H, 12.29%.
18. Compound **10**: White solid, mp 155–158°C (EtOAc/hexane 1:8); R_f 0.58 (2:5 EtOAc/hexane); $[\alpha]_D^{22}=-9.2$ (*c* 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.50 (br. q, J_{HB} 90 Hz, 6 H), 1.35 (d, $^3J_{HP}$ 14.3 Hz, 18 H), 1.72–1.81 (m, 6 H), 1.98–2.15 (m, 2 H), 2.32–2.38 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.93 (d, J_{CP} 35.3 Hz), 27.00, 27.46, 32.45 (d, J_{CP} 22.2 Hz), 32.49 (d, J_{CP} 22.2 Hz), 32.82–33.04 (m); IR (KBr): 2980, 2490, 2260, 1470, 1300, 1060 cm^{-1}. Anal. calcd for $C_{13}H_{34}B_2P_2$: C, 56.99; H, 12.51%. Found: C, 57.17; H, 12.67%. HRMS (FAB) calcd for $C_{13}H_{34}B_2P_2K$: 313.08. Found: 313.1965.
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