# *P*-Stereogenic $\beta$ -Aminophosphines: Preparation and Applications in Enantioselective Organocatalysis

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## **Supporting Information**

**ABSTRACT:** The synthesis of stereodefined  $\beta$ -aminophosphines having both carbon- and phosphorus-based chirality centers is described. The method involves resolution of a mixture of  $\beta$ -aminophosphine oxide diastereomers accessed by ring-opening of an amino alcohol-derived cyclic sulfamidate. A stereospecific, borane-promoted reduction of  $\beta$ -aminophosphine oxides, which occurs under mild conditions and with inversion of configuration at phosphorus, is a key step in this process. The products obtained are new building blocks for the



synthesis of *P*-chiral ligands and organocatalysts. In a proof-of-concept application in organocatalysis, the diastereomeric *P*-chiral  $\beta$ -aminophosphine-based bifunctional thioureas displayed significantly different activities in the Morita–Baylis–Hillman reaction of methyl acrylate with benzaldehyde derivatives.

# INTRODUCTION

P-Stereogenic phosphines have been used extensively in enantioselective catalysis, particularly as chiral ligands or organocatalysts.<sup>1</sup> Preparing these compounds in enantioenriched form is a challenge, and continues to inspire the development of new synthetic methods. Approaches that have been implemented successfully include resolution,<sup>2</sup> the use of chiral auxiliaries,<sup>3</sup> kinetic and dynamic kinetic resolution,<sup>4,5</sup> desymmetrization<sup>6</sup> and enantioselective P-arylation<sup>7</sup> or Palkylation.<sup>8</sup> Phosphines that possess an additional element of chirality along with the P-stereogenic center present unique potential advantages. Opportunities exist to prepare such compounds efficiently, taking advantage of methods for the selective synthesis or separation of diastereomers. The ability to vary the relative configuration of the two chirality centers, in addition to other steric and electronic properties, may also be useful when optimizing catalyst performance. Several types of P-stereogenic phosphines containing one or more additional chirality centers or other elements of chirality (e.g., chirality axes) have been synthesized (Figure 1).9

We recently developed a protocol for the synthesis of chiral  $\beta$ -aminophosphines by ring-opening of amino alcohol-derived



Figure 1. Examples of reported *P*-stereogenic phosphines having an additional element of chirality.

cyclic sulfamidates with metal diarylphosphinites (Scheme 1a).<sup>10</sup> Using secondary phosphine oxides rather than secondary

Scheme 1. (a) Preparation of  $\beta$ -Aminophosphines from Cyclic Sulfamidates and Diarylphosphinites; (b) Envisioned Synthesis of *P*-Chiral Congeners



phosphines<sup>11,12</sup> as pro-nucleophiles for ring-opening proved to be particularly advantageous for the synthesis of derivatives having substituted aryl groups at phosphorus, as it minimized the purification and handling of air-sensitive phosphine intermediates.<sup>13</sup>  $\beta$ -Aminophosphines are useful precursors to chiral ligands<sup>14–19</sup> and organocatalysts,<sup>20–23</sup> and access to *P*aryl-substituted derivatives creates opportunities to explore structure–activity relationships for these types of catalytic applications. The ability to vary the phosphine substituents also suggested the possibility of generating *P*-stereogenic  $\beta$ -amino-

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phosphines from unsymmetrical phosphine oxides (Scheme 1b). The reaction of an enantiopure sulfamidate with a metal diarylphosphinite derived from a racemic secondary phosphine oxide would result in a mixture of diastereomers. Phosphines of defined configuration at the two chirality centers could be accessed by separation of the diastereomers-by chromatography or recrystallization, again taking advantage of the ease of isolation and handling of phosphine oxide derivativesfollowed by stereospecific reduction. Here, we describe the successful realization of this strategy, and the preparation of novel, stereodefined  $\beta$ -aminophosphines having both carbonand phosphorus-based chirality centers. In addition to the sulfamidate/diarylphosphinite coupling mentioned above, a stereospecific, borane-mediated reduction of  $\beta$ -aminophosphine oxides was a key step in the reaction sequence. The products were employed to synthesize the first examples of bifunctional organocatalysts having a P-stereogenic phosphine moiety, revealing an unexpected effect of relative configuration on catalytic activity in the asymmetric Morita-Baylis-Hillman reaction.

# RESULTS AND DISCUSSION

**Preparation and Resolution of** *P***-Chiral** *β***-Aminophosphine Oxides.** The targets for our initial studies were diastereomeric ligands  $(S,R_p)$ -1a and  $(S,S_p)$ -1b shown in Scheme 2a, which combine a *tert*-leucinol-derived chirality

Scheme 2. (a) Structures of  $\beta$ -Aminophosphines  $(S,R_p)$ -1a and  $(S,S_p)$ -1b Targeted in This Study; (b) Approaches to Previously Reported  $\beta$ -Aminophosphines 4,  $(R_p,R)$ -5a and  $(S_p,R)$ -5a<sup> $\alpha$ </sup>



center with the (*o*-anisyl) (phenyl)phosphine substitution pattern characteristic of the iconic *P*-stereogenic phosphines PAMP and DIPAMP.<sup>24</sup> Related examples of stereodefined  $\beta$ aminophosphines having chirality centers at the phosphorus atom at the  $\alpha$ - or  $\beta$ -position are **4**, which was prepared by diastereoselective addition of enantioenriched, lithiated PAMP-borane to an imine (Scheme 2b),<sup>9c</sup> and the diastereomers ( $R_{\rm p}$ ,R)-**5a** and ( $S_{\rm p}$ ,R)-**5b**, which were generated from the borane complex of enantiopure *trans*-1-phenylphospholane-2-carboxylic acid.<sup>9d</sup> Unsymmetric phosphine oxide 2, the starting material needed for the preparation of (*o*-anisyl) (phenyl)phosphines  $(S,R_{\rm P})$ -1a and  $(S,S_{\rm P})$ -1b, was prepared according to reported protocols.<sup>25</sup> Compound 2 was then coupled with sulfamidate 3 using the procedure developed in our laboratory, yielding a mixture of diastereomeric, *tert*-butoxycarbonyl- (Boc)-protected aminophosphine oxides (Scheme 3a). Removal of the Boc

Scheme 3. (a) Preparation of Diastereomeric Hydrochloride Salts  $(S,R_p)$ -8a·HCl and  $(S,S_p)$ -8b·HCl from Secondary Phosphine Oxide 2 and Enantioenriched Sulfamidate 3; (b) Epimerization of the Tertiary Phosphine Oxide Chirality Center under Conditions for Deprotection of the Boc Group<sup>a</sup>





<sup>*a*</sup>Conditions A: CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C. Conditions B: BF<sub>3</sub>·OEt<sub>2</sub>, 4 Å MS, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C.

Conditions B: >40:1 d.r.

group was accomplished by treatment with trifluoroacetic acid in dichloromethane, and the resulting amine was treated with anhydrous hydrogen chloride in diethyl ether to generate a 1:1 mixture of diastereomeric ammonium salts  $(S_{\mu}R_{\rm P})$ -8a·HCl and  $(S,S_p)$ -8b·HCl. A 70% yield was obtained over the three-step process of sulfamidate ring-opening, deprotection and salt formation. It should be noted that the phosphine oxide chirality center is subject to epimerization under the conditions for Boc deprotection shown in Scheme 3a. This fact was established by subjecting diasterometically pure  $(S,R_p)$ -7a—obtained from the mixture by preparative thin layer chromatography on silica gel, using a mixture of diethyl ether, hexanes and triethylamine (15:5:1 by volume) as the mobile phase—to trifluoroacetic acid in dichloromethane (Scheme 3b). The product aminophosphine oxide  $(S,R_P)$ -8a was obtained as a 9:1 mixture of diastereomers, as assessed by <sup>31</sup>P NMR spectroscopy. Presumably, the epimerization follows a pathway similar to that proposed by Mislow and co-workers for the racemization of tertiary phosphine oxides by HCl.<sup>26</sup> Epimerization could be suppressed by using boron trifluoride diethyl etherate<sup>27</sup> rather than trifluoroacetic acid as the reagent for deprotection of the Boc group. Since the present approach involves separation of the diastereomers after cleavage of the Boc group, the configurational instability of the phosphine oxide in the presence of acid is not an issue, and the deprotection was conducted using TFA.

Separation of the diastereomeric ammonium salts was accomplished by fractional recrystallization from a mixture of acetonitrile and diisopropyl ether (3:1 by volume, Scheme 4). The less soluble isomer was obtained with a diasteomeric ratio Scheme 4. Separation of Diastereomeric  $\beta$ -Aminophosphine Oxide Hydrochloride Salts by Fractional Recrystallization



of greater than 40:1. It was found to have the *R* configuration at phosphorus, as determined by X-ray crystallography (Supporting Information, Figure S1). The filtrate was enriched in the  $(S,S_P)$  isomer, with a diastereomeric ratio of 3:1. The mixture of diastereomers obtained from the filtrate was carried through subsequent manipulations until column chromatography could be used to obtain diastereomerically pure material (see below). The hydrochloride salts were converted to the corresponding free amines by treatment with Amberlite IRA-400, a basic anion exchange resin.

Stereospecific Reduction of *P*-Chiral  $\beta$ -Aminophosphine Oxides. Having established that the diastereometric  $\beta$ aminophosphines could be separated by recrystallization of their hydrochloride salts, we turned our attention to the stereospecific reduction of the phosphine oxide group. When  $(S_{1}R_{P})$ -8a was subjected to diphenylsilane in the absence of solvent at 140 °C,<sup>10,28</sup> the reduction was achieved in quantitative yield, but the aminophosphine was obtained as a 1:1 mixture of diastereomers (Scheme 5a). Based on the reported rate constants for racemization of (alkyl)diarylphosphines via pyramidal inversion, the product is unlikely to be configurationally stable at 140 °C.<sup>29</sup> Other silane-derived reagents, including chlorosilane (with or without amine additives) and phenylsilane, have been used to reduce optically active phosphine oxides to phosphines.<sup>30</sup> Using such reagents, racemization at phosphorus can usually be minimized, but not entirely eliminated, and care is often needed to avoid oxidation of the phosphine product during the workup and purification steps. Stereospecific reductions of phosphine oxides have also been achieved using methyl triflate and lithium aluminum hydride, but the former reagent would not likely be compatible with the free amine group in the present system. On the other hand, the mild conditions that have been employed for stereospecific reductions of  $\alpha$ - and  $\beta$ -hydroxyphosphine oxides appeared to be particularly promising as a solution to this problem.<sup>31</sup> Reaction of tertiary  $\hat{\alpha}$ - and  $\beta$ -hydroxyphosphine oxides with borane complexes  $(BH_3 \cdot THF \text{ or } BH_3 \cdot SMe_2)$ resulted in the efficient formation of the corresponding phosphine-borane complexes in THF at room temperature or 60 °C.<sup>31c</sup> Unfunctionalized tertiary phosphine oxides were unreactive under these conditions, and it was proposed that the formation of a cyclic complex from BH<sub>3</sub> and the hydroxyphosphine oxide served to activate the phosphorus-oxygen bond toward reduction. On the basis of this proposal, reductions of  $\beta$ -aminophosphine oxides such as 8a and 8b under similar conditions could be envisioned, with the amino group interacting with the boron Lewis acid in place of the OH

Scheme 5. (a) Epimerization upon Reduction of Phosphine Oxide  $(S,R_p)$ -8a by Diphenylsilane; (b) Stereospecific, Borane-Mediated Reduction of Epimeric Phosphine Oxides  $(S,R_p)$ -8a and  $(S,S_p)$ -8b<sup>a</sup>





<sup>*a*</sup>The relative configuration of  $(S,S_{\rm P})$ -**8b** was established by conversion to  $(S,S_{\rm P})$ -**9b**-BH<sub>3</sub> and structural determination by X-ray crystallog-raphy.

group. Indeed, treatment of  $(S,R_{\rm P})$ -**8a** with BH<sub>3</sub>·SMe<sub>2</sub> in THF at 70 °C resulted in the evolution of hydrogen gas and the reduction of the phosphine oxide, leading to the formation of phosphine—borane complex  $(S,R_{\rm P})$ -**1a**·BH<sub>3</sub> (Scheme 5b). In a similar way, the mixture of aminophosphine oxide diastereomers enriched in  $(S,S_{\rm P})$ -**8b** (3:1 d.r.) was reduced under these conditions, leading to phosphine—borane complexes that could be separated by flash column chromatography on silica gel. Complex  $(S,S_{\rm P})$ -**1b**·BH<sub>3</sub> was obtained in 20:1 d.r. The formation of air-stable phosphine—borane complexes that can be purified by column chromatography is an advantage of the borane-mediated reduction protocol. As was observed previously, unfunctionalized tertiary phosphine oxides were unreactive under these conditions, as were *N*-Boc-protected  $\beta$ aminophosphine oxide derivatives (data not shown).

In contrast to the retention of configuration that has generally been observed for silane-mediated reductions of phosphine oxides, inversion of configuration at phosphorus has been documented for reductions of  $\alpha$ - and  $\beta$ -hydroxyphosphine oxides with BH<sub>3</sub> complexes.<sup>31b,c</sup> The stereochemical outcome of the BH<sub>3</sub>-mediated reduction was rationalized in terms of a mechanism involving S<sub>N</sub>2-type cleavage of the P–O bond by an external hydride nucleophile. As shown in Scheme 5b, reductions of  $\beta$ -aminophosphine oxides by BH<sub>3</sub>·SMe<sub>2</sub> also proceed with inversion of configuration. The configuration of the phosphine–borane obtained from (*S*,*S*<sub>P</sub>)-**8b** was assigned by single crystal X-ray diffraction analysis of the corresponding *para*-nitrophenylurea derivative, (*S*,*S*<sub>P</sub>)-**9b**·BH<sub>3</sub> (Supporting Information, Figure S2). Thus, it appears that a similar mechanistic pathway to that proposed for hydroxyphosphine oxide reduction—namely, formation of a cyclic borane adduct and  $S_N$ 2-type attack of hydride on the activated P–O bond—is operative.

The free aminophosphines  $(S,R_p)$ -1a and  $(S,S_p)$ -1b were obtained by treatment of the phosphine—borane complexes with an excess of 1,4-diazabicyclo[2.2.2]octane (DABCO) in degassed toluene at 40 °C (Scheme 6). This reaction proceeds

Scheme 6. Synthesis of  $\beta$ -Aminophosphines  $(S,R_p)$ -1a and  $(S,S_p)$ -1b by Decomplexation of Phosphine–Borane Adducts



with retention of configuration at phosphorus.<sup>3a</sup> Under the relatively mild conditions of the decomplexation reaction, epimerization of the *P*-stereogenic center could be largely suppressed. The products were purified by flash chromatography on silica gel with degassed solvents, using compressed nitrogen gas to speed the flow of the eluent through the column.

Preparation and Application of Bifunctional Organocatalysts Derived from *P*-Stereogenic  $\beta$ -Aminophosphines. As an initial application in asymmetric catalysis, we explored the synthesis of bifunctional organocatalysts based on  $(S,R_{\rm P})$ -1a and  $(S,S_{\rm P})$ -1b. Ureas, thioureas, amides and sulfonamides derived from chiral  $\beta$ -aminophosphines are useful catalysts for enantioselective Morita-Baylis-Hillman reactions and for a range of related transformations.<sup>21-23</sup> Although Pstereogenic phosphines have been employed as chiral Lewis base catalysts (for example, for [3 + 2] annulations,<sup>32</sup>  $\gamma$ additions to allenoates<sup>33</sup> and acvlations of secondary alcohols<sup>34</sup>), bifunctional hydrogen bond donor/phosphine Lewis base catalysts having a P-stereogenic center have not been explored previously. On the basis of reported structureactivity relationships for Morita-Baylis-Hillman reactions catalyzed by bifunctional phosphines,<sup>21a</sup> we prepared electron-deficient thioureas derived from the epimeric aminophosphines (Scheme 7).

The phosphine-thioureas depicted in Scheme 7 were evaluated as catalysts for the Morita-Baylis-Hillman reaction of methyl acrylate and benzaldehyde (Table 1). The conditions employed for this reaction are based on those developed by Lu and co-workers.<sup>21a</sup> The 4 Å molecular sieves (MS) were substituted for 5 Å MS, which gave higher yields without appreciably altering the enantioselectivity. The configuration of the phosphorus chirality center had a significant effect on the yield of this transformation, with the  $(S, R_P)$ -configured catalysts showing higher activity than the  $(S, S_P)$ -configured variants.

Although the results of Table 1 pointed toward differences in the behavior of the epimeric catalysts for both thiourea substitution patterns, we sought to put this result on more solid ground through further comparisons of the 4-nitrophenyl-





Table 1. Influence of the Relative Configuration of the *P*-Stereogenic Phosphine–Thiourea Catalyst on Yield and Enantioselectivity for the Morita–Baylis–Hillman Reaction

O H	+ $\begin{bmatrix} CO_2Me \\ \end{bmatrix}$ $\begin{bmatrix} catalys \\ 5 \\ (3 equiv) \end{bmatrix}$ THF, 2	t (20 mol %) Å MS 23 °C, 72 h	OH CO <sub>2</sub> Me
entry	catalyst	% yield <sup>a</sup>	% ee <sup>b</sup>
1	( <i>S</i> , <i>R</i> <sub>P</sub> )-10a	57	76
2	( <i>S</i> , <i>S</i> <sub>P</sub> )-10b	10	73
3	$(S,R_{\rm P})$ -11a	53	73
4	( <i>S</i> , <i>S</i> <sub>p</sub> )-11b	12	72

<sup>*a*</sup>Yield after purification by flash column chromatography on silica gel. <sup>*b*</sup>Determined by high performance liquid chromatography (HPLC) using a chiral stationary phase. The absolute configuration was assigned by comparing the sign of the optical rotation to the literature data.

substituted thiourea catalysts  $(S_r, R_p)$ -10a and  $(S_r, S_p)$ -10b with (S)-10c, a variant lacking the *P*-stereogenic center. These comparisons were conducted for benzaldehyde itself, using the results from entries 1 and 2 of Table 1, and for two relatively electron-rich, substituted variants, 4-bromobenzaldehyde and *para*-tolualdehyde, which show relatively poor reactivity in Morita–Baylis–Hillman reactions catalyzed by bifunctional thioureas. The results are summarized in Table 2. A consistent trend was evident across the three aldehyde substrates, with catalyst turnover numbers decreasing in the order  $(S_r, R_p)$ -10a > 10c >  $(S_r, S_p)$ -10b. A small but consistent increase in enantioselectivity for *P*-chiral  $(S_r, R_p)$ -10a versus 10c was also observed.

Stereochemical models have been proposed for Morita-Baylis-Hillman and related reactions catalyzed by chiral  $\beta$ aminophosphines,<sup>22a,b</sup> and insight has been gained through computational modeling.<sup>35</sup> A rationale for the difference in activity between the P-stereogenic aminophosphine epimers studied here would be of interest, but the issues involved are complex. Using diazabicyclo [2.2.2] octane (DABCO) as catalyst, the aldol-type addition step and/or the elimination step may be rate-limiting, depending on the reaction conditions. Experimental kinetic or isotope effect data are not available for the bifunctional phosphine-catalyzed variant of this reaction. Thus, it is not clear which step(s) of the catalytic cycle are influenced by the change in configuration of the P-stereogenic center. Nonetheless, we used density functional theory (DFT) calculations using the B3LYP functional and the 6-31G(d,p)basis set to model the adducts of catalysts  $(S,R_{\rm P})$ -10a and  $(S,S_{\rm P})$ -10b with methyl acrylate (Figure 2). The starting Table 2. Comparison of Yield and Enantioselectivity Data for *P*-Chiral Catalysts  $(S,R_p)$ -10a and  $(S,S_p)$ -10b, and Catalyst 10c Lacking the *P*-Stereogenic Center<sup>*a*</sup>



aldehyde	catalyst $(S,R_{\rm P})$ -10a	catalyst (S)- <b>10c</b>	catalyst (S,S <sub>P</sub> )- <b>10b</b>
PhCHO	57% yield	33% yield	10% yield
	76% ee	68% ee	73% ee
4-BrC <sub>6</sub> H <sub>4</sub> CHO	80% yield	63% yield	<5% yield
	81% ee	74% ee	% ee ND
4-MeC <sub>6</sub> H <sub>4</sub> CHO	41% yield	21% yield	<5% yield
	73% ee	68% ee	% ee ND

<sup>*a*</sup>Yields are of isolated products after purification by flash column chromatography on silica gel. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) using a chiral stationary phase.



**Figure 2.** Calculated structures (B3LYP/6-31G(d,p)) and relative energies of the adducts of methyl acrylate with  $(S,R_P)$ -10a and  $(S,S_P)$ -10b. Ar denotes 4-nitrophenyl.

geometries for these optimizations were based on the calculated structures of related adducts of naphthyl acrylate with a sulfonamide-functionalized bifunctional phosphine, from a study conducted by Lu, Huang and co-workers.35a The minimum-energy geometries of the adducts derived from the thiourea-functionalized, P-chiral variants preserve the intramolecular NH-O hydrogen bond that was identified in the previously reported computational study. The calculated free energy of the acrylate adduct of  $(S,S_p)$ -10b was 1.79 kcal/mol higher than that of  $(S,R_p)$ -10a. In the structure of the higherenergy diastereomer, the o-anisyl methoxy substituent occupies a position close to the acrylate-derived moiety. In contrast, these groups are oriented in opposite directions in the structure of the lower-energy diastereomer. To the extent that this energy difference is reflected in the relative concentrations of kinetically relevant species derived from  $(S_{,R_{\rm P}})$ -10a and  $(S_{,S_{\rm P}})$ -10b, the calculations may provide a plausible rationale for the effect of configuration of the P-stereogenic center on the activity of these bifunctional catalysts.

The results described above indicate that employing a Pstereogenic (o-anisyl) (phenyl)phosphino group of appropriate configuration provides an appreciable increase in catalytic activity, along with a more modest increase in enantioselectivity, relative to the diphenylphosphino group on which the most widely employed bifunctional organocatalysts are based. It should be noted that the best-in-class aminophosphinebifunctional catalysts for Morita-Baylis-Hillman reactions are not derived from tert-leucine, but rather from threonine derivatives bearing bulky O-silyl substituents.<sup>21a</sup> Further improvements upon the results shown in Table 2 may be possible using P-chiral variants of the threonine-derived catalysts. It will also be of interest to identify other pairs of substituents on the P-stereogenic center that lead to more dramatic effects on activity and enantioselectivity for this and other organocatalytic reactions.

# CONCLUSIONS

Ring-opening of enantiopure cyclic sulfamidates by unsymmetrical secondary phosphine oxide nucleophiles, followed by resolution of the mixture of diastereomers, provides access to new  $\beta$ -aminophosphines having a *P*-stereogenic center. The stereospecific, borane-mediated reduction of  $\beta$ -aminophosphine oxides to  $\beta$ -aminophosphine—boranes was important to the successful implementation of this approach. A mechanistic link to previously reported reductions of  $\alpha$ - and  $\beta$ -hydroxyphosphine oxides by borane complexes is likely, with both classes of substrates reacting with inversion of configuration at phosphorus.

Extending this process to other combinations of phosphine substituents will be of interest. The scope of the (symmetrical) secondary phosphine oxide–sulfamidate coupling reaction, which tolerates electron-deficient, electron-rich and sterically hindered aromatic substituents at phosphorus, is encouraging from this perspective.<sup>10</sup> For the (*o*-anisyl)(phenyl)phosphine substitution pattern, resolution of the diastereomeric phosphine oxides was carried out by fractional recrystallization. However, the ability to separate the epimeric phosphine–borane complexes by column chromatography on silica gel was also important in providing access to the more soluble diastereomer in high purity. The possibility of achieving separation of diastereomers by two techniques, and at different stages of the process, may be useful in extending this approach to other phosphine substitution patterns.

The organocatalysis experiments described here indicate that the configuration of the P-chiral phosphine substituent can influence the behavior of bifunctional thioureas derived from 1a and 1b. The primary effect is on catalyst activity, with the  $(S,R_{\rm p})$ -configured diastereomer showing higher activity than the diphenylphosphino variant and the  $(S,S_P)$ -configured diastereomer being significantly less active. A modest but consistent beneficial effect of the R<sub>p</sub>-configured (o-anisyl)phenylphosphino substituent on enantioselectivity was also observed. Evaluating other P-chiral phosphine substituents may help to elucidate the factors responsible for this effect, and could lead to more pronounced improvements in catalytic properties. Given that  $\beta$ -aminophosphines are components of useful classes of chiral ligands, applications of P-chiral variants in transition metal catalysis are another potential direction for future studies.

### EXPERIMENTAL SECTION

**General Procedures.** Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Flash column chromatography was carried out using  $35-75 \ \mu m$  particle size silica gel.

**Materials.** All commercially available reagents and chemicals were used as received without purification. Benzaldehyde, *p*-tolualdehyde and 4-bromobenzaldehyde were purified by passing through a short plug of activated  $Al_2O_3$  (basic, Brockmann I) immediately before use. All solvents were dried using a solvent purification system and degassed through three freeze–pump–thaw cycles. Deuterated solvents were degassed through three freeze–pump–thaw cycles. Unless otherwise stated, all reactions and purifications were carried out under argon atmosphere using Schlenk, vacuum line, or glovebox techniques in dry, oxygen-free solvents. Unsymmetrical secondary phosphine oxide  $2^{25}$  and the *tert*-butyl cyclic sulfamidate  $3^{11}$  were synthesized according to published protocols.

Instrumentation. 500 and 400 MHz spectrometers were employed for recording <sup>1</sup>H (400 MHz), <sup>13</sup>C{<sup>1</sup>H} (125 and 100 MHz), <sup>31</sup>P{<sup>1</sup>H} (160 MHz), <sup>11</sup>B (128 MHz) and <sup>19</sup>F{<sup>1</sup>H} (376 MHz) NMR spectra at ambient temperature. <sup>1</sup>H chemical shifts are reported as ppm relative to tetramethylsilane, and were measured by referencing the spectra to residual protium in the solvent. <sup>31</sup>P chemical shifts are reported in parts per million (ppm) relative to 85% H<sub>3</sub>PO<sub>4</sub> as an external reference. <sup>19</sup>F chemical shifts are reported in ppm relative to  $CFCl_3$  as an external reference. Coupling constants (*J*) are given in Hz. <sup>1</sup>H data are reported as multiplicity (br = broad singlet, s = singlet, d = doublet, t = triplet, q = quartet). Attenuated total reflectance infrared (IR) spectra were obtained in the solid form or as neat liquid, as indicated. High resolution mass spectroscopy (HRMS) experiments were carried out using a time-of-flight mass spectrometer equipped with a direct analysis in real time (DART) ion source. Melting points were as measured and are uncorrected. Enantiomeric excesses (ee) were determined by normal-phase HPLC analysis with a commercially available chiral stationary phase, using a mixture of hexanes-2propanol as eluent and with UV detector set at 254 or 210 nm.

( $\bar{R}$ )-((S)-2-Amino-3,3-dimethylbutyl)(2-methoxyphenyl)(phenyl)phosphine oxide (8a). In a nitrogen-filled gloxebox, an oven-dried screw-cap reaction tube equipped with a magnetic stirring bar was charged with KOt-Bu (0.31 g, 2.8 mmol). THF (6 mL) was then added outside of the glovebox. Racemic phosphine oxide 2 (0.65 g, 2.8 mmol) was dissolved in THF (6 mL) in a separate oven-dried pearshaped flask and transferred dropwise into the reaction mixture via a syringe. The reaction was stirred at 23 °C for 10 min. Sulfamidate 3 (0.78 g, 2.8 mmol) was dissolved in THF (6 mL) in another ovendried pear-shaped flask and transferred dropwise into the reaction mixture via a syringe. The reaction tube was then sealed and stirred at 60 °C for 17 h. The reaction was quenched with H<sub>2</sub>SO<sub>4</sub> (80 mL, 2 M) and stirred vigorously at 23 °C for 45 min. It was then extracted two times with Et<sub>2</sub>O, and the combined organic extracts were washed with saturated Na<sub>2</sub>CO<sub>3</sub>, followed by brine. The solution was dried over anhydrous  $\rm Na_2SO_4$  , filtered and concentrated in vacuo to give a brown oil.

The oil was taken up in CH<sub>2</sub>Cl<sub>2</sub> (12 mL) and cooled to 0 °C. Trifluoroacetic acid (5.5 mL, 72 mmol) was added dropwise. The reaction mixture was stirred at 23 °C overnight. The volatiles were then removed on the rotary evaporator the next day. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and washed with saturated Na<sub>2</sub>CO<sub>3</sub>. The aqueous layer was separated and extracted four times with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were then combined, washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give a brown oil.

To a round-bottom flask equipped with a magnetic stirring bar was added the oil. Et<sub>2</sub>O (50 mL) was added. Anhydrous HCl (2.8 mL, 1 M, 2.8 mmol) was added dropwise at 23 °C with vigorous stirring. The white suspension was filtered over a Buchner funnel under vacuum to give  $8a \cdot HCl + 8b \cdot HCl$  (1:1 d.r., 0.71 g, 70%) as a white solid.

To a round-bottom flask equipped with a magnetic stirring bar was added the white solid. MeCN (27 mL) was added. The white suspension was stirred at 90 °C in an oil bath until homogeneity was observed. The flask was then removed from the oil bath and  $iPr_2O$  (9 mL) was added. The flask was sealed and allowed to cool down to 23 °C. The solvents were then removed on the rotary evaporator upon formation of a white precipitate until very little solvent remained. The resulting slurry was filtered over a Buchner funnel under vacuum to give enriched 8a·HCl as a white solid. The process was repeated twice using MeCN (36 and 45 mL) and  $iPr_2O$  (12 and 15 mL) to give the final enriched 8a·HCl (>40:1 d.r., 0.21 g) as a white solid. The filtrates containing 8b·HCl were combined and concentrated in vacuo to give a light brown residue (3:1 d.r., 0.49 g, 69%).

The white solid consisting of 8a·HCl was taken up in MeOH (40 mL) in a round-bottom flask. Amberlite IRA-400 (OH) resin (5.0 g per gram of white solid) was added and stirred vigorously at 23 °C for 30 min. The suspension was then filtered and the filtrate was concentrated in vacuo to give product 8a with high analytical purity (>40:1 d.r., 0.19 g, 30%) as a colorless oil. <sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.91 (ddd, J = 13.0, 7.6, 1.8 Hz, 1H), 7.83 (ddt, J = 11.6, 6.9,1.5 Hz, 2H), 7.46 (ttdd, J = 8.6, 6.6, 3.3, 1.7 Hz, 4H), 7.11-7.04 (m, 1H), 6.90 (dd, J = 8.2, 5.4 Hz, 1H), 3.83 (s, 3H), 3.00 (ddd, J = 12.5, 11.2, 1.2 Hz, 1H), 2.73 (ddd, J = 15.1, 10.9, 1.2 Hz, 1H), 2.40 (s, 2H), 2.25 (ddd, J = 15.1, 13.4, 11.2 Hz, 1H), 0.91 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  159.6 (d, J = 4.0 Hz), 133.8 (d, J = 2.0 Hz), 133. Eight (d, J = 9.0 Hz), 133.6 (d,  ${}^{1}J_{CP} = 99.0 \text{ Hz}$ ), 131.3 (d, J = 3.0 Hz), 131.0 (d, J = 10.0 Hz), 128.2 (d, J = 12.0 Hz), 122.2 (d,  ${}^{1}J_{CP} = 95.0 \text{ Hz}$ ), (d, J = 10.0 Hz), 120.2 (d, J = 12.0 Hz), 122.2 (d,  $J_{CP} = 25.0 \text{ Hz})$ , 121.3 (d, J = 11.0 Hz), 111.0 (d, J = 7.0 Hz), 55.4, 55.3 (d,  $^2J_{CP} = 5.0 \text{ Hz}$ ), 35.0 (d,  $^3J_{CP} = 13.0 \text{ Hz}$ ), 31.8 (d,  $^1J_{CP} = 73.0 \text{ Hz}$ ), 25.9.  $^{31}\text{P}$  NMR (160 MHz, CDCl<sub>3</sub>)  $\delta$  31.96. IR (neat, cm <sup>-1</sup>) 2958 (w), 1592 (m), 1579 (m), 1477 (m), 1466 (m), 1435 (m), 1240 (m), 1181 (s), 1141 (m), 1108 (m), 1078 (m), 1024 (m), 923 (br), 801 (m), 776 (s), 741 (s), 703 (s). Optical rotation  $[\alpha]_{589}^{20} = +31.2$  (c = 0.10 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/z) calculated for  $C_{19}H_{27}NO_2P$  [(M + H)<sup>+</sup>]: 332.1774. Found: 332.1779.

(S)-1-((S)-(2-Methoxyphenyl)(phenyl)phosphanylborane)-3,3-dimethylbutan-2-amine ( $1b \cdot BH_3$ ). The light brown residue consisting of  $8b \cdot HCl$  was taken up in MeOH (60 mL). Amberlite IRA-400 (OH) resin (5.0 g per gram of residue) was added and stirred vigorously at 23 °C for 30 min. The suspension was then filtered and the filtrate was concentrated in vacuo to give crude 8b (3:1 d.r., 0.47 g) as a light brown oil.

To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added crude **8b** (0.47 g, 1.4 mmol). THF (15 mL) was added and cooled down to 0 °C. BH<sub>3</sub>·SMe<sub>2</sub> (0.48 mL, 5.1 mmol) was then added dropwise via a syringe at 0 °C under a positive pressure of argon. The reaction was stirred at 70 °C for 4 h. The reaction was quenched with saturated NH<sub>4</sub>Cl (20 mL) and extracted four times with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (100 g of Si<sub>2</sub>O per gram of crude product; 1% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) gave **1b**·BH<sub>3</sub> (80 mg, 25% over two steps) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.88 (ddd, *J* = 13.6, 7.6, 1.6 Hz, 1H), 7.72–7.63 (m, 2H), 7.51–7.45 (m, 1H), 7.44–7.33 (m, 3H), 7.05 (tdd, *J* = 7.5, 1.9)

0.9 Hz, 1H), 6.89 (dd, J = 8.1, 3.2 Hz, 1H), 3.72 (s, 3H), 2.93 (ddd, J = 12.3, 10.4, 1.7 Hz, 1H), 2.57 (ddd, J = 14.4, 12.6, 1.7 Hz, 1H), 2.45 (ddd, J = 14.4, 12.3, 10.4 Hz, 1H), 1.19–1.10 (m, 2H), 0.90 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.3 (d, J = 2.0 Hz), 135.9 (d, J = 14.0 Hz), 133.7 (d, J = 2.0 Hz), 131.9 (d, J = 9.0 Hz), 130.6 (d, J = 58.0 Hz), 130.5 (d, J = 2.0 Hz), 121.4 (d, J = 12.0 Hz), 131.9 (d, J = 4.0 Hz), 130.5 (d, J = 52.0 Hz), 111.5 (d, J = 4.0 Hz), 55.6 (d, J = 33.0 Hz), 35.3 (d, J = 11.0 Hz), 27.9 (d, J = 38.0 Hz), 26.0. <sup>31</sup>P NMR (160 MHz, CDCl<sub>3</sub>)  $\delta$  14.27 (d,  $J^{1}_{\rm BP} = 83$  Hz). <sup>1B</sup> NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  -38.44 (m). IR (neat, cm<sup>-1</sup>) 2958 (m), 2380 (m), 1589 (m), 1574 (m), 1477 (s), 1464 (m), 1433 (s), 1277 (s), 1248 (s), 1060 (s), 1019 (s), 909 (m), 801 (m), 756 (s), 728 (s), 696 (s). Optical rotation  $[\alpha]_{\rm S89}^{20} = +13.4$  (c = 0.04 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/z) calculated for C<sub>19</sub>H<sub>28</sub>BNOP [(M + H)<sup>+</sup>]: 328.2008. Found: 328.2002.

(S)-1-((R)-(2-Methoxyphenyl)(phenyl)phosphanylborane)-3,3-dimethylbutan-2-amine) (1a-BH<sub>3</sub>). To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added phosphine oxide 8a (0.19 g, 0.57 mmol). THF (5 mL) was added and cooled down to 0 °C. BH<sub>3</sub>·SMe<sub>2</sub> (0.2 mL, 2.1 mmol) was then added dropwise via a syringe at 0 °C under a positive pressure of argon. The reaction was stirred at 70 °C for 4 h. The reaction was quenched with saturated NH<sub>4</sub>Cl (30 mL) and extracted four times with CH<sub>2</sub>Cl<sub>2</sub>. The organic extracts were combined, dried over anhydrous Na2SO4, filtered and concentrated in vacuo to give the crude product. Purification by flash chromatography on silica gel (2% MeOH/CH2Cl2) gave 1a·BH3 (81 mg, 43%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.04 (ddd, J = 13.8, 7.6, 1.7 Hz, 1H), 7.63–7.50 (m, 3H), 7.43–7.33 (m, 3H), 7.11 (tdd, J = 7.5, 2.1, 1.0 Hz, 1H), 6.87 (ddd, J = 8.3, 3.2, 0.9 Hz, 1H), 3.63 (s, 3H), 3.03 (ddd, J = 17.7, 14.1, 1.3 Hz, 1H), 2.55 (ddd, J = 14.2, 10.1, 1.3 Hz, 1H), 1.99 (ddd, J = 14.1, 10.1, 6.1 Hz, 1H), 1.65 (s, 2H), 0.82 (s, 9H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  161.2 (d, J = 2.0 Hz), 137.6 (d, J = 15.0 Hz), 134.2, (d, J = 2.0 Hz), 131.4 (d, J = 59.0 Hz), 131.2 (d, J = 9.0 Hz), 130.3 (d, J = 3.0 Hz), 128.4 (d, J = 10.0 Hz), 121.4 (d, J = 12.0 Hz), 115.2 (d, J = 53.0 Hz), 111.0 (d, J = 4.0 Hz), 55.7 (d, J = 90.0 Hz), 35.1 (d, J = 11.0 Hz), 27.7 (d, J = 38.0 Hz), 25.9. <sup>31</sup>P NMR (160 MHz, CDCl<sub>3</sub>)  $\delta$  15.27 (d,  $J^{1}_{RP}$  = 69 Hz). <sup>11</sup>B NMR (128 MHz, CDCl<sub>3</sub>)  $\delta$  -37.35 (m). IR (neat, cm <sup>-1</sup>) 2959 (m), 2371 (s), 1589 (m), 1574 (m), 1477 (s), 1463 (s), 1431 (s), 1278 (s), 1249 (s), 1061 (s), 1020 (s), 756 (s), 735 (s), 726 (s), 697 (s), 689 (s). Optical rotation  $[\alpha]_{589}^{20} = +5.4$  (c = 0.04 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/z) calculated for  $C_{19}H_{28}BNOP$  [(M + H)<sup>+</sup>]: 328.2016. Found: 328.2002.

Formation of X-ray Quality Crystal for 8a·HCl. To a 2-dram vial was charged the filter cake consisting of 8a·HCl from the recrystallization experiment (>40:1 d.r., 10 mg).  $CH_2Cl_2$  was added to dissolve the solid.  $Et_2O$  was then carefully layered on top of the solution and left aside undisturbed at 23 °C for a day to give a colorless crystal that was subjected to X-ray crystallographic analysis. mp (°C) 131–132.

Synthesis and X-ray Crystallographic Analysis of Phosphine Borane 9b·BH<sub>3</sub>. To an oven-dried round-bottom flask equipped with a magnetic stirring bar was added phosphine borane 1b·BH<sub>3</sub> (47 mg, 0.14 mmol).  $CH_2Cl_2$  (3 mL) was added and cooled down to 0 °C. 4-Nitrophenyl isocyanate (26 mg, 0.16 mmol) was added in one portion. The reaction was stirred at 23 °C overnight. The volatiles were concentrated in vacuo and the crude product was purified by flash chromatography on silica gel (1.7% MeOH/ $CH_2Cl_2$ ) to give 9b·BH<sub>3</sub> (57 mg, 83%) as a light yellow solid. To a 2-dram vial was charged 9b· BH<sub>3</sub>.  $CH_2Cl_2$  was added to dissolve the solid. MeOH was then layered carefully on top of the solution and left aside undisturbed at 23 °C for 10 days to give a yellow crystal that was subjected to X-ray crystallographic analysis. mp (°C) 167–169.

General Procedure for the DABCO-Mediated Deprotection of Phosphine Borane. To an oven-dried 2-dram vial equipped with a magnetic stirring bar was added the phosphine borane. Toluene (0.1 M) was added, followed by DABCO (1.5 equiv). The vial was sealed and stirred at 40 °C for 17 h. The volatiles were then concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel using a positive pressure of  $N_2$  and solvents presparged with  $N_2~(2.5\%~MeOH/CH_2Cl_2)$  to give the pure product.

(S)-((R)-(2-Methoxyphenyl)(phenyl)phosphanyl)-3,3-dimethylbutan-2-amine (1a). This compound was synthesized according to the general procedure using phosphine borane 1a·BH<sub>3</sub> (39 mg, 0.12 mmol) and DABCO (20 mg, 0.18 mmol, 1.5 equiv) in toluene (1.2 mL). The crude product was purified by flash chromatography on silica gel (2.5% MeOH/CH<sub>2</sub>Cl<sub>2</sub>) to give the pure product (27:1 d.r., 30 mg, 79%) as a colorless oil.<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.45 (td, J = 7.6, 2.3 Hz, 2H), 7.37–7.28 (m, 4H), 7.18 (ddd, J = 7.6, 6.1, 1.7 Hz, 1H), 6.93 (t, J = 7.3 Hz, 1H), 6.86 (dd, J = 8.0, 4.0 Hz, 1H), 3.77 (s, 3H), 2.67 (ddd, J = 11.2, 9.2, 2.2 Hz, 1H), 2.59 (ddd, J = 13.9, 3.7, 2.2 Hz, 1H), 1.79 (ddd, J = 13.9, 11.2, 3.0 Hz, 1H), 0.93 (s, 9H).  $^{13}\mathrm{C}$  NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  143.0, 133.3, 132.9 (d, J = 19.0 Hz), 130.6, 128.5, 128.4 (d, J = 7.0 Hz), 121.1 (d, J = 4.0 Hz), 110.6 (d, J = 2.0 Hz), 58.6 (d,  ${}^{2}J_{CP}$  = 14.0 Hz), 55.6, 35.1 (d,  ${}^{3}J_{CP}$  = 7.0 Hz), 31.0 (d,  ${}^{1}J_{CP} = 10.0 \text{ Hz}$ , 26.2.  ${}^{31}P$  NMR (160 MHz, CDCl<sub>3</sub>)  $\delta$  -28.50. IR (neat, cm<sup>-1</sup>) 2960 (s), 1586 (m), 1474 (s), 1432 (s), 1273 (m), 1241 (s), 1070 (w), 1025 (m), 754 (s), 698 (m). Optical rotation  $[\alpha]_{589}^{20} =$ +83.8 (c = 0.01 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/z) calculated for  $C_{19}H_{27}NOP$  [(M + H)<sup>+</sup>]: 316.1835. Found: 316.1830.

(S)-1-((S)-(2-Methoxyphenyl)(phenyl)phosphanyl)-3,3-dimethylbutan-2-amine (1b). This compound was synthesized according to the general procedure using phosphine borane 1b·BH<sub>3</sub> (50 mg, 0.15 mmol) and DABCO (26 mg, 0.23 mmol, 1.5 equiv) in toluene (1.5 mL). The crude product was purified by flash chromatography on silica gel (2.5%  $MeOH/CH_2Cl_2$ ) to give the pure product (20:1 d.r., 31 mg, 66%) as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.57– 7.49 (m, 2H), 7.37 (dp, J = 5.1, 1.7 Hz, 3H), 7.29 (ddd, J = 8.8, 7.8, 1.7 Hz, 1H), 7.01 (ddd, J = 6.6, 4.8, 1.7 Hz, 1H), 6.89 (tt, J = 7.4, 0.9 Hz, 1H), 6.84 (ddd, J = 8.0, 4.4, 0.8 Hz, 1H), 3.80 (s, 3H), 2.43 (ddd, J = 11.4, 9.7, 1.7 Hz, 1H), 2.36 (ddd, J = 13.7, 5.7, 1.7 Hz, 1H), 1.90 (br, 2H), 1.89 (ddd, J = 13.6, 11.5, 4.6 Hz, 1H), 0.87 (s, 9H). <sup>13</sup>C NMR  $(100 \text{ MHz}, \text{CDCl}_3) \delta 160.8 \text{ (d, } I = 13.3 \text{ Hz}\text{)}, 136.7 \text{ (d, } I = 12.1 \text{ Hz}\text{)},$ 134.1 (d, J = 19.8 Hz), 132.2 (d, J = 3.0 Hz), 129.9, 129.2, 128.5 (d, J = 8.1 Hz), 127.7 (d, J = 14.0 Hz), 121.0 (d, J = 2.2 Hz), 110.5 (d, J = 1.4 Hz), 100.1, 57.7 (d,  ${}^{2}J_{CP}$  = 13.0 Hz), 55.7, 35.0 (d,  ${}^{3}J_{CP}$  = 6.0 Hz), 30.4 (d,  ${}^{1}J_{CP}$  = 10.2 Hz), 26.1.  ${}^{31}P$  NMR (160 MHz, CDCl<sub>3</sub>)  $\delta$  -29.94. IR (neat, cm<sup>-1</sup>) 2954 (m), 1584 (m), 1573 (m), 1463 (s), 1431 (s), 1362 (w), 1271 (w), 1239 (s), 1069 (w), 1024 (s), 793 (w), 745 (s), 727 (m), 696 (s). Optical rotation  $[\alpha]_{589}^{20} = +10.3$  (c = 0.01 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/z) calculated for C<sub>19</sub>H<sub>27</sub>NOP [(M + H)<sup>+</sup>]: 316.1836. Found: 316.1830.

General Procedure for the Synthesis of Phosphinothioureas. To an oven-dried 2-dram vial equipped with a magnetic stirring bar was added the *P*-chiral aminophosphine.  $CH_2Cl_2$  (0.03 M) was added, followed by isothiocyanate (1.1 equiv). The vial was sealed and stirred at 23 °C overnight. The crude product was purified by flash chromatography on silica gel using a positive pressure of N<sub>2</sub> and solvents presparged with N<sub>2</sub> to give the pure product.

1-((S)-1-((R)-(2-Methoxyphenyl)(phenyl)phosphanyl)-3,3-dimethylbutan-2-yl)-3-(4-nitrophenyl)thiourea (10a). This compound was synthesized according to the general procedure using aminophosphine 1a (46 mg, 0.14 mmol) and 4-nitrophenyl isothiocyanate (29 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The crude product was purified by flash chromatography on silica gel using a positive pressure of  $N_2$  and solvents presparged with  $N_2$  (17–20% EtOAc/hexanes) to give the pure product (37 mg, 53%) as a yellow amorphous solid. <sup>1</sup>H NMR (400 MHz, Methanol- $\tilde{d}_4$ )  $\delta$  8.16 (d, J = 9.2 Hz, 2H), 7.81 (d, J = 9.1 Hz, 2H), 7.49 (ddd, J = 9.3, 6.1, 2.3 Hz, 2H), 7.34 (td, J = 7.7, 1.4 Hz, 1H), 7.27–7.26 (m, 3H), 7.18 (td, J = 7.2, 1.4 Hz, 1H), 6.98–6.89 (m, 2H), 3.74 (s, 3H), 3.13 (d, J = 0.7 Hz, 1H), 2.81 (dt, J = 15.0, 2.4 Hz, 1H), 2.09 (dt, J = 25.7, 15.2 Hz, 1H), 1.04 (s, 9H). <sup>13</sup>C NMR (125 MHz, Methanol- $d_4$ )  $\delta$  182.2, 162.6 (d, J = 10.0 Hz), 147.6, 144.0, 134.3 (d, J = 20.0 Hz), 134.2 (d, J = 11.0 Hz), 131.4, 129.5, 129.3 (d, J = 7.0 Hz), 125.1, 121.8, 121.8 (d, J = 4.0 Hz), 111.8, 61.2 (d,  ${}^{2}J_{CP}$  = 15.0 Hz), 55.9, 52.5, 37.5 (d,  ${}^{3}J_{CP}$  = 8.0 Hz), 30.1 (d,  ${}^{1}J_{CP}$  = 13.0 Hz), 26.9. <sup>31</sup>P NMR (160 MHz, Methanol- $d_4$ )  $\delta$  –26.38. IR (neat, cm <sup>-1</sup>) 2962 (w), 1595 (m), 1499 (m), 1432 (s), 1329 (s), 1273 (s), 1237 (s), 1177 (m), 1110 (m), 1021 (m), 850 (m), 749 (s), 696 (s). Optical

rotation  $[a]_{589}^{20} = -44.3 \ (c = 0.01 \ \text{g mL}^{-1}, \text{CHCl}_3)$ . HRMS (DART, m/z) calculated for C<sub>26</sub>H<sub>31</sub>N<sub>3</sub>O<sub>3</sub>PS  $[(M + H)^+]$ : 496.1821. Found: 496.1824.

1-(3,5-Bis(trifluoromethy)phenyl)-3-((S)-1-((R)-(2methoxyphenyl)(phenyl)phosphanyl)-3,3-dimethylbutan-2-yl)thiourea (11a). This compound was synthesized according to the general procedure using aminophosphine 1a (46 mg, 0.14 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (43 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The crude product was purified by flash chromatography on silica gel using a positive pressure of N2 and solvents presparged with  $N_2$  (14–20% EtOAc/hexanes) to give the pure product (50 mg, 61%) as a white amorphous solid. <sup>1</sup>H NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.10 (s, 2H), 7.59 (s, 1H), 7.50 (td, J = 8.0, 1.6 Hz, 2H), 7.37–7.21 (m, 4H), 7.14 (td, J = 6.8, 1.6 Hz, 1H), 6.97– 6.86 (m, 2H), 3.75 (s, 3H), 2.79 (dt, J = 14.4, 2.0 Hz, 1H), 2.12 (dd, J = 14.3, 11.4 Hz, 1H), 1.04 (s, 9H). <sup>13</sup>C NMR (125 MHz, Methanol $d_4$ )  $\delta$  182.7, 162.6 (d, J = 11.3 Hz), 143.2, 139.6, (d, J = 12.5 Hz), 134.5 (d, J = 20.0 Hz), 134.1 (d, J = 11.3 Hz), 132.4 (d, J = 33.8 Hz), 131.4, 129.5, 129.2 (d, J = 7.5 Hz), 127.7 (d, J = 15.0 Hz), 124.8 (d, J = 270.0 Hz), 123.3 (m), 121.8 (d, J = 3.8 Hz), 117.3 (m), 111.8, 61.4  $(d, {}^{2}J_{CP} = 16.3 \text{ Hz}), 55.9, 37.4 (d, {}^{3}J_{CP} = 8.8 \text{ Hz}), 29.9 (d, {}^{1}J_{CP} = 13.8 \text{ Hz})$ Hz), 26.9. <sup>31</sup>P NMR (160 MHz, Methanol- $d_4$ )  $\delta$  –22.48. <sup>19</sup>F NMR (376 MHz, Methanol- $d_4$ )  $\delta$  -60.53. IR (neat, cm<sup>-1</sup>) 2969 (w), 2938 (w), 1533 (m), 1469 (m), 1340 (w), 1276 (s), 1237 (m), 1173 (s), 1129 (s), 1023 (m), 954 (m), 884 (m), 749 (m), 697 (m). Optical rotation  $[\alpha]_{589}^{20}$  = +16.3 (c = 0.01 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/ z) calculated for  $C_{28}H_{30}F_6N_2OPS$  [(M + H)<sup>+</sup>]: 587.1713. Found: 587.1721.

1-((S)-1-((S)-(2-Methoxyphenyl)(phenyl)phosphanyl)-3,3-dimethylbutan-2-yl)-3-(4-nitrophenyl)thiourea (10b). This compound was synthesized according to the general procedure using aminophosphine 1b (53 mg, 0.17 mmol) and 4-nitrophenyl isothiocyanate (35 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL). The crude product was purified by flash chromatography on silica gel using a positive pressure of N<sub>2</sub> and solvents presparged with N<sub>2</sub> (17-20% EtOAc/hexanes) to give the pure product (46 mg, 55%) as a yellow amorphous solid. <sup>1</sup>H NMR (400 MHz, Methanol- $d_4$ )  $\delta$  8.22–8.15 (m, 2H), 7.89 (d, I = 9.2Hz, 2H), 7.55 (tq, J = 6.2, 2.7, 2.1 Hz, 3H), 7.35-7.27 (m, 4H), 7.21 (ddd, J = 7.6, 5.6, 1.4 Hz, 1H), 6.96–6.87 (m, 2H), 4.62 (td, J = 10.0, 2.0 Hz, 1H), 3.71 (s, 3H), 2.47 (dt, J = 13.9, 2.7 Hz, 1H), 2.29 (ddd, J = 14.1, 11.5, 2.8 Hz, 1H), 0.98 (s, 9H).<sup>13</sup>C NMR (125 MHz, Methanol- $d_4$ )  $\delta$  182.6, 162.4 (d, J = 11.0 Hz), 147.7, 134.6 (d, J = 20.0 Hz), 133.8 (d, J = 10.0 Hz), 131.3, 129.7, 129.1 (d, J = 8.0 Hz), 125.2, 122.0, 121.9 (d, J = 3.0 Hz), 111.9 (d, J = 2.0 Hz), 60.1 (d,  ${}^{2}J_{CP} = 14.0$ Hz), 56.0, 37.4 (d,  ${}^{3}J_{CP}$  = 7.0 Hz), 30.2 (d,  ${}^{1}J_{CP}$  = 12.0 Hz), 26.9.  ${}^{31}P$ NMR (160 MHz, Methanol- $d_4$ )  $\delta$  -30.67. IR (neat, cm<sup>-1</sup>) 2962 (w), 1596 (m), 1509 (m), 1431 (w), 1336 (s), 1309 (s), 1293 (s), 1243 (m), 1179 (w), 1111 (w), 1023 (w), 851 (w), 752 (m). Optical rotation  $[\alpha]_{589}^{20}$  = +5.5 (*c* = 0.01 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, *m*/ z) calculated for  $C_{26}H_{31}N_3O_3PS$  [(M + H)<sup>+</sup>]: 496.1816. Found: 496.1824.

1-(3,5-Bis(trifluoromethyl)phenyl)-3-((S)-1-((S)-(2methoxyphenyl)(phenyl)phosphany)-3,3-dimethylbutan-2-yl)thiourea (11b). This compound was synthesized according to the general procedure using aminophosphine 1b (53 mg, 0.17 mmol) and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (52 mg, 0.19 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL). The crude product was purified by flash chromatography on silica gel using a positive pressure of N2 and solvents presparged with  $N_2$  (14–20% EtOAc/hexanes) to give the pure product (65 mg, 65%) as a white amorphous solid. <sup>1</sup>H NMR (400 MHz, Methanol-d<sub>4</sub>) δ 8.20 (s, 2H), 7.61 (s, 1H), 7.54 (m, 2H), 7.37-7.27 (m, 4H), 7.23 (t, J = 6.8 Hz, 1H), 6.96-6.85 (m, 2H), 4.65 (td, J = 10.5, 2.2 Hz, 1H), 3.71 (s, 3H), 2.47 (dt, J = 13.8, 2.7 Hz, 1H), 2.33 (ddd, J = 13.8, 11.4, 2.1 Hz, 1H), 0.99 (s, 9H). <sup>13</sup>C NMR (125 MHz, Methanol- $d_4$ )  $\delta$  183.2, 162.5 (d, J = 10.0 Hz), 143.4, 139.4 (d, J = 11.3 Hz), 134.5 (d, J = 18.8 Hz), 133.9 (d, J = 10.0 Hz), 132.4 (q,  ${}^{2}J_{CF}$  = 32.5 Hz), 131.3, 129.6, 129.1 (d, J = 7.5 Hz), 127.9 (d, J = 13.8 Hz), 124.8 (q,  ${}^{1}J_{CF}$  = 270.0 Hz), 123.4 (m), 121.9 (d, J = 3.8 Hz), 117.3 (m), 111.9, 60.2 (d,  ${}^{2}J_{CP}$  = 13.8 Hz), 55.9, 37.4 (d,  ${}^{3}J_{CP}$  = 7.5 Hz), 30.0 (d,  ${}^{1}J_{CP}$  = 11.2 Hz), 26.9.  ${}^{31}P$  NMR (160 MHz, Methanol $d_4$ ) δ −30.28. <sup>19</sup>F NMR (376 MHz, Methanol- $d_4$ ) δ −64.42. IR (neat, cm <sup>-1</sup>) 3357 (w), 2961 (w), 1588 (w), 1508 (m), 1473 (m), 1384 (s), 1274 (s), 1165 (s), 1127 (s), 744 (m), 882 (m). Optical rotation  $[\alpha]_{509}^{389}$  = +50.8 (c = 0.01 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, *m/z*) calculated for C<sub>28</sub>H<sub>30</sub>F<sub>6</sub>N<sub>2</sub>OPS [(M + H)<sup>+</sup>]: 587.1726. Found: 587.1721.

(S)-1-(1-(Diphenylphosphanyl)-3,3-dimethylbutan-2-yl)-3-(4nitrophenyl)thiourea (10c). This compound was synthesized according to the general procedure using (S)-1-(diphenylphosphanyl)-3,3-dimethylbutan-2-amine<sup>11</sup> (73 mg, 0.26 mmol) and 4-nitrophenyl isothiocyanate (52 mg, 0.29 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9 mL). The crude product was purified by flash chromatography on silica gel using a positive pressure of  $N_2$  and solvents presparged with  $N_2$  (14–20%) EtOAc/hexanes) to give the pure product (76 mg, 63%) as a white amorphous solid. <sup>1</sup>H NMR (300 MHz, Methanol- $d_4$ )  $\delta$  8.21–8.12 (m, 2H), 7.87 (d, J = 9.1 Hz, 2H), 7.57-7.40 (m, 4H), 7.37-7.20 (m, 6H), 4.72 (ddd, J = 11.8, 9.6, 2.1 Hz, 1H), 2.57 (dt, J = 14.2, 2.7 Hz, 1H), 2.15 (ddd, J = 13.9, 11.7, 2.0 Hz, 1H), 0.99 (s, 9H). <sup>13</sup>C NMR (125 MHz, Methanol- $d_4$ )  $\delta$  182.6, 147.7, 144.1, 140.6 (d,  ${}^{1}J_{CP}$  = 12.5 Hz), 140.3 (d,  ${}^{1}J_{CP}$  = 13.8 Hz), 134.3 (d,  ${}^{2}J_{CP}$  = 18.8 Hz), 133.8 (d,  ${}^{2}J_{\rm CP}$  = 20.0 Hz), 129.8, 129.5, 129.4 (d,  ${}^{3}J_{\rm CP}$  = 6.3 Hz), 129.3 (d,  ${}^{3}J_{\rm CP}$  = 7.5 Hz), 125.2, 122.0, 60.4 (d,  ${}^{2}J_{\rm CP}$  = 15.0 Hz), 37.4 (d,  ${}^{3}J_{\rm CP}$  = 7.5 Hz), 32.4 (d,  ${}^{1}J_{\rm CP}$  = 13.8 Hz), 26.9.  ${}^{31}$ P NMR (120 MHz, Methanol- $d_4$ )  $\delta$ -22.06. IR (neat, cm<sup>-1</sup>) 2962 (w), 1596 (w), 1506 (s), 1434 (w), 1325 (s), 1302 (s), 1258 (m), 1245 (m), 1175 (m), 1110 (m), 849 (m), 740 (s), 693 (s). Optical rotation  $[\alpha]_{589}^{20} = +51.4$  (c = 0.03 g mL<sup>-1</sup>, CHCl<sub>3</sub>). HRMS (DART, m/z) calculated for C<sub>25</sub>H<sub>29</sub>N<sub>3</sub>O<sub>2</sub>PS  $[(M + H)^+]$ : 466.1716. Found: 466.1718.

General Procedure for the Morita-Baylis-Hillman Reaction. Methyl (R)-2-(Hydroxyl(phenyl)methyl)acrylate (12). To an ovendried 2-dram vial equipped with a magnetic stirring bar was added thiourea catalyst 10a (5.0 mg, 0.01 mmol) in the glovebox. Five Å molecular sieves (50 mg) and methyl acrylate (13 mg, 0.15 mmol) were added. THF (0.3 mL) was then added. Benzaldehyde (5.2 mg, 0.05 mmol) was added and the vial was sealed. The reaction was stirred at 23 °C for 72 h and then filtered over a short plug of Celite. The filtrate was concentrated in vacuo to give the crude product that was purified by flash chromatography on silica gel (13-17% EtOAc/ hexanes) to give the pure product (5.0 mg, 57%) as a colorless oil. The enantiomeric excess was 76%, as judged by HPLC with a chiral stationary phase. Characterization data were consistent with those reported previously.<sup>21a</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.40-7.31 (m, 4H), 7.31-7.25 (m, 1H), 6.33 (s, 1H), 5.84 (s, 1H), 5.56 (d, J = 4.9 Hz, 1H), 3.71 (s, 3H), 3.14 (d, J = 5.5 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.9, 142.1, 141.4, 128.6, 128.0, 126.7, 126.2, 73.4, 52.1. Optical rotation  $[\alpha]_{589}^{20} = -7.2$  (c = 0.003 g mL<sup>-1</sup>, CHCl<sub>3</sub>). Lit. (S enantiomer, 75% ee): + 47.3 (c = 0.1, CHCl<sub>3</sub>).<sup>37</sup> HPLC conditions Chiralpak IB, 2.0% isopropanol/hexanes, 0.75 mL/min, 254 nm, tr: 23.75 and 25.66 min.

*Methyl* (*R*)-2-((4-Bromophenyl)(hydroxyl)methyl)acrylate (13). This compound was synthesized according to the general procedure using catalyst **10a** (5.0 mg, 0.01 mmol), methyl acrylate (13 mg, 0.15 mmol), and 4-bromobenzaldehyde (9.3 mg, 0.05 mmol) in THF (0.3 mL). The crude product was purified by chromatography on silica gel (10–17% EtOAc/hexanes) to give the pure product (11 mg, 80%) as a colorless oil. The enantiomeric excess was 81%, as judged by HPLC with a chiral stationary phase. Characterization data were consistent with those reported previously.<sup>21a</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.50–7.42 (m, 2H), 7.27–7.21 (m, 2H), 6.33 (s, 1H), 5.83 (s, 1H), 5.49 (d, *J* = 5.2 Hz, 1H), 3.72 (s, 3H), 3.18 (d, *J* = 5.6 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.7, 141.7, 140.5, 131.6, 128.4, 126.5, 121.9, 72.8, 52.2. Optical rotation [ $\alpha$ ]<sup>20</sup><sub>589</sub> = +2.9 (*c* = 0.006 g mL<sup>-1</sup>, CHCl<sub>3</sub>). Lit. (83% ee): + 7.9 (*c* = 1.0, CHCl<sub>3</sub>).<sup>21a</sup> HPLC conditions Chiralcel OD-H, 0.8% isopropanol/hexanes, 210 nm, 1.0 mL/min, *t<sub>r</sub>*: 44.45 and 49.92 min.

*Methyl* (*R*)-2-(*Hydroxy*(*p*-tolyl)*methyl*)*acrylate* (14). This compound was synthesized according to the general procedure using catalyst 10a (5.0 mg, 0.01 mmol), methyl acrylate (13 mg, 0.15 mmol), and *p*-tolualdehyde (6.0 mg, 0.05 mmol) in THF (0.3 mL). The crude product was purified by chromatography on silica gel (10–

17% EtOAc/hexanes) to give the pure product (4.2 mg, 41%) as a colorless oil. The enantiomeric excess was 73%, as judged by HPLC with a chiral stationary phase. Characterization data were consistent with those reported previously.<sup>21a</sup> <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.26 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.33 (s, 1H), 5.85 (s, 1H), 5.53 (s, 1H), 3.72 (s, 3H), 2.95 (s, 1H), 2.34 (s, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  166.9, 142.2, 138.5, 137.7, 129.3, 126.6, 126.0, 73.3, 52.0, 21.3. Optical rotation  $[\alpha]_{289}^{289} = -13.4$  (*c* = 0.002 g mL<sup>-1</sup>, CHCl<sub>3</sub>). Lit (83% ee) -57.4 (*c* = 0.54, CHCl<sub>3</sub>).<sup>21a</sup> HPLC conditions Chiralpak IB, 2.0% isopropanol/hexanes, 0.5 mL/min, 254 nm, *t<sub>r</sub>*: 29.84 and 32.29 min.

**Computational Methods.** DFT calculations were carried out using the Gaussian 09 suite of programs,<sup>38</sup> at the B3LYP/6-31G(d,p) level of theory.<sup>39</sup> Vibrational frequency calculations were carried out to ensure that the obtained structures are minima on the potential energy surface (no imaginary frequencies). Frequency calculations were carried out at 1 atm and 298.15 K. Structures were visualized using Avogadro 1.2.0.

# ASSOCIATED CONTENT

# **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00199.

Copies of <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra; Cartesian coordinates and energies of calculated structures (PDF) Crystallographic information file for  $(S,R_P)$ -8a·HCl (CIF)

Crystallographic information file for  $(S,S_P)$ -9b·BH<sub>3</sub> (CIF)

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#### Notes

The authors declare no competing financial interest.

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