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Improved synthetic routes to methylene-bridged *P*-chiral diphosphine ligands via secondary phosphine–boranes

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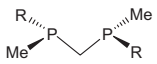
Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

Improved methods for the preparation of methylene-bridged diphosphine ligands are described. Both enantiomers of the key intermediate *tert*-butylmethylphosphine–borane were prepared via resolution or by the conversion of one enantiomer into the opposite enantiomer. The precursor borane complexes of bis(*tert*-butylmethylphosphino)methane (*t*-Bu-MiniPHOS), bis((1,1,3,3-tetramethylbutyl)methylphosphino)methane (*t*-Oct-MiniPHOS), and (*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)methane (trichickenfootphos) were prepared in good yields and enantiopure form.

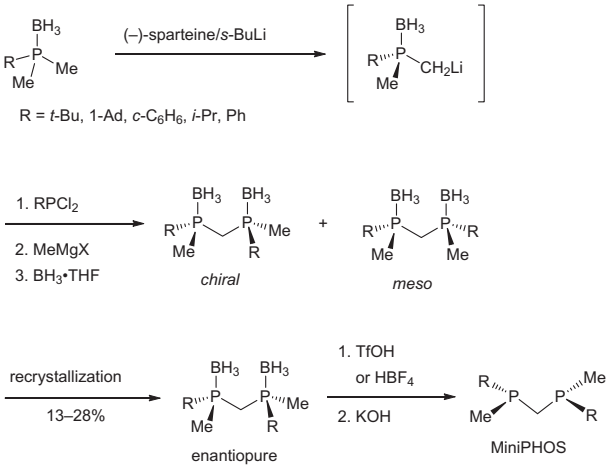
1. Introduction

Among the numerous chiral phosphine ligands reported so far,[1] *P*-stereogenic bis(alkylmethylphosphino)methanes (MiniPHOS) are known to have unique stereochemical properties. They are a class of electron-rich diphosphines and their low-valent transition-metal complexes are more susceptible to oxidative addition than the corresponding complexes that have ligands possessing diarylphosphino groups. In addition, they are methylene-bridged diphosphines and would form rigid four-membered metal complexes. In fact, we have previously synthesized four-membered chelates by reaction with $[Rh(nbd)_2]X$ (X = BF_4, PF_6).[2] Among the several known MiniPHOS ligands, (*R*,*R*)-bis(*tert*-butylmethylphosphino)methane ((*R*,*R*)-*t*-Bu-MiniPHOS) has proven to be the most useful chiral ligand not only in the Rh-catalyzed asymmetric hydrogenation[2,3] but also in other asymmetric catalyses, such as the hydrosilylation of simple ketones,[2a,4] the conjugate addition of dialkylzinc reagents to α,β-enones,[2a,5] and the ring-opening reaction of azabenzonorbornadienes.[6]



MiniPHOS

The ligand (*R*,*R*)-*t*-Bu-MiniPHOS and its analogues can be prepared from alkyl(dimethyl)phosphine–borane via a short synthetic route (Scheme 1).[2] This method, however, involves the formation of considerable amounts of *meso* compounds and eventually affords the desired enantiopure MiniPHOS precursors in low yields (13–28%). Another problem of this method is that it uses (−)-sparteine as the chiral source which only gives the (*R*,*R*)-enantiomer ligands, and the opposite enantiomer (*S*,*S*)-ligands cannot be synthesized by the same methodology because of the practical unavailability of (+)-sparteine.[7] These drawbacks in the synthesis have hampered their widespread application in asymmetric catalyses and thus, it is strongly desired that an efficient method for the synthesis of this class of chiral ligands, including both enantiomers, be developed.



Scheme 1. Previously reported synthetic route to MiniPHOS ligands.

Recently, O'Brien et al. reported a synthetic route from *tert*-butyldimethylphosphine sulfide to (*S*,*S*)-*t*-Bu-MiniPHOS.[8] Their

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method uses (−)-sparteine as the chiral source and involves (*S*)-*tert*-butyl(methyl)(trimethylsilylmethyl)phosphine sulfide as the key intermediate; the protocol is also applicable to the synthesis of analogous *P*-chiral phosphine ligands. On the other hand, Jackson and Lennon prepared a methylene-bridged analogue (*R*,*R*)-1,2-bis(2,5-diphenylphospholano)methane from a secondary phosphine–borane (*R*,*R*)-2,5-diphenylphospholane–borane.[9]

We attempted to develop efficient procedures for the synthesis of both enantiomers of *t*-Bu-MiniPHOS and related compounds. Herein, we report our synthetic approach to these compounds together with the preparation of a precursor of (*S*)-(*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)methane (trichickenfootphos)[10] which was developed by Hoge and co-workers.

2. Results and discussion

2.1. Preparation of the precursor of (*R*,*R*)-bis(*tert*-butylmethylphosphino)methane [(*R*,*R*)-*t*-Bu-MiniPHOS]

In our previous study, optically active *tert*-butyl(hydroxymethyl)methylphosphine–borane **2** was obtained in good yield by the enantioselective deprotonation of *tert*-butyl(dimethyl)phosphine–borane **1** with the (−)-sparteine/*s*-BuLi reagent, followed by the oxidation with molecular oxygen.[11] We found also that compound (*R*)-**2** was subjected to stereospecific, oxidative one-carbon degradation on treatment with $K_2S_2O_8$ in the presence of $RuCl_3$ as a catalyst to afford secondary phosphine–borane (*S*)-**3** in high yield.[11] It was also observed that the phosphido anions derived from chiral secondary phosphine–boranes exhibited strong nucleophilicity during substitution reaction with alkyl halides while keeping the stereochemical integrity at the *P*-stereogenic center.[12] Based on these facts, we envisioned that the reaction of compound (*S*)-**3** with a sulfonate derivative of compound (*R*)-**2** would yield the precursor of (*R*,*R*)-*t*-Bu-MiniPHOS (Scheme 2).

In order to realize this idea, compound (*R*)-**2** with 92% ee was converted into its benzoyl derivative, and this derivative was recrystallized from hexane/ethyl acetate (20:1).[13] The resulting enantiopure compound was returned to (*R*)-**2** by hydrolysis and this was converted into (*S*)-**3** and (*R*)-**4**. Compound (*S*)-**3** was treated with *n*-BuLi and the subsequent reaction with (*R*)-**4** afforded MiniPHOS precursor (*R*,*R*)-**5** in 62% yield.

One of the features of this method is that the desired compound was obtained in good yield without the formation of a *meso*-isomer. Another feature is that the two chiral components (*S*)-**3** and (*R*)-**4** were prepared from the same intermediate (*R*)-**2**. These results suggest that similar diphosphine ligands, including unsymmetric ones, can be prepared by this methodology.

2.2. Preparation of both enantiomers of *tert*-butylmethylphosphine–borane

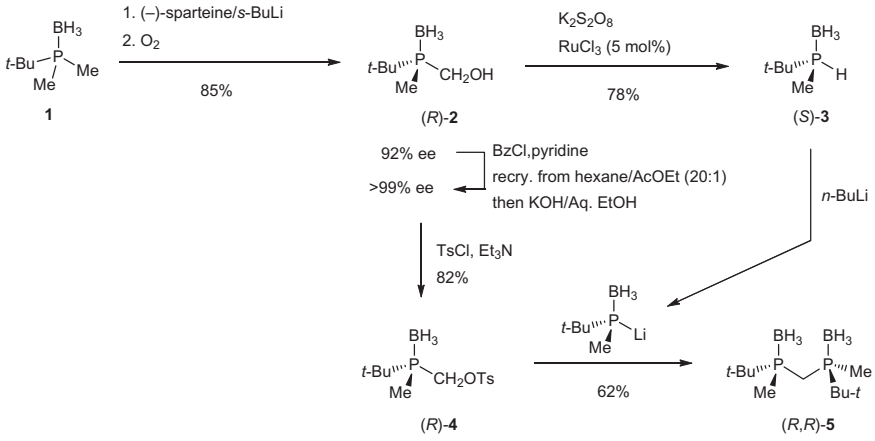
Our main aim in this study was to establish a procedure for the large-scale preparation of both enantiomers of *t*-Bu-MiniPHOS. Our first approach was to employ resolution.[14] In this regard, *tert*-butylphosphine–borane **6** was methylated and the resulting racemic compound **3** was converted into a mixture of diastereomers **7** with a bornyl group. Fractional recrystallization of **7** provided (*R*)-**7** with 95% de and (*S*)-**7** with 52% de. Compound (*R*)-**7** was hydrolyzed to give (*S*)-**3** without any decease in enantiomeric purity and (*S*)-**3** was further converted into (*R*)-**2** upon treatment with paraformaldehyde in the presence of NaH in THF (Scheme 3). This approach was effective for the preparation of one enantiomer (*S*)-**3**, but was not suitable for the preparation of enantiomer (*R*)-**3** with high ee.

An alternative route is shown in Scheme 4. Racemic secondary phosphine–borane **3** was reacted with (*S*)-α-methylbenzylisocyanate to give a mixture of two diastereomers (*S*)-**8** and (*R*)-**8**. Recrystallization from a mixed solvent of hexane and ethyl acetate afforded one diastereomer (*S*)-**8** with 97% de in 37% yield. Subsequent removal of the chiral auxiliary by treatment with KOH in MeOH/DMF led to (*R*)-**3** in 73% yield. The ee of this product was found to be 86% to indicate that partial racemization had occurred under the reaction conditions.

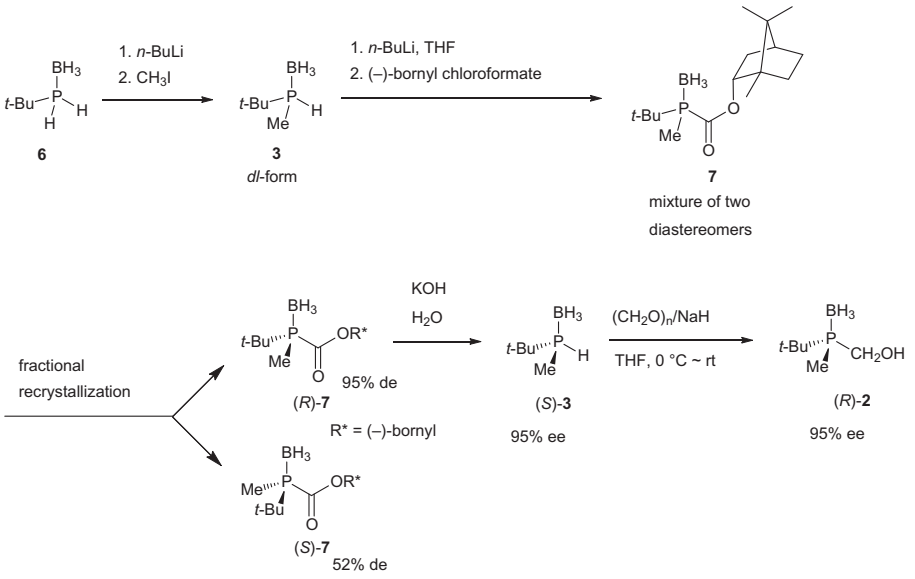
It should be noted that the two methods mentioned above can be employed for the large-scale preparation of both enantiomers (*S*)-**3** and (*R*)-**3**. These enantiomers can be used for the production of not only MiniPHOS ligands but also other *P*-chiral phosphine ligands. In fact, they have been used for the kilogram-scale production of both enantiomers of 2,3-bis(*tert*-butylmethylphosphino)-quinoxaline (QuinoxP*).[15]

2.3. Conversion of (*S*)-*tert*-butylmethylphosphine–borane into the opposite enantiomer

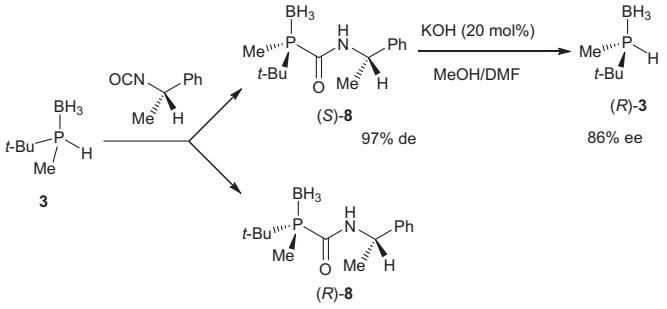
Previously, we studied nucleophilic substitution reactions occurring at the *P*-stereogenic center, using in situ generated (*R*)-bromo(*tert*-butyl)methylphosphine–borane.[16] A notable fact found in that study is that alkynyllithium reagents reacted smoothly to give the substitution products in high yields and almost exclusively with inversion of configuration. The results led us to envisage that the use of hydride reagents, such as $LiAlH_4$, would give the inversion product, and hence this reaction would become an interconversion process between one enantiomer of a secondary phosphine–borane and its opposite isomer.



Scheme 2. Preparation of the precursor of *t*-Bu-MiniPHOS.

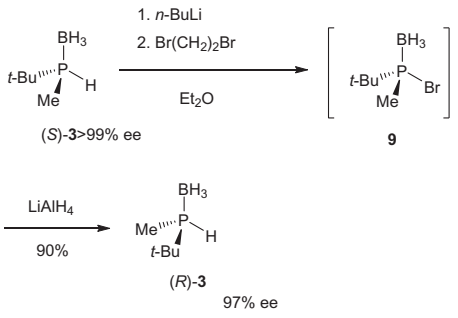


Scheme 3. Preparation of compounds (*S*)-**3** and (*R*)-**2** via resolution.



Scheme 4. Preparation of (*R*)-*tert*-butylmethylphosphine–borane via resolution.

The transformation was simple: secondary phosphine–borane (*S*)-**3** with >99% ee was reacted successively with *n*-BuLi and 1,2-dibromoethane to generate intermediate **9** at −80 °C through −40 °C. The addition of $LiAlH_4$ to the mixture, followed by warming to 0 °C, afforded the counter enantiomer (*R*)-**3** with 97% ee in 90% yield (Scheme 5). In this transformation, the solvent choice was important; the use of THF in place of diethyl ether resulted in very low product yields. Replacing the hydride reagent $LiAlH_4$ with $NaBH_4$ resulted in no trace of the desired compound.



Scheme 5. Conversion of (*S*)-*tert*-butylmethylphosphine–borane to the opposite enantiomer.

2.4. Preparation of borane complex of (*S*)-(*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)methane

Different from many chiral C_2-symmetric diphosphine ligands, (*S*)-(*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)methane (trichickenfootphos) is unique, because it is C_1-symmetric and its four-membered rhodium complex forms three hindered quadrants. Most notable is that the rhodium complex exhibits extremely high catalytic activity and almost perfect enantioselectivity in the asymmetric hydrogenation of dehydroamino acids and related compounds.[10] Therefore, these features make the asymmetric hydrogenation reaction a potentially useful tool for the industrial production of a pharmaceutically important chiral compound.

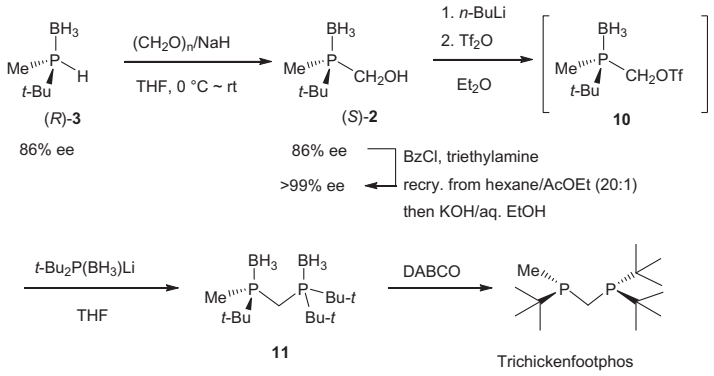
This ligand was previously prepared via chiral preparative HPLC.[10a] We attempted to prepare this important chiral ligand from optically active *tert*-butylmethylphosphine–borane with a view to large-scale production. Our initial trial was conducted with (*R*)-**3** (86% ee) prepared by the method shown in Scheme 4.

The reaction pathway to the precursor of trichickenfootphos is shown in Scheme 6. Compound (*R*)-**3** was converted into (*S*)-**2** and after increasing the ee to >99%, it was reacted successively with *n*-BuLi and trifluoromethanesulfonic anhydride to generate triflate **10**. Subsequent reaction with the lithio derivative of di-*tert*-butylphosphine–borane provided **11** in a synthetically acceptable yield. It is worthy of note that the isolated tosylate or mesylate of compound (*S*)-**2** reacted sluggishly with the bulky nucleophile to give **11** in very low yields. Attempts to isolate triflate intermediate **10** in the pure form were unsuccessful because it was unstable and decomposed during chromatography on silica gel.

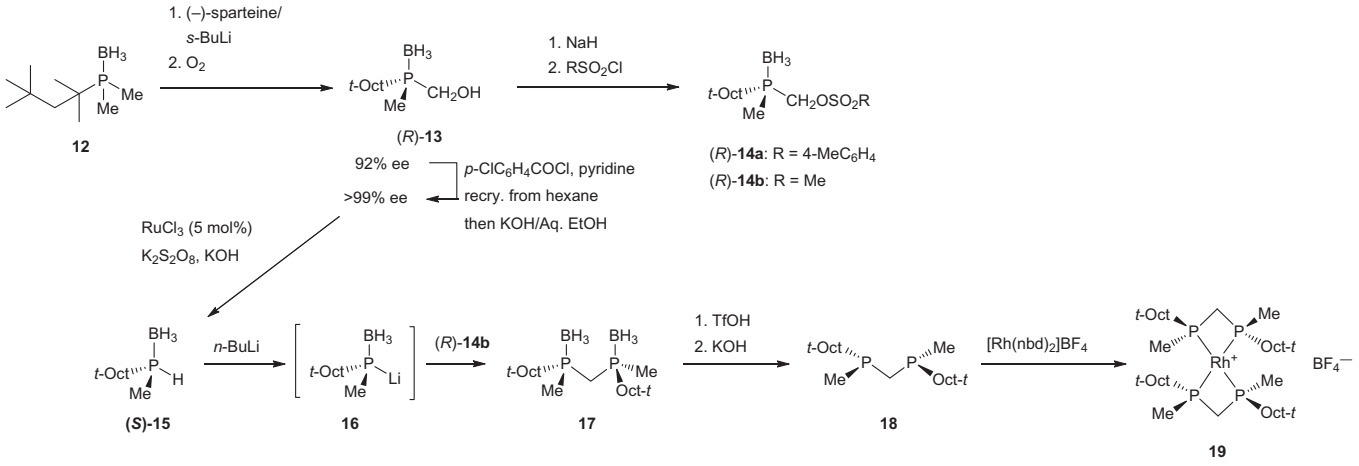
This procedure employing the in situ generation of **10** yielded many by-products; nevertheless, compound **11** was crystallized from the reaction mixture. Overall, this process utilizes no chromatography and hence is suitable for large-scale production.

2.5. Preparation of (*R*,*R*)-bis(methyl(1,1,3,3-tetramethylbutyl) phosphino)methane [(*R*,*R*)-*t*-Oct-MiniPHOS]

Based on the experimental results mentioned above, we tried to prepare a new MiniPHOS ligand possessing *tert*-octyl groups. Scheme 7 shows the transformation from starting phosphine–borane **12** to target compound **18** and its rhodium complex **19**. The conversion of **12** into (*R*)-**13** was carried out in the usual manner,



Scheme 6. Preparation of borane adduct of (*S*)-(*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)methane.



Scheme 7. Synthesis of (*R*,*R*)-*t*-Oct-MiniPHOS and its rhodium complex.

but without the addition of triethylphosphite.[11] To increase the ee of the resulting compound, its benzoyl derivative was prepared but the product was a pasty oil and did not crystallize. Therefore, we prepared the *p*-chlorobenzoyl derivative. Recrystallization of the derivative from hexane increased the ee from 92% to >99%, and this derivative was converted into (*R*)-**13** by hydrolysis. This compound was transformed into tosyl and mesyl derivatives (*R*)-**14a** and (*R*)-**14b** and secondary phosphine–borane (*S*)-**15**. The coupling reaction of lithio derivative **16** with tosyl derivative (*R*)-**14a** resulted in only a trace amount of **17**, probably because of the steric hindrance by the bulky tosyl group. In contrast, use of the mesyl derivative provided the product, although the yield was moderate. Compound **17** was subjected to borane deprotection to give desired (*R*,*R*)-*t*-Oct-MiniPHOS **18**. As this ligand was sensitive upon exposure to air, it was immediately converted into rhodium complex **19**. The enantioinduction ability of this complex was tested by probing of the Rh-catalyzed asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate (s/c = 100) in methanol under 2 atm of hydrogen pressure for 12 h to give 99.4% ee of the hydrogenation product in quantitative yield.

3. Conclusion

Improved synthetic routes to *P*-chiral methylene-bridged diphosphine ligands are presented. These procedures involve the nucleophilic reactions of the secondary phosphine–boranes with sulfonate derivatives to give the desired compounds without the formation of *meso*-isomers. Both enantiomers of key intermediate *tert*-butylmethylphosphine–borane could be synthesized on a large-scale and hence this methodology is applicable to the industrial production of *t*-Bu-MiniPHOS and related compounds.

4. Experimental

4.1. General methods

All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or glove box techniques under prepurified argon. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500.00 MHz for ^{1}H, 125.65 MHz for ^{13}C, and 202.35 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal standard [tetramethylsilane for ^{1}H NMR, chloroform-*d* (δ 77.0) for ^{13}C NMR, and phosphoric acid for ^{31}P NMR]. Mass spectra were recorded on a JEOL JMS-HX110 and a JEOL LC-AccuTOF. Melting points were determined with a YANACO Micro Melting Point Apparatus. HPLC analysis was performed using a Shimadzu LC-10AD VP pump, an SPD-10A VP UV detector, and a Shimadzu CTO-10AC VP column oven. Anhydrous THF, Et_2O, and *tert*-butyl methyl ether (MTBE) were purchased from Kanto Chemical and used as received.

4.2. Preparation of precursor of (*R*,*R*)-bis(*tert*-butylmethylphosphino)methane ((*R*,*R*)-*t*-Bu-MiniPHOS) (*R*,*R*)-5

To a solution of (*S*)-**3** (302 mg, 256 mmol) in THF (8 mL) was added *n*-BuLi (1.73 mL of 1.55 M/L hexane solution, 2.68 mmol)

with stirring at 0 °C under argon. After 15 min, tosyl derivative (*R*)-**4** (775 mg, 2.56 mmol) was added and the mixture was stirred at 60 °C for 2 h. The reaction was quenched with 1 M HCl and the mixture was extracted with ethyl acetate three times. The combined extracts were washed with saturated $NaHCO_3$ solution and brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residual solid was recrystallized from methanol to afford (*R*,*R*)-**5** (394 mg, 62%). The spectral data of this product were consistent with those of the authentic sample.

4.3. (*S*$_P$,*S*)-*tert*-Butyl(methyl)(1-phenylethylcarbamoyl) phosphine–borane (*S*)-8

An oven-dried, four-necked, 4-L, round-bottomed flask was equipped with a mechanical stirrer, a nitrogen inlet, a pressure-equalizing dropping funnel, and a thermometer. The flask was flushed with nitrogen and charged with racemic *tert*-butylmethylphosphine–borane (141.8 g, 1.202 mol) and THF (600 mL). The resulting solution was cooled in an ice bath and *n*-BuLi (75 mL of 1.59 M/L hexane solution, 0.12 mol) was added dropwise while keeping the temperature below 10 °C. To the solution was slowly added (*S*)-α-methylbenzylisocyanate (176.8 g, 1.201 mol), and stirring was continued for 12 h at room temperature. The reaction was quenched by adding 5% HCl (90 g) and the mixture was well stirred with hexane (240 mL) and water (240 mL). The organic layer was separated, washed with 2.5% $NaHCO_3$ solution and water, and evaporated under reduced pressure. The residual solid was recrystallized from a mixed solvent of ethyl acetate (240 mL) and hexane (1800 mL) to give a white powder (118.6 g, 0.447 mol, 37%). The diastereomeric excess of this product was determined to be 97% by ^{1}H NMR analysis. Mp 114–116 °C; $[\alpha]_D^{25} = -46.7$ (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.5–1.0 (br q, 3H), 1.14 (d, *J* = 14.7 Hz, 9H), 1.45 (d, *J* = 10.5 Hz, 3H), 1.53 (d, *J* = 6.9 Hz, 3H), 5.15 (dt, *J* = 6.9 Hz, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 3.4 (d), 21.7, 25.3, 28.6 (d), 49.6 (d), 126.0, 127.6, 128.8, 142.2, 167.5 (d); ^{31}P NMR ($CDCl_3$) δ 33.6 (s). HRMS (TOF): calcd for $C_{14}H_{22}NNaOP$ ($M-BH_3+Na^+$): 274.1337; found: 274.1342.

4.4. Preparation of (*R*)-*tert*-butylmethylphosphine–borane (*R*)-3 from (*S*$_P$,*S*)-*tert*-butyl(methyl)((1-phenylethyl)carbamoyl) phosphine–borane (*S*)-8

A solution of (*S*$_P$,*S*)-*tert*-butyl(methyl)(1-phenylethylcarbamoyl)phosphine–borane (7.97 g, 30.1 mmol) in DMF (30 mL) was cooled in an ice bath, and to this solution was added 10% KOH methanol solution (3.4 g, 6.0 mmol, 0.2 equiv). The ice bath was removed and stirring was continued at room temperature for 12 h. The flask was again immersed in an ice bath and hexane (30 mL), water (60 mL), and 5% HCl (3.8 g, 6.0 mmol) were added successively. The organic layer was separated and the aqueous layer was extracted with hexane five times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure (17 mmHg) at 25–30 °C. The residue was purified by column chromatography on silica gel using hexane/*tert*-butyl methyl ether (100:3) as the eluent to give (*R*)-*tert*-butylmethylphosphine–borane (2.57 g, 73%, 86% ee[17]).

4.5. Conversion of (*S*)-*tert*-butylmethylphosphine–borane (*S*)-3 into the opposite enantiomer (*R*)-3

A solution of (*S*)-*tert*-butylmethylphosphine–borane (*S*)-**3** (590 mg, 5 mmol) in diethyl ether (15 mL) was cooled to −80 °C under argon and *n*-BuLi (3.8 mL of 1.57 M/L hexane solution, 6 mmol) was added with stirring. The temperature was maintained for 30 min, and then 1,2-dibromoethane (0.69 mL, 8 mmol) was added to the suspension. The temperature was gradually increased to −40 °C and maintained for an additional 1 h. After the complete consumption of the starting material as monitored by thin layer chromatography on silica gel (hexane/ethyl acetate = 10:3), $LiAlH_4$ (340 mg, 10 mmol) was added portionwise to the mixture and the temperature was gradually elevated to 0 °C. The reaction mixture was carefully transferred into saturated aq NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with diethyl ether three times. The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was removed at 25–30 °C under reduced pressure (17 mmHg) to give (*R*)-*tert*-butylmethylphosphine–borane (*R*)-**3** (530 mg, 90%, 97% ee).[17]

4.6. Preparation of the precursor of (*S*)-(*tert*-butylmethylphosphino)(di-*tert*-butylphosphino)methane (trichickenfootphos)

To a solution of (*S*)-*tert*-butyl(hydroxymethyl)methylphosphine–borane (1.76 g, 6 mmol) in diethyl ether (12 mL) was slowly added *n*-BuLi (4.0 mL of 1.5 M/L hexane solution, 6.0 mmol) cooled to −80 °C under argon. After 15 min, trifluoromethanesulfonic anhydride (1.00 mL, 6 mmol) was added to the milky suspension via a syringe over 15 min with vigorous stirring. The temperature was gradually increased to −40 °C and to the mixture was added a solution of the lithium derivative of di-*tert*-butylphosphine–borane prepared by the metalation of the secondary phosphine–borane (0.97 g, 6 mmol) in THF (12 mL) with *n*-BuLi (4.0 mL of 1.5 M/L hexane solution, 6.0 mmol) at 0 °C under argon. The mixture was gradually warmed to room temperature, and then water and ethyl acetate were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure at a temperature below 30 °C. The residual pasty oil was triturated with hexane to form a crystalline solid, which was collected by filtration and washed with hexane. Yield: 0.98 g, 56%. Further purification by dissolving the product in the minimum amount of ethyl acetate at room temperature and diluting with hexane afforded colorless crystals.

4.7. (*R*)-Hydroxymethyl(methyl)(1,1,3,3-tetramethylbutyl) phosphine–borane (*R*)-13

To a stirred and cooled (−78 °C) solution of (−)-sparteine (7.6 mL, 33 mmol) in Et_2O (30 mL) was added *s*-BuLi (33 mL of 1.0 M solution in cyclohexane and *n*-hexane solution, 33 mmol) under nitrogen atmosphere. After 30 min, a solution of dimethyl(1,1,3,3-tetramethylbutyl)phosphine–borane **12**[18] (5.64 g, 30 mmol) in Et_2O (30 mL) was added dropwise and the reaction mixture was stirred at the same temperature for 3 h and then gradually warmed to −40 °C. After 1 h, oxygen gas was blown through the solution with vigorous stirring and stirring was continued for an additional 1 h. Then, the reaction solution was stirred at 0 °C for 1 h and warmed at ambient temperature. After 1 h, the reaction was quenched by the addition of 1 M HCl. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2) to give (*R*)-hydroxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-**13** (5.24 g, 84% yield, 92% ee) as a white solid; mp 67–68 °C; $[\alpha]_D^{25} = -7.5$ (*c* 1.0, $CHCl_3$) >99% ee; ^{1}H NMR ($CDCl_3$) δ 0.12–0.68 (br m, 3H), 1.05 (s, 9H), 1.25 (d, *J* = 9.9 Hz, 3H), 1.35 (d, *J* = 16.1 Hz, 6H), 1.55 (dd, *J* = 7.7, 2.0 Hz, 2H), 2.04 (m, 1H), 3.92 (ddd, *J* = 13.1, 7.0, 3.0 Hz, 1H), 4.06 (dd, *J* = 12.9, 5.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 2.94 (d, *J* = 34.2 Hz), 22.79, 22.85, 32.04, 32.19 (d, *J* = 29.2 Hz), 33.38 (d, *J* = 8.1 Hz), 47.34, 56.75 (d, *J* = 36.3 Hz). ^{31}P

NMR ($CDCl_3$) δ 33.54 (m). MS (FAB) m/z 201(M^+-3H), 191 (M^+-BH_3+H). HRMS (TOF): calcd for $C_{10}H_{26}BNaOP$ ($M+Na^+$): 227.1712; found: 227.1717.

4.8. (*R*)-*p*-Chlorobenzoylmethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane

To a stirred solution of (*R*)-hydroxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-**13** (2.04 g, 10 mmol, 92% ee) and triethylamine (3.34 mL, 24 mmol) in THF (20 mL) was added dropwise *p*-chlorobenzoyl chloride (1.54 mL, 12 mmol) at 0 °C. After stirring at room temperature for 2 h, the reaction was quenched by the addition of H_2O. The mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The solvent was evaporated under reduced pressure and the residual solid was recrystallized from hexane to give optically pure (*R*)-*p*-chlorobenzoylmethyl(methyl) (1,1,3,3-tetramethylbutyl)phosphine–borane (2.15 g, 63% yield, >99% ee) as colorless crystals; mp 91–92 °C; $[\alpha]_D^{25} = -9.7$ (>99% ee, *c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.21–0.75 (br m, 3H), 1.05 (s, 9H), 1.36 (d, *J* = 9.6 Hz, 3H), 1.41 (dd, *J* = 16.3, 3.0 Hz, 6H), 1.63 (ddd, *J* = 31.9, 14.1, 7.8 Hz, 2H), 4.70 (dd, *J* = 15.8, 1.0 Hz, 1H), 4.77 (dd, *J* = 14.0, 2.3 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 3.44 (d, *J* = 33.2 Hz), 22.84, 22.86, 32.03, 32.71 (d, *J* = 28.7 Hz), 33.41 (d, *J* = 13.3 Hz), 47.43, 57.96 (d, *J* = 35.5 Hz), 127.46, 129.01, 131.11, 140.18, 165.02 (d, *J* = 4.0 Hz). ^{31}P NMR ($CDCl_3$) δ 34.62 (m). MS (FAB) m/z 341 (M^+-H), 329 (M^+-BH_3+H). HRMS (TOF): $C_{17}H_{29}BClNaO_2P$ ($M+Na^+$): 365.1584; found: 365.1610. The enantiomeric excess was determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralcel AD–H); hexane/*i*-PrOH = 99:1, flow rate = 1.0 mL/min, wavelength = 254 nm, t_1 = 7.4 min (major), t_2 = 8.6 min.

This product was converted into (*R*)-hydroxymethyl(methyl) (1,1,3,3-tetramethylbutyl)phosphine-borane (*R*)-**13** on treatment with 5 M aq KOH solution.

4.9. (*R*)-*p*-Toluenesulfonyloxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-14a

To a stirred and cooled (0 °C) mixture of sodium hydride (48 mg, 2.0 mmol) and (*R*)-hydroxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-**13** (204 mg, 1.0 mmol) was added THF (4 mL) under nitrogen atmosphere, and the mixture was stirred for 30 min at the same temperature. Toluenesulfonyl chloride (380 mg, 2.0 mmol) was added and the reaction mixture was stirred for 30 min and then gradually warmed to room temperature. After 2 h, the reaction was quenched by the addition of H_2O. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate = 7:1) to give (*R*)-*p*-toluenesulfonyloxymethyl(methyl) (1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-**14a** (324 mg, 90% yield) as a clear oil; $[\alpha]_D^{25} = -8.3$ (*c* 1.0, $CHCl_3$) >99% ee; ^{1}H NMR ($CDCl_3$) δ 0.00–0.56 (br m, 3H), 1.01 (s, 9H), 1.30–1.34 (m, 9H), 1.41 (dd, *J* = 14.3, 7.4 Hz, 1H), 1.58 (dd, *J* = 14.3, 8.8 Hz, 1H), 2.47 (s, 3H), 4.14 (dd, *J* = 13.0, 1.6 Hz, 1H), 4.42 (dd, *J* = 13.0, 1.7 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 2.45 (d, *J* = 34.5 Hz), 21.50, 22.62, 22.82, 31.78, 32.76 (d, *J* = 28.9 Hz), 33.17 (d, *J* = 13.9 Hz), 46.83 (d, *J* = 2.3 Hz), 62.59 (d, *J* = 26.7 Hz), 127.95, 130.03, 131.23, 145.60. ^{31}P NMR ($CDCl_3$) δ 34.31 (m). MS (FAB) m/z 357 (M^+-H), 345 (M^+-BH_3+H).

4.10. (*R*)-Methanesulfonyloxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-14b

To a stirred and cooled (0 °C) mixture of sodium hydride (72 mg, 3.0 mmol) and (*R*)-hydroxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-**13** (306 mg, 1.5 mmol) was added THF (4 mL) under nitrogen atmosphere, and stirring was continued for 30 min at the same temperature. Methanesulfonyl chloride (0.23 mL, 3.0 mmol) was added and the temperature was gradually increased to room temperature. After 2 h, the reaction was quenched by the addition of H_2O. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (CH_2Cl_2/hexane = 20:1) to give (*R*)-methanesulfonyloxymethyl(methyl) (1,1,3,3-tetramethylbutyl)phosphine–borane (*R*)-**14b** (350 mg, 83% yield) as a clear oil; $[\alpha]_D^{25} = -14.3$ (*c* 1.0, $CHCl_3$) >99% ee; ^{1}H NMR ($CDCl_3$) δ 0.13–0.66 (br m, 3H), 1.06 (s, 9H), 1.37–1.40 (m, 9H), 1.54 (dd, *J* = 14.2, 7.8 Hz, 1H), 1.62 (dd, *J* = 14.2, 8.5 Hz, 1H), 3.10 (s, 3H), 4.44 (dd, *J* = 13.0, 1.8 Hz, 1H), 4.63 (dd, *J* = 13.0, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 2.73 (m), 3.00 (m), 22.82, 22.88, 32.01, 32.94 (d, *J* = 29.5 Hz), 33.42 (d, *J* = 13.1 Hz), 37.38, 47.11 (m), 62.31 (d, *J* = 29.2 Hz). ^{31}P NMR ($CDCl_3$) δ 34.82 (m). MS (FAB) m/z 281 (M^+-H), 269 (M^+-BH_3+H). HRMS (TOF): calcd for $C_{11}H_{28}BNaO_3PS$ ($M+Na^+$): 305.1488; found: 305.1524.

4.11. (*S*)-Methyl(1,1,3,3-tetramethylbutyl)phosphine–borane (*S*)-15

To a stirred solution of (*R*)-hydroxymethyl(methyl)(1,1,3,3-tetramethylbutyl)phosphine-borane (*R*)-**13** (582 mg, 2.85 mmol) in acetone (5 mL) was added a solution of potassium hydroxide (1.68 g, 30 mmol) and potassium persulfate (2.31 g, 8.55 mmol) in water (6 mL). Ruthenium trichloride trihydrate (40 mg, 0.14 mmol) was added to the solution with vigorous stirring at 0 °C. After stirring at room temperature for 2 h, the reaction was quenched by the addition of 1 M HCl. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (hexane/ethyl acetate = 5:1) to give (*S*)-methyl(1,1,3,3-tetramethylbutyl)phosphine–borane (*S*)-**15** (370 mg, 75% yield) as a clear oil; $[\alpha]_D^{25} = +4.7$ (*c* 1.0, $CHCl_3$) >99% ee; ^{1}H NMR ($CDCl_3$) δ 0.21–0.77 (br m, 3H), 1.05 (s, 9H), 1.30 (dd, *J* = 10.6, 6.0 Hz, 3H), 1.34 (dd, *J* = 16.5, 7.2 Hz, 6H), 1.49 (dd, *J* = 14.5, 11.5 Hz, 1H), 1.63 (dd, *J* = 14.5, 9.7 Hz, 1H), 4.41 (dm, *J* = 357 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 2.15 (d, *J* = 34.5 Hz), 24.34, 24.64, 30.65 (d, *J* = 33.0 Hz), 31.88, 33.24 (d, *J* = 11.1 Hz), 49.22 (m). ^{31}P NMR ($CDCl_3$) δ 18.44 (m).

4.12. (*R,R*)-Bis(boranato(methyl)(1,1,3,3-tetramethylbutyl) phosphino)methane 17

To a stirred and cooled (−78 °C) solution of (*S*)-methyl(1,1,3,3-tetramethylbutyl)phosphine–borane (*S*)-**15** (196 mg, 1.13 mmol) in THF (0.5 mL) was added *n*-BuLi (0.75 mL of 1.50 M hexane solution, 1.13 mmol) under a nitrogen atmosphere. After 30 min, (*R*)-methanesulfonyloxymethyl(methyl)(1,1,3,3-tetramethylbutyl) phosphine–borane (*R*)-**14b** (350 mg, 1.24 mmol) in THF (1.0 mL) was added and the solution was heated at 60 °C for 3 h. The mixture was cooled to room temperature and the reaction was quenched by the addition of H_2O. The mixture was extracted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1),

followed by recycling preparative HPLC ($CHCl_3$) to give (*R*,*R*)-bis(boranato(methyl)(1,1,3,3-tetramethylbutyl)phosphino)methane **17** (159 mg, 39% yield) as a white solid; mp 114–115 °C; $[\alpha]_D^{25} = -9.3$ (*c* 1.0, $CHCl_3$) >99% ee; ^{1}H NMR ($CDCl_3$) δ 0.27–0.80 (br m, 6H), 1.06 (s, 18H), 1.32 (d, J = 16.5 Hz, 12H), 1.50–1.52 (m, 10H), 1.77 (t, J = 11.8 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 6.31 (d, J = 32.8 Hz), 11.97 (t, J = 8.6 Hz), 21.92 (d, J = 4.8 Hz), 32.00, 33.21 (d, J = 12.1 Hz), 33.49 (d, J = 3.8 Hz), 33.73 (d, J = 4.5 Hz), 46.65. ^{31}P NMR ($CDCl_3$) δ 33.05. MS (FAB) *m*/*z* 359 (M^+-H), 355 (M^+-6H+H), 345 (M^+-BH_3-H), 333 (M^+-2BH_3+H). HRMS (TOF): calcd for $C_{19}H_{48}B_2NaP_2$ ($M+Na^+$): 383.3315; found: 383.3392.

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