Synthesis of α-Aminophosphonates by Umpolung-Enabled Cu-Catalyzed Regioselective Hydroamination

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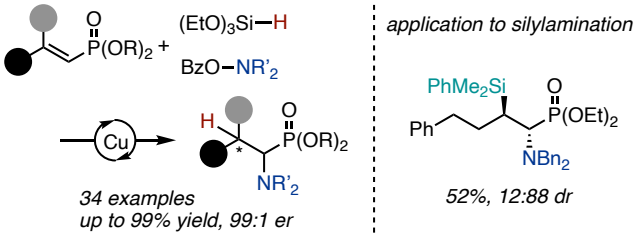
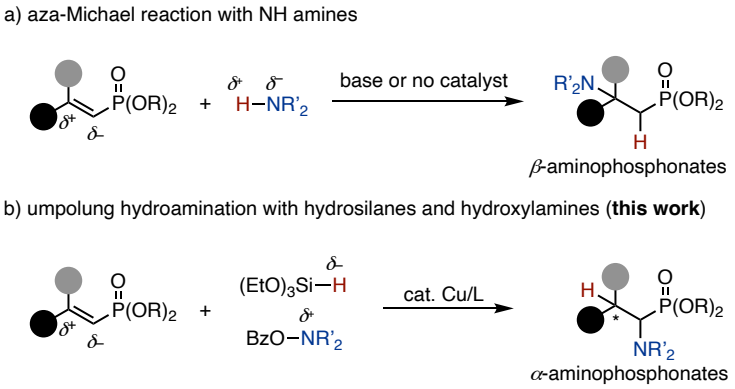


A copper-catalyzed regioselective hydroamination of α,β-unsaturated phosphonates has been developed to form corresponding α-aminophosphonates of interest in medicinal chemistry. The introduction of an umpolung, electrophilic amination strategy with the hydroxylamine derivative is the key to achieving the α-amination regioselectivity, which is otherwise difficult under the conventional nucleophilic

hydroamination conditions with the parent amine. Asymmetric synthesis with a chiral bisphosphine ligand and application to a related silylamination reaction are also described.

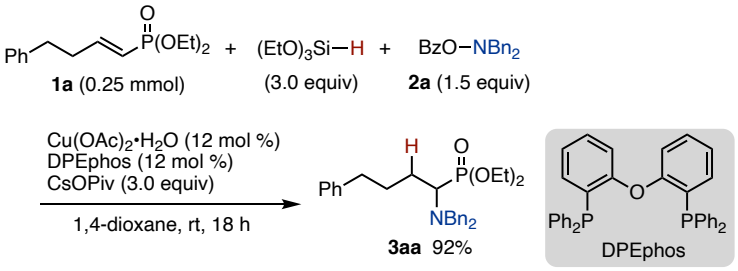
An α-aminophosphonic acid is a phosphorus analogue of α-amino acid and frequently found in bioactive molecules and pharmaceutical agents, as exemplified by alafosfalin, prodipine, and incadronate.[1] Accordingly, such a structural motif has great potential in medicinal and pharmaceutical applications, and several preparative methods thus have been developed by synthetic chemists.[2] The aza-Michael reaction of readily available α,β-unsaturated phosphonates with NH amines also seems to be a concise approach to the targeted molecule. However, due to their inherent polarization of the C=C bond, the product obtained is not the desired α-aminophosphonate but the regioisomeric β-aminophosphonate (Scheme 1a).[3] On the contrary, we recently reported the copper-catalyzed regioselective hydroamination[4] reaction of α,β-unsaturated esters with the hydrosilane and hydroxylamine to deliver the corresponding α-amino acid with high α-amination selectivity.[5] The key to success is the polarity inversion (umpolung)[6] concept using the nucleophilic hydride (hydrosilane) and electrophilic amino source (hydroxylamine).[7] Because of our continuing interest in this chemistry, we have now developed a copper-catalyzed umpolung-enabled regioselective hydroamination of α,β-unsaturated phosphonates, giving the α-aminophosphonates in good yields (Scheme 1b). By using a suitable ancillary chiral bisphosphine ligand, the asymmetric induction can also form the enantioenriched α-aminophosphonate. Additionally, the use of a silylborane instead of the hydrosilane enables the regioselective silylamination[8] reaction. Detailed optimization studies and the substrate scope are described herein.

Scheme 1. Approaches to Aminophosphonic Acids from α,β-Unsaturated Phosphonates and Amines



We began our optimization studies with β-phenethyl-α,β-unsaturated phosphonate **1a**, *O*-benzoyl-*N,N*-dibenzylhydroxylamine (**2a**), and $(EtO)_3SiH$ to identify the suitable copper catalyst, ligand, additives, and solvent. After the extensive screening, we found that by using a combination of a $Cu(OAc)_2•H_2O$/DPEphos catalyst and a CsOPiv additive, the reaction proceeded smoothly in 1,4-dioxane even at room temperature to deliver the desired α-aminophosphonate **3aa** in 92% isolated yield with exclusive α-amination regioselectivity (Scheme 2). Some observations in optimization studies are noted. Several monodentate and bidentate phosphine ligands showed moderate to good performance, but no reaction occurred in the absence of phosphine ligands or Cu salts. The CsOPiv additive was not indispensable but remarkably increased the reaction efficiency. The yield of **3aa** was less dependent on the leaving group of the amine, and thus, the most readily available benzoyl derivative, **2a**, was employed as the optimal amination reagent (see the Supporting Information for more details).

Scheme 2. Optimal Conditions for Cu-Catalyzed Regioselective Hydroamination of 1a with $(EtO)_3SiH$ and 2a.



Under the conditions described in Scheme 2, we investigated the scope of α,β-unsaturated phosphonates **1** and hydroxylamines **2**. The structures of representative products **3** are shown in Figure 1. In addition to the primary alkyl substituents (**3aa** and **3ba**), the more congested cyclopropyl- and cyclohexyl substituents were well tolerated under the standard conditions (**3ca** and **3da**, respectively). The copper catalysis was compatible with a wide range of functional groups, including benzyl ether, acetal, silyl ether, ester, Boc-protected amine, and alkyl bromide (**3ea**–**ja**, respectively). Aromatic substrate **1k** was also amenable to the hydroamination to form the corresponding α-aminophosphonate **3ka** with high regioselectivity (>20/1 in the crude mixture). Moreover, the electron-rich (**3la**), electron-deficient (**3ma**), halogenated (**3na**), higher-fused (**3oa**), and heteroatom-incorporated (**3pa** and **3qa**) aromatic rings all were accommodated to deliver the targeted hydroaminated products in good yields. The scope of hydroxylamines was also substantially broad. Both acyclic (**3ab**–**ad**) and cyclic (**3ae**–**ah**) amines were coupled with α,β-unsaturated phosphonate **1a** to furnish the hydroaminated products in good yields. Notably, the antidepressant drug, nortriptyline, was also successfully conjugated with **1a**, and the corresponding complex α-aminophosphonate **3ai** was obtained in 84% yield.

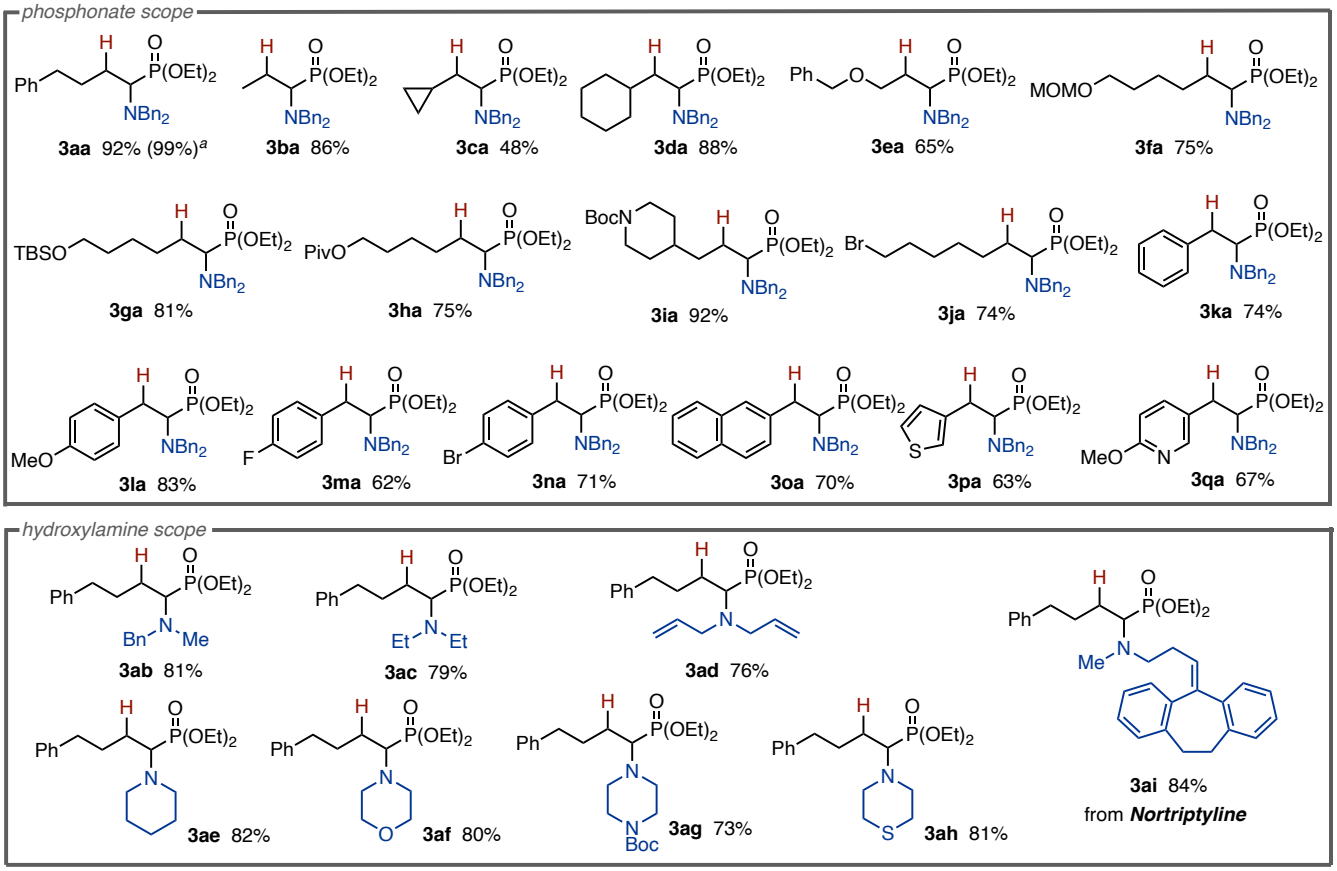
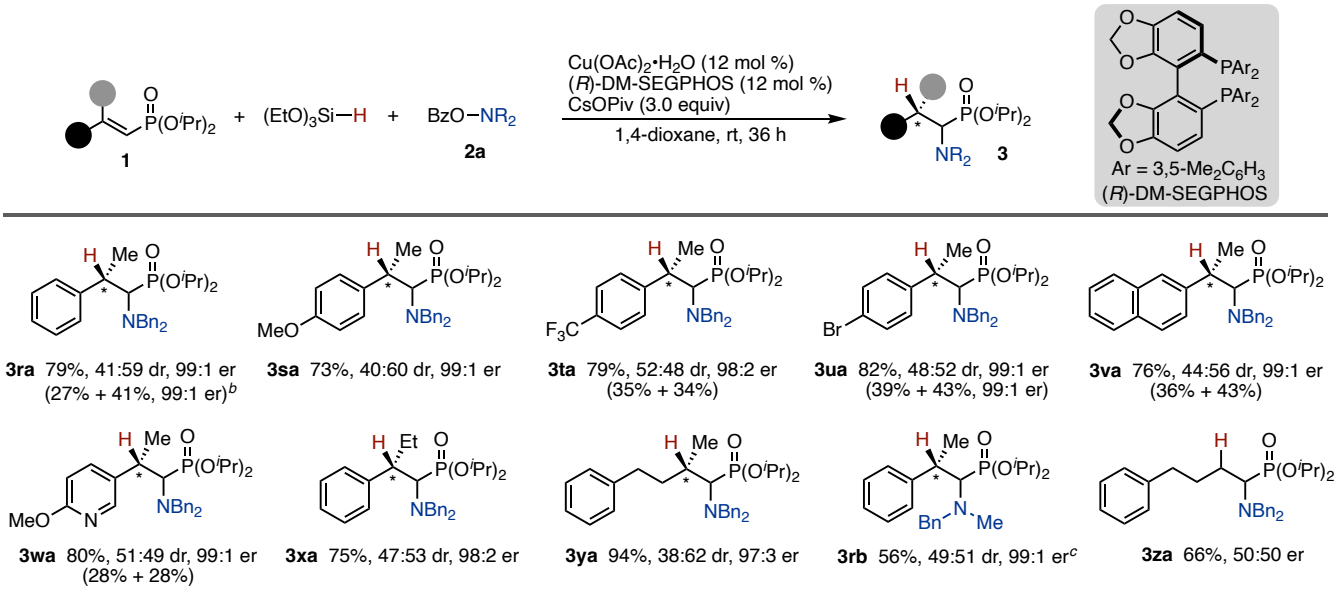


Figure 1. Structures of α-aminophosphonates **3** synthesized by Cu-catalyzed hydroamination. Isolated yields are given. Reaction conditions: $Cu(OAc)_2•H_2O$ (0.030 mmol), DPEphos (0.030 mmol), **1** (0.25 mmol), $(EtO)_3SiH$ (0.75 mmol)**, 2** (0.38 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 18–36 h. [a] On a 1.0 mmol scale.

The umpolung-enabled copper-catalyzed hydroamination protocol could also be applied to the β,β-disubstituted α,β-unsaturated phosphonates (Scheme 3). In this case, the asymmetric synthesis was possible by using the (*R*)-DM-SEGPHOS ligand, and the corresponding enantioenriched α-aminophosphonates were formed with high enantioselectivity. For example, β-methyl-β-phenyl phosphonate **1r** was converted to optically active **3ra** in 79% yield with a 99/1 enantiomeric ratio (er). Unfortunately, the point chirality at the α-position was not controlled well, and the diastereomeric ratio was thus low (41/59 dr). However, both diastereomers could be separated from each other and isolated in stereochemically pure forms by chromatographic purification. Additionally, the benzyl group on

nitrogen could be readily deprotected under the standard hydrogenolysis conditions using $Pd(OH)_2$ to deliver the optically active primary α-NH_2 phosphonate (see the Experimental Section for details). The asymmetric copper catalysis was tolerant of the electronically diverse aryl groups at the β-position, such as methoxy-, trifluoromethyl-, and bromo-substituted phenyl rings (**3sa**–**ua**, respectively). Naphthalene and pyridine were also viable substituents (**3va** and **3wa**, respectively). Furthermore, the β-ethyl-β-phenyl- and β,β-dialkyl-substituted phosphonates underwent the enantioselective hydroamination to afford **3xa** and **3ya**, respectively, with high enantioselectivity. The absolute configuration at the β-position was assigned by the reported enantioselective conjugated reduction of α,β-unsaturated phosphonates with a similar CuH/(*R*)-SEGPHOS catalytic system.[9] On the contrary, attempts to apply β-monosubstituted substrates such as **1z** remained unsuccessful, thus again indicating negligible stereocontrol at the α-position (**3za**).[10]



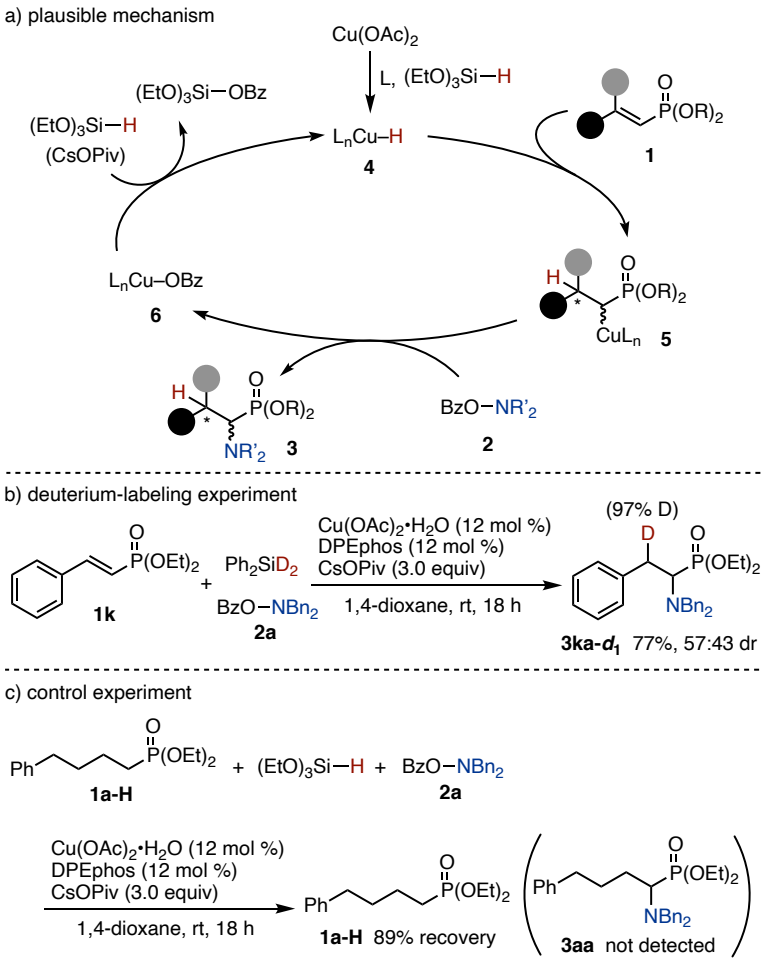
Scheme 3. Cu-Catalyzed Regio- and Enantioselective Hydroamination of β,β-Disubstituted α,β-Unsaturated Phosphonates 1.[a]

[a] Reaction conditions: $Cu(OAc)_2$•H_2O (0.030 mmol), (*R*)-DM-SEGPHOS (0.030 mmol), **1** (0.25 mmol), $(EtO)_3SiH$ (0.75 mmol), **2** (0.38 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 36 h. Isolated yields are given. The relative stereochemistry was analogously assigned by the previous umpolung-

enabled CuH-catalyzed hydroamination of α,β-unsaturated esters.[5] [b] On a 1.0 mmol scale. [c] With $(2,6\text{-MeO})_2C_6H_3COO$–NBnMe **2b-(OMe)$_2$** instead of **2b**.

Our mechanistic proposal is shown in Scheme 4a. Catalytically active copper hydride **4** is initially formed by the reduction of $Cu(OAc)_2$ with $(EtO)_3SiH$ and ligand (L) coordination.[11] The regioselective insertion of α,β-unsaturated phosphonate **1** into the Cu–H bond of **4** then generates phosphonate α-cuprate **5**, in which the stereochemistry at the β-position is well controlled when the chiral (*R*)-DM-SEGPHOS ligand is used.[9,12] On the contrary, the stereochemical information at the α-position is labile or easily lost by the tautomerization.[13] Subsequent electrophilic amination with **2** occurs to deliver the observed α-aminophosphonate **3** and L_nCu-OBz species **6**. The catalytic cycle is completed by a final σ-bond metathesis with $(EtO)_3SiH$. The exact role of CsOPiv remains unclear, but it can accelerate the σ-bond metathesis between the Cu salt and $(EtO)_3SiH$ or suppress the nonproductive decomposition of hydroxylamine **2** with copper hydride **4**[5] to increase the overall reaction efficiency. The deuterium labeling experiment with $PhSiD_2$ in Scheme 4b supports the proposed reaction mechanism, where the hydride at the β-position of the product is incorporated from the hydrosilane via formation of the copper hydride intermediate. Additionally, we also confirmed the lack of product formation from saturated phosphonate **1a-H** (Scheme 4c), thus excluding the possibility of stepwise conjugate reduction and base-promoted electrophilic amination at the α-position of the saturated phosphonate.

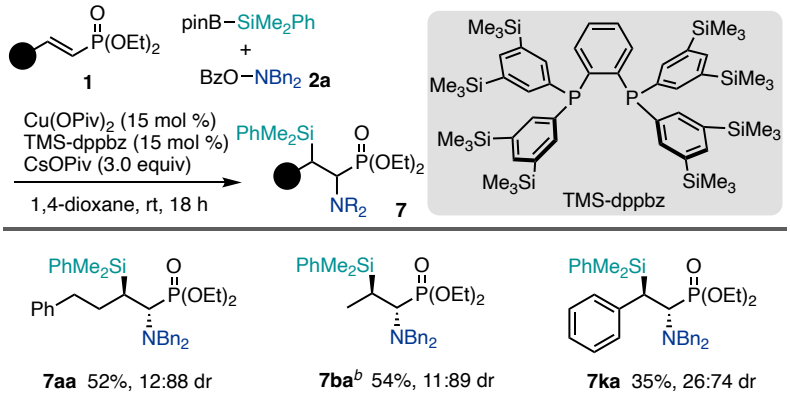
Scheme 4.



According to the tentative reaction mechanism in Scheme 4a, external nucleophiles other than the hydrosilane could be used to develop the aminative difunctionalization of the α,β-unsaturated phosphonate. After our preliminary survey, the silylborane, pinB–$SiMe_2Ph$, was found to work as the efficient silyl nucleophile in $Cu(OPiv)_2$/TMS-dppbz catalysis to produce the corresponding β-silyl-α-aminophosphonate **7aa** in 52% yield with 12/88 dr (Scheme 5). Similar to our previous work,[5,8] the *anti*-diastereomer might be mainly formed probably because of intramolecular P=O to Si coordination of the phosphorus α-cuprate intermediate corresponding to **5** in Scheme 4a. The crotonate and cinnamate-

type substrates also participated in the reaction, and the corresponding silylaminated products **7ba** and **7ka** were obtained with similar efficiency and diastereoselectivity.

Scheme 5. Cu-Catalyzed Silylamination of α,β-Unsaturated Phosphonates 1.[a]



[a] Reaction conditions: $Cu(OPiv)_2$ (0.038 mmol), TMS-dppbz (0.038 mmol), **1** (0.25 mmol), pinB–$SiMe_2Ph$ (0.88 mmol)**,** **2** (0.38 mmol), CsOPiv (0.75 mmol), 1,4-dioxane (1.0 mL), rt, 18 h. Isolated yields are given. [b] With PivO–NBn_2 **2a-Piv** instead of **2a.**

In conclusion, we have developed a copper-catalyzed regio- and enantioselective hydroamination of α,β-unsaturated phosphonates with hydrosilanes and hydroxylamines to form the corresponding α-aminophosphonates of important pharmacophores in bioactive molecules and pharmaceutical agents. An umpolung, electrophilic amination strategy using the hydroxylamine is critical to induce the desired α-amination selectivity. Asymmetric induction can also be realized by using the commercially available DM-SEGPHOS ligand to deliver the enantioenriched α-aminophosphonates. Moreover, with the silylborane instead of the hydrosilane, the nitrogen umpolung strategy also enables the silylamination reaction, which is difficult to achieve by other means. Improvement of diastereoselectivity and further development of related aminofunctionalizations based on the concept of nitrogen umpolung are currently underway in our laboratory.

Experimental Section

Instrumentation and Chemicals ^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$, and $^{31}P\{^{1}H\}$ NMR spectra were recorded at 400, 100, 376, and 162 MHz, respectively, for $CDCl_3$ solutions (qd, quartet of doublets; dd, doublet of doublets; td, triplet of doublets; ddt, doublet of doublet of triplets; ddd, doublet of doublet of doublets). HRMS data were obtained by APCI using TOF. GC analysis was carried out using a silicon OV-17 column [2.6 mm (inside diameter) x 1.5 m] or a CBP-1 capillary column [0.5 mm (inside diameter) x 25 m]. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck silica gel $60F_{254}$. Silica gel (Wakosil-200 or 60 N, spherical neutral, Kanto Chemical Co.) was used for column chromatography. Gel permeation chromatography (GPC) was performed with a model LC-20AR pump (Shimadzu, 7.5 mL of $CHCl_3$/min) and a model SPD-20A UV detector (Shimadzu, 254 nm) with two in-line YMC-GPC T2000 preparative columns (20 mm x 600 mm, particle size of 10 μm) YMC). Chiral high-performance liquid chromatography (HPLC) analysis on a chiral stationary phase was performed using alliance (Waters e2695).

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. 1,4-Dioxane was dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.) prior to use. The silylborane pinB-$SiMe_2Ph$ should be further purified by filtration through a neutral alumina, long-body Sep-Pak cartridge (waters). CsOPiv obtained from Aldrich should be crushed to pieces with a mortar and a pestle in a glovebox filled with nitrogen and then dried at 100 ˚C under high vacuum overnight (note that this preactivation was essential for reproducibility). $Cu(OPiv)_2$ was prepared according to the literature method.[14] TMS-dppbz was synthesized from 1,2-bis(dichlorophosphino)benzene and 1,3-bis(trimethylsilyl)phenyl magnesium bromide.[15] The α,β-unsaturated phosphonates **1** were generally prepared by the HWE reaction of the corresponding aldehydes and ketones.[16] The *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**) and *O*-benzoyl-*N*,*N*-diethylhydroxylamine (**2c)** were prepared from the corresponding *N,N*-dialkylhydroxylamines and

benzoyl chloride. Others were obtained by the nucleophilic substitution reaction of parent NH amines and benzoyl peroxide.[17] Unless otherwise noted, all reactions were performed under nitrogen conditions.

General Procedure for the Cu-Catalyzed Hydroamination of α,β-Unsaturated Phosphonates with Hydrosilanes and Hydroxylamines. $Cu(OAc)_2•H_2O$ (6.0 mg, 0.030 mmol, 12 mol %), DPEphos (16 mg, 0.030 mmol, 12 mol %), and CsOPiv (176 mg, 0.75 mmol, 3.0 equiv) were placed in a 20 mL Schlenk tube, which was filled with nitrogen by the standard Schlenk technique. 1,4-Dioxane (1.0 mL) was added, and the mixture was stirred for 15 min at room temperature. $(EtO)_3SiH$ (0.14 mL, 0.75 mmol, 3.0 equiv) was then added, and the suspension was stirred for an additional 5 min. Finally, α,β-unsaturated phosphonate **1** (0.25 mmol, 1.0 equiv) and *O*-benzoyl-*N*,*N*-dialkylhydroxylamine **2** (0.38 mmol, 1.5 equiv) were added, and the mixture was stirred for 18 h at the same temperature. The resulting mixture was directly filtered through a short pad of neutral alumina and Na_2SO_4. The filtrate was evaporated in vacuo and purified by silica gel (Wakosil-200) column chromatography with hexane/ethyl acetate to give hydroaminated product **3**. In some cases, additional purification was performed by GPC to obtain the pure product.

1.0 mmol Scale Synthesis of 3aa. $Cu(OAc)_2•H_2O$ (24 mg, 0.12 mmol), DPEphos (64 mg, 0.12 mmol), and CsOPiv (704 mg, 3.0 mmol) were placed in a 25 mL two-neck reaction flask, which was filled with nitrogen by the standard Schlenk technique. 1,4-Dioxane (4.0 mL) was added, and the mixture was stirred for 15 min at room temperature. $(EtO)_3SiH$ (0.56 mL, 3.0 mmol) was then added, and the suspension was stirred for additional 5 min. Finally, diethyl (*E*)-(4-phenylbut-1-en-1-yl)phosphonate (**1a**; 268 mg, 1.0 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**; 476 mg, 1.50 mmol) were added, and the mixture was stirred for 18 h at the same temperature. The resulting mixture was directly filtered through a short pad of neutral alumina and Na_2SO_4. The filtrate was evaporated in vacuo and purified by silica gel (Wakosil-200) column chromatography with hexane/ethyl acetate (1/1, v/v) to give diethyl [1-(dibenzylamino)-4-phenylbutyl]phosphonate (**3aa**, 461 mg, 0.99 mmol) in 99% yield.

Diethyl [1-(Dibenzylamino)-4-phenylbutyl]phosphonate (3aa). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 107 mg (92%, 0.25 mmol scale); white solid; mp 75.6 ºC dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.21 (m, 12H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 2H), 4.14-4.06 (m, 4H), 3.91-3.84 (m, 4H), 2.99 (ddd, *J* = 15.5, 10.0, 3.7 Hz, 1H), 2.45-2.30 (m, 2H), 1.93-1.74 (m, 2H), 1.66-1.60 (m, 2H), 1.321 (t, *J* = 7.0 Hz, 3H), 1.317 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 142.1, 139.8, 129.3, 128.5, 128.3 (2C), 127.0, 125.7, 61.3 (d, *J* = 7.2 Hz), 60.9 (d, *J* = 7.4 Hz), 54.9, 54.8 (d, *J* = 131.3 Hz), 35.1, 28.1 (d, *J* = 12.2 Hz), 26.9 (d, *J* = 6.3 Hz), 16.72 (d, *J* = 6.0 Hz), 16.66 (d, *J* = 6.1 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 29.13; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{28}H_{37}NO_3P$ 466.2499, found 466.2506.

Diethyl [1-(Dibenzylamino)propyl]phosphonate (3ba). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 81 mg (86%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, *J* = 7.0 Hz, 4H), 7.30 (t, *J* = 7.4 Hz, 4H), 7.23 (t, *J* = 7.2 Hz, 2H), 4.19-4.05 (m, 4H), 3.92-3.86 (m, 4H), 2.85 (ddd, *J* = 14.4, 9.8, 4.5 Hz, 1H), 1.84-1.64 (m, 2H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 0.96 (td, *J* = 7.2, 0.7 Hz, 3H);^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.8, 129.1, 128.1, 126.8, 61.2 (d, *J* = 7.2 Hz), 60.9 (d, *J* = 7.4 Hz), 56.9 (d, *J* = 131.1 Hz), 54.7 (d, *J* = 2.1 Hz), 20.6 (d, *J* = 6.4 Hz), 16.6 (d, *J* = 4.8 Hz), 16.5 (d, *J* = 5.1 Hz), 12.0 (d, *J* = 12.8 Hz), ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 29.16; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{21}H_{31}NO_3P$ 376.2036, found 376.2052.

Diethyl [2-Cyclopropyl-1-(dibenzylamino)ethyl]phosphonate (3ca). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 48 mg (48%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 7.1 Hz, 4H), 7.30 (t, *J* = 7.3 Hz, 4H), 7.22 (t, *J* = 7.2 Hz, 2H), 4.14-4.04 (m, 4H), 3.95-3.87 (m, 4H), 3.13 (ddd, *J* = 15.9, 9.6, 4.3 Hz, 1H), 2.04-1.94 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27-1.20 (m, 1H), 1.08-0.98 (m,

1H), 0.53-0.47 (m, 1H), 0.26-0.19 (m, 1H), 0.10-0.04 (m, 1H), -0.13- -0.19 (m, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 129.1, 128.2, 126.9, 61.4 (d, *J* = 7.1 Hz), 61.0 (d, *J* = 7.4 Hz), 55.9 (d, *J* = 132.7 Hz), 54.9 (d, *J* = 2.8 Hz), 33.0 (d, *J* = 6.7 Hz), 16.7 (d, *J* = 5.0 Hz), 16.6 (d, *J* = 5.1 Hz), 9.5 (d, *J* = 14.5 Hz), 5.8, 4.8; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.98; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{23}H_{33}NO_3P$ 402.2193, found 402.2194.

Diethyl [2-Cyclohexyl-1-(dibenzylamino)ethyl]phosphonate (3da). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 98 mg (88%, 0.25 mmol scale); white solid; mp 76.2-77.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.29 (m, 8H), 7.23 (t, *J* = 6.9 Hz, 2H), 4.19-4.07 (m, 4H), 3.91 (d, *J* = 13.4 Hz, 2H), 3.84 (dd, *J* = 13.4, 4.6 Hz, 2H) 3.04 (ddd, *J* = 15.8, 10.5, 3.1 Hz, 1H), 1.70-1.55 (m, 5H), 1.46-1.43 (m, 1H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 1.31-1.16 (m, 2H), 1.13-0.86 (m, 4H), 0.45 (qd, *J* = 12.2, 3.5 Hz, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 140.0, 129.3, 128.1, 127.0, 61.3 (d, *J* = 7.1 Hz), 61.1 (d, *J* = 7.8 Hz), 54.8 (d, *J* = 1.0 Hz), 52.0 (d, *J* = 130.0 Hz), 35.4 (d, *J* = 5.9 Hz), 34.3, 33.4 (d, *J* = 11.5 Hz), 31.8, 26.7, 26.6, 26.1, 16.74 (d, *J* = 6.1 Hz), 16.67 (d, *J* = 6.2 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 29.94; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{26}H_{39}NO_3P$ 444.2662, found 444.2671.

Diethyl [3-(Benzyloxy)-1-(dibenzylamino)propyl]phosphonate (3ea). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 79 mg (65%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.17 (m, 15H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.27 (d, *J* = 11.8 Hz, 1H), 4.14-4.04 (m, 4H), 3.91 (dd, *J* = 13.5, 3.9 Hz, 2H), 3.86 (d, *J* =13.5 Hz, 2H), 3.63-3.58 (m, 1H), 3.46-3.41 (m, 1H), 3.20 (ddd, *J* = 16.0, 8.4, 5.1 Hz, 1H), 2.04-1.96 (m, 2H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.8, 138.5, 129.2, 128.21, 128.19, 127.6, 127.4, 127.0, 72.7, 67.3 (d, *J* = 12.5 Hz), 61.5 (d, *J* = 6.9 Hz), 61.1 (d, *J* = 7.4 Hz), 54.9 (d, *J* = 2.4 Hz), 52.1 (d, *J* = 135.1 Hz), 28.0 (d, *J* = 6.6 Hz), 16.62 (d, *J* = 5.4 Hz), 16.58 (d, *J* = 5.4 Hz),

$^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.47; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{28}H_{37}NO_4P$ 482.2455, found 482.2443.

Diethyl [1-(Dibenzylamino)-6-(methoxymethoxy)hexyl]phosphonate (3fa). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 89 mg (75%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 6.9 Hz, 4H), 7.30 (t, J = 7.1 Hz, 4H), 7.23 (t, J = 7.2 Hz, 2H), 4.60 (s, 2H), 4.17-4.07 (m, 4H), 3.89 (d, J = 13.5 Hz, 2H), 3.85 (dd, J = 13.5, 3.8 Hz, 2H), 3.48-3.39 (m, 2H), 3.35 (s, 3H), 2.93 (ddd, J = 15.8, 10.2, 3.4 Hz, 1H), 1.83-1.73 (m, 1H), 1.64-1.45 (m, 4H), 1.34 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.0 Hz, 3H) 1.27-1.03 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 129.3, 128.2, 127.1, 96.4, 67.8, 61.4 (d, J = 7.2 Hz), 61.1 (d, J = 7.4 Hz), 55.1, 54.9 (d, J = 131.2 Hz), 54.8 (d, J = 1.9 Hz), 29.7, 27.4 (d, J = 6.1 Hz), 26.6 (d, J = 11.9 Hz), 25.7, 16.8 (d, J = 5.1 Hz), 16.7 (d, J = 5.2 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 29.31; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{26}H_{41}NO_5P$ 478.2717, found 478.2705.

Diethyl [6-((*tert*-Butyldimethylsilyl)oxy)-1-(dibenzylamino)hexyl]phosphonate (3ga). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 109 mg (81%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, J = 6.9 Hz, 4H), 7.30 (t, J = 7.2 Hz, 4H), 7.23 (t, J = 7.2 Hz, 2H), 4.17-4.07 (m, 4H), 3.91-3.84 (m, 4H), 3.57-3.47 (m, 2H), 2.93 (ddd, J = 15.6, 10.2, 3.4 Hz , 1H), 1.82-1.73 (m, 1H), 1.63-1.53 (m, 2H), 1.49-1.40 (m, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.0 Hz, 3H) 1.28-1.02 (m, 3H), 0.89 (s, 9H), 0.043 (s, 3H), 0.041 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 129.2, 128.2, 127.0, 63.2, 61.4 (d, J = 7.2 Hz), 61.1 (d, J = 7.6 Hz), 54.9 (d, J = 131.1 Hz), 54.8 (d, J = 1.7 Hz), 32.8, 27.5 (d, J = 5.5 Hz), 26.6 (d, J = 11.9 Hz), 26.1, 25.3, 18.4, 16.8 (d, J = 5.4 Hz), 16.7 (d, J = 5.6 Hz), -5.2; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 29.33; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{30}H_{51}NO_4PSi$ 548.3319, found 548.3304.

6-(Dibenzylamino)-6-(diethoxyphosphoryl)hexyl Pivalate (3ha). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 97 mg (75%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, *J* = 6.8 Hz, 4H), 7.31 (t, *J* = 7.1 Hz, 4H), 7.23 (t, *J* = 7.0 Hz, 2H), 4.18-4.08 (m, 4H), 4.01-3.82 (m, 6H), 2.93 (ddd, *J* = 15.8, 10.3, 3.4 Hz , 1H), 1.82-1.73 (m, 1H), 1.61-1.47 (m, 4H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.27-1.17 (m, 1H), 1.19 (s, 9H), 1.15-0.99 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 178.6, 139.8, 129.2, 128.2, 127.0, 64.3, 61.4 (d, *J* = 7.1 Hz), 61.1 (d, *J* = 7.4 Hz), 54.80 (d, *J* = 1.8 Hz), 54.75 (d, *J* = 131.2 Hz), 38.7, 28.5, 27.4 (d, *J* = 6.3 Hz), 27.2, 26.3 (d, *J* = 11.9 Hz), 25.3, 16.71 (d, *J* = 5.5 Hz), 16.66 (d, *J* = 5.5 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 29.27; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{45}NO_5P$ 518.3030, found 518.3013.

***tert*-Butyl 4-[3-(Dibenzylamino)-3-(diethoxyphosphoryl)propyl]piperidine-1-carboxylate (3ia).** The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 129 mg (92%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 6.6 Hz, 4H), 7.30 (t, *J* = 7.1 Hz, 4H), 7.24 (t, *J* = 6.9 Hz, 2H), 4.21-4.07 (m, 4H), 4.00 (br, 2H), 3.89 (d, *J* = 13.3 Hz, 2H), 3.85 (dd, *J* = 13.5, 4.3 Hz, 2H), 2.91 (ddd, *J* = 15.6, 10.0, 3.9 Hz, 1H), 2.50 (br, 2H), 1.79-1.54 (m, 3H), 1.45 (s, 9H), 1.42-1.21 (m, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H) 1.03-0.88 (m, 3H);^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 154.8, 139.8, 129.2, 128.2, 127.0, 79.1, 61.4 (d, *J* = 7.2 Hz), 61.1 (d, *J* = 7.5 Hz), 54.7, 54.6 (d, *J* = 130.8 Hz), 43.8, 34.6, 32.9 (d, *J* = 11.8 Hz), 32.4, 31.4, 28.5, 24.2 (d, *J* = 6.4 Hz), 16.72 (d, *J* = 5.1 Hz), 16.66 (d, *J* = 5.2 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 29.30; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{31}H_{48}N_2O_5P$ 559.3295, found 559.3308.

Diethyl [7-Bromo-1-(dibenzylamino)heptyl]phosphonate (3ja)

The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 92 mg (74%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, *J* = 6.8 Hz, 4H), 7.31 (t, *J* = 7.2 Hz, 4H), 7.24 (t, *J* = 7.1 Hz, 2H), 4.18-4.08 (m, 4H), 3.90 (d, *J* = 13.9 Hz,

2H), 3.86 (dd, *J* = 13.9, 4.4 Hz, 2H), 3.36 (t, *J* = 13.7 Hz, 2H), 2.93 (ddd, *J* = 15.6, 10.1, 3.3 Hz , 1H), 1.79-1.72 (m, 3H), 1.59-1.49 (m, 2H),1.37-1.32 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H) 1.31-1.18 (m, 2H) 1.12-0.93 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 129.2, 128.2, 127.0, 61.4 (d, *J* = 7.2 Hz), 61.1 (d, *J* = 7.5 Hz), 54.8 (d, *J* = 1.8 Hz), 54.7 (d, *J* = 130.9 Hz), 34.0, 32.7, 28.1, 28.0, 27.3 (d, *J* = 6.3 Hz), 26.3 (d, *J* = 12.1 Hz), 16.74 (d, *J* = 5.4 Hz), 16.68 (d, *J* = 5.5 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 29.38; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{25}H_{38}BrNO_3P$ 510.1767, found 510.1747.

Diethyl [1-(Dibenzylamino)-2-phenylethyl]phosphonate (3ka). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 79 mg (74%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.17 (m, 9H), 7.13-7.11 (m, 4H), 7.03-7.01 (m, 2H), 4.15-4.05 (m, 4H), 3.93 (dd, *J* = 13.8, 4.1 Hz, 2H), 3.86 (d, *J* = 13.8 Hz, 2H), 3.35 (ddd, *J* = 16.2, 9.1 5.6 Hz, 1H), 3.09-2.99 (m, 2H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.4, 139.1 (d, *J* = 13.8 Hz), 129.6, 128.9, 128.14, 128.12, 126.9, 126.3, 61.5 (d, *J* = 7.2 Hz), 61.3 (d, *J* = 7.4 Hz), 55.6 (d, *J* = 134.5 Hz), 54.6 (d, *J* = 2.5 Hz), 33.8 (d, *J* = 7.4 Hz), 16.7 (d, *J* = 6.4 Hz), 16.6 (d, *J* = 6.3 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.08; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{26}H_{33}NO_3P$ 438.2193, found 438.2174.

Diethyl [1-(Dibenzylamino)-2-(4-methoxyphenyl)ethyl]phosphonate (3la). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 97 mg (83%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23-7.13 (m 10H), 6.94 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 2H), 4.15-4.05 (m, 4H), 3.93 (dd, *J* = 13.8, 4.0 Hz, 2H), 3.86 (d, *J* = 13.8 Hz, 2H), 3.84 (s, 3H), 3.30 (ddd, *J* = 16.2, 9.2, 5.5 Hz, 1H), 3.01-2.96 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 158.2, 139.4, 131.6 (d, *J* = 14.0 Hz), 130.5, 128.9, 128.1, 126.8, 113.5, 61.5 (d, *J* = 7.2 Hz), 61.2 (d, *J* = 7.4 Hz), 57.2 (d, *J* = 133.8 Hz), 55.4, 54.6 (d,

J = 2.5 Hz), 32.9 (d, *J* = 7.5 Hz), 16.7 (d, *J* = 6.1 Hz), 16.6 (d, *J* = 6.1 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.27; HRMS (APCI) m/z $(M+H)^+$ calcd for $C_{27}H_{35}NO_4P$ 468.2298, found 468.2302.

Diethyl [1-(dibenzylamino)-2-(4-fluorophenyl)ethyl]phosphonate (3ma). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 70 mg (62%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.19 (m, 6H), 7.13-7.11 (m, 4H), 6.96-6.89 (m, 4H), 4.17-4.07 (m, 4H), 3.94-3.86 (m, 4H), 3.29 (ddd, *J* = 16.0, 9.2, 5.5 Hz, 1H), 3.34- 2.93 (m, 2H), 1.343 (t, *J* = 7.0 Hz, 3H), 1.336 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 161.6 (d, *J* = 242.4 Hz), 139.2, 134.7 (dd, *J* = 14.0, 3.0 Hz), 130.9 (d, *J* = 7.8 Hz), 128.9, 128.2, 127.0, 114.8 (d, *J* = 21.1 Hz), 61.6 (d, *J* = 7.2 Hz), 61.3 (d, *J* = 7.5 Hz), 57.1 (d, *J* = 133.3 Hz), 54.6, 33.1 (d, *J* = 7.7 Hz), 16.71 (d, *J* = 6.2 Hz), 16.65 (d, *J* = 6.4 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 27.99; $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz) δ -117.20; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{26}H_{32}FNO_3P$ 456.2098, found 456.2082.

Diethyl [2-(4-bromophenyl)-1-(dibenzylamino)ethyl]phosphonate (3na). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 92 mg (71%, 0.25 mmol scale); white solid; mp 118.3-119.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.24-7.18 (m, 6H), 7.12-7.10 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.18-4.07 (m, 4H), 3.93-3.86 (m, 4H), 3.28 (ddd, *J* = 16.2, 9.2, 5.4 Hz, 1H), 3.00-2.92 (m, 2H), 1.344 (t, *J* = 7.1 Hz, 3H), 1.339 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.1, 138.2 (d, *J* = 14.3 Hz), 131.2, 131.1, 128.8, 128.2, 127.0, 120.0, 61.6 (d, *J* = 7.2 Hz), 61.3 (d, *J* = 7.5 Hz), 57.0 (d, *J* = 133.4 Hz), 54.6 (d, *J* = 2.0 Hz), 33.4 (d, *J* = 6.0 Hz), 16.7 (d, *J* = 5.9 Hz), 16.6 (d, *J* = 6.3 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 27.79; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{26}H_{32}BrNO_3P$ 516.1298, found 516.1277.

Diethyl [1-(Dibenzylamino)-2-(naphthalen-2-yl)ethyl]phosphonate (3oa). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 86 mg (70%,

0.25 mmol scale); yellow solid; mp 69.1-70.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86-7.83 (m 1H), 7.72-7.70 (m 2H), 7.51-7.45 (m, 3H), 7.17-7.05 (m, 11H), 4.19-4.09 (m, 4H), 3.97-3.89 (m, 4H), 3.46 (ddd, *J* = 16.0, 9.0, 5.6 Hz, 1H), 3.24-3.14 (m, 2H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.3, 136.6 (d, *J* = 14.3 Hz), 133.4, 132.3, 128.9, 128.2, 128.1, 128.0, 127.70, 127.66, 127.59, 126.9, 125.9, 125.4, 61.6 (d, *J* = 7.2 Hz), 61.3 (d, *J* = 7.4 Hz), 57.0 (d, *J* = 133.6 Hz), 54.7 (d, *J* = 1.9 Hz), 34.0 (d, *J* = 7.6 Hz), 16.8 (d, *J* = 5.6 Hz), 16.6 (d, *J* = 5.7 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 28.13; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{30}H_{35}NO_3P$ 488.2349, found 488.2328.

Diethyl [1-(Dibenzylamino)-2-(thiophen-3-yl)ethyl]phosphonate (3pa). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 70 mg (63%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24-7.17 (m, 11H), 6.87 (s, 1H), 6.69 (d, *J* = 4.9 Hz, 1H), 4.16-4.05 (m, 4H), 3.93 (dd, *J* = 13.8, 4.2 Hz, 2H), 3.85 (d, *J* = 13.8 Hz, 2H), 3.34 (ddd, *J* = 16.1, 9.8, 4.8 Hz, 1H), 3.17-3.00 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.4, 139.2 (d, *J* = 14.3 Hz), 129.0, 128.8, 128.2, 126.9, 125.0, 122.1, 61.5 (d, *J* = 7.2 Hz), 61.3 (d, *J* = 7.4 Hz), 56.6 (d, *J* = 135.0 Hz), 54.6, (d, *J* = 2.7 Hz), 28.3 (d, *J* = 8.0 Hz), 16.7 (d, *J* = 5.8 Hz), 16.6 (d, *J* = 5.8 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 27.95; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{24}H_{31}NO_3PS$ 444.1757, found 444.1777.

Diethyl [1-(dibenzylamino)-2-(6-methoxypyridin-3-yl)ethyl]phosphonate (3qa). The reaction time was 36 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 79 mg (67%, 0.25 mmol scale); yellow solid; mp 64.6 °C dec; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (s, 1H), 7.24-7.15 (m 10H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 4.17-4.10 (m, 4H), 3.96 (s, 3H), 3.94-3.86 (m, 4H), 3.21 (ddd, *J* = 16.3, 8.4, 6.1 Hz, 1H), 2.95-2.91 (m, 2H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 162.9,147.0, 139.5, 139.1, 128.9, 128.2, 127.2 (d, *J* = 13.6 Hz), 127.0, 110.2, 61.6 (d, *J* = 7.2 Hz), 61.3 (d, *J* = 7.4 Hz), 57.0 (d, *J* = 133.4 Hz), 54.6, 53.4 (d,

J = 1.1 Hz), 30.3 (d, *J* = 7.8 Hz), 16.7 (d, *J* = 5.7 Hz), 16.6 (d, *J* = 5.8 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 27.76; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{26}H_{34}N_2O_4P$ 469.2251, found 469.2268.

Diethyl [1-(Benzyl(methyl)amino)-4-phenylbutyl]phosphonate (3ab). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 79 mg (81%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.16 (m, 10H), 4.16-4.05 (m, 4H), 3.88 (dd, *J* = 13.6, 1.4 Hz, 1H), 3.82 (dd, *J* = 13.6, 2.9 Hz, 1H), 2.98 (ddd, *J* = 14.4, 10.1, 4.0 Hz, 1H), 2.67-2.52 (m, 2H), 2.38 (d, *J* = 3.4 Hz, 3H), 1.98-1.65 (m, 4H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.0 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.2,139.9, 128.8, 128.4, 128.3,128.2, 126.9, 125.8, 61.5 (d, *J* = 7.3 Hz), 61.1 (d, *J* = 7.4 Hz), 60.1 (d, *J* = 132.5 Hz), 59.5 (d, *J* = 2.2 Hz), 38.2 (d, *J* = 2.8 Hz), 35.4, 28.6 (d, *J* = 12.4 Hz), 26.8 (d, *J* = 6.1 Hz), 16.7 (d, *J* = 6.0 Hz), 16.6 (d, *J* = 6.0 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.78; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{22}H_{33}NO_3P$ 390.2193, found 390.2212.

Diethyl [1-(Diethylamino)-4-phenylbutyl]phosphonate (3ac). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 68 mg (79%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 4.12-4.02 (m, 4H), 3.00 (ddd, *J* = 17.0, 8.7, 6.3 Hz , 1H), 2.77-2.55 (m, 6H), 1.93-1.84 (m, 1H),1.74-1.65 (m, 3H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.1 Hz, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.3, 128.4, 128.3, 125.7, 61.7 (d, *J* = 7.4 Hz), 60.9 (d, *J* = 7.5 Hz), 57.5 (d, *J* = 136.4 Hz), 45.1 (d, *J* = 3.7 Hz), 35.6, 29.0 (d, *J* = 12.0 Hz), 26.9 (d, *J* = 7.4 Hz), 16.6 (d, *J* = 5.7 Hz), 16.5 (d, *J* = 5.6 Hz), 14.9; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 29.21; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{18}H_{33}NO_3P$ 342.2193, found 342.2198.

Diethyl [1-(Diallylamino)-4-phenylbutyl]phosphonate (3ad). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 70 mg (76%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.28 (m, 2H), 7.19-7.16 (m, 3H), 5.74 (ddt,

J = 17.2, 10.2, 6.4 Hz, 2H), 5.19 (dd, *J* = 17.2, 1.8 Hz, 2H), 5.09 (dd, *J* = 10.2, 1.8 Hz, 2H), 4.15-4.03 (m, 4H), 3.33-3.31 (m, 4H), 3.12 (ddd, *J* = 16.6, 8.8, 5.2 Hz, 1H), 2.68-2.53 (m, 2H), 1.92-1.78 (m, 1H), 1.76-1.63 (m, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.3, 137.3, 128.4, 128.3, 125.8, 117.0, 61.7 (d, *J* = 7.3 Hz), 61.1 (d, *J* = 7.4 Hz), 55.7 (d, *J* = 135.9 Hz), 53.8, (d, *J* = 3.0 Hz), 35.5, 28.7 (d, *J* = 11.9 Hz), 26.8 (d, *J* = 6.9 Hz), 16.7 (d, *J* = 5.6 Hz), 16.6 (d, *J* = 5.6 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.92; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{20}H_{33}NO_3P$ 366.2193, found 366.2194.

Diethyl [4-Phenyl-1-(piperiadin-1-yl)butyl]phosphonate (3ae). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 73 mg (82%, 0.25 mmol scale); yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.26 (m, 2H), 7.19-7.15 (m, 3H), 4.17-4.02 (m, 4H), 2.86-2.77 (m, 3H), 2.66-2.54 (m, 4H), 1.90-1.63 (m, 4H), 1.53-1.40 (m, 6H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.4, 128.4, 128.3, 125.7, 62.5 (d, *J* = 136.2 Hz), 61.8 (d, *J* = 7.4 Hz), 60.9 (d, *J* = 7.4 Hz), 51.3 (d, *J* = 3.8 Hz), 35.5, 29.1 (d, *J* = 12.0 Hz), 26.9, 26.1 (d, *J* = 6.3 Hz), 24.6, 16.7 (d, *J* = 5.5 Hz), 16.6 (d, *J* = 5.7 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.28; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{19}H_{33}NO_3P$ 354.2191, found 354.2191.

Diethyl (1-Morpholino-4-phenylbutyl)phosphonate (3af). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/2, v/v): 72 mg (80%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.29 (m, 2H), 7.19-7.17 (m, 3H), 4.19-4.04 (m, 4H), 3.86-3.59 (m, 4H), 2.84-2.56 (m, 7H), 1.92-1.66 (m, 4H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.1, 128.41, 128.36, 125.8, 67.8, 62.01 (d, *J* = 138.7 Hz), 61.99 (d, *J* = 7.3 Hz), 61.2 (d, *J* = 7.4 Hz), 50.5 (d, *J* = 4.1 Hz), 35.5, 29.0 (d, *J* = 12.3 Hz), 25.8 (d, *J* = 5.8 Hz), 16.7 (d, *J* = 5.5 Hz), 16.6 (d, *J* = 5.6 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 27.38; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{18}H_{31}NO_4P$ 356.1985, found 356.1985.

***tert*-Butyl 4-[1-(Diethoxyphosphoryl)-4-phenylbutyl]piperazine-1-carboxylate (3ag).** The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 83 mg (73%, 0.25 mmol scale); yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29-7.26 (m, 2H), 7.20-7.16 (m, 3H), 4.15-4.03 (m, 4H), 3.35-3.30 (m, 4H), 2.89-2.77 (m, 3H), 2.68-2.55 (m, 4H), 1.92-1.63 (m, 4H), 1.45 (s, 9H), 1.31 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 154.8, 142.1, 128.39, 128.36, 125.8, 79.6, 61.94 (d, *J* = 7.2 Hz), 61.90 (d, *J* = 137.6 Hz), 61.2 (d, *J* = 7.0 Hz), 49.8 (d, *J* = 3.4 Hz), 44.5, 35.5, 28.9 (d, *J* = 12.1 Hz), 28.4, 26.0 (d, *J* = 5.6 Hz), 16.7 (d, *J* = 5.6 Hz), 16.6 (d, *J* = 5.6 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 27.31; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{23}H_{40}N_2O_5P$ 455.2699, found 455.2673.

Diethyl (4-Phenyl-1-thiomorpholinobutyl)phosphonate (3ah). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 76 mg (81%, 0.25 mmol scale); pale red oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-7.27 (m, 2H), 7.20-7.17 (m, 3H), 4.18-4.03 (m, 4H), 3.11-3.07 (m, 2H), 2.98-2.93 (m, 2H), 2.77 (ddd, *J* = 16.7, 9.9, 4.4 Hz , 1H), 2.68-2.54 (m, 6H), 1.92-1.63 (m, 4H), 1.33 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 142.1, 128.39, 128.35, 125.8, 63.4 (d, *J* = 138.0 Hz), 61.9 (d, *J* = 7.3 Hz), 61.2 (d, *J* = 7.5 Hz), 52.7 (d, *J* = 3.8 Hz), 35.4, 28.92 (d, *J* = 12.2 Hz), 28.86, 26.1 (d, *J* = 6.5 Hz), 16.7 (d, *J* = 5.5 Hz), 16.6 (d, *J* = 5.5 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 27.51; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{18}H_{31}NO_3PS$ 372.1757, found 372.1755.

Diethyl (1-{3-[10,11-Dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-ylidene)propyl](methyl)amino}-4-phenylbutyl)phosphonate (3ai). The reaction time was 18 h. It was purified by silica gel column chromatography with hexane/ethyl acetate (1/1, v/v): 112 mg (84%, 0.25 mmol scale); yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27-7.08 (m, 12H), 7.02 (dd, *J* = 7.5, 1.6 Hz, 1H), 5.87 (br, 1H), 4.10-4.01 (m, 4H), 3.40-3.22 (m, 2H), 2.95-2.51 (m, 7H), 2.34 (d, *J* = 2.1 Hz, 3H), 2.26-2.25 (m, 2H), 1.84-1.67 (m, 4H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 143.3, 142.2,

141.3, 140.2, 139.3, 137.0, 130.0, 129.7, 128.6, 128.4, 128.3 (2C), 128.0, 127.3, 127.0, 126.0, 125.7 (2C), 61.6, (d, J = 7.3 Hz), 61.5 (d, J = 134.9 Hz), 61.0 (d, J = 7.4 Hz), 55.3, 38.2, 35.6, 33.8, 32.1, 29.0 (d, J = 12.4 Hz), 28.8, 26.8 (d, J = 6.1 Hz), 16.63 (d, J = 5.3 Hz), 16.58 (d, J = 5.3 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.55; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{33}H_{43}NO_3P$ 532.2975, found 532.2995.

General Procedure for the Cu-Catalyzed Enantioselective Hydroamination of α,β-Unsaturated Phosphonates with Hydrosilanes and Hydroxylamines. $Cu(OAc)_2•H_2O$ (6.0 mg, 0.030 mmol, 12 mol %), (*R*)-DM-SEGPHOS (22 mg, 0.030 mmol, 12 mol %), and CsOPiv (176 mg, 0.75 mmol, 3.0 equiv) were placed in a 20 mL Schlenk tube, which was filled with nitrogen by the standard Schlenk technique. 1,4-Dioxane (1.0 mL) was added, and the mixture was stirred for 15 min at room temperature. $(EtO)_3SiH$ (0.14 mL, 0.75 mmol, 3.0 equiv) was then added, and the suspension was stirred for an additional 5 min. Finally, α,β-unsaturated phosphonate **1** (0.25 mmol, 1.0 equiv) and *O*-acylated-*N*,*N*-alkylhydroxylamine **2a** (0.38 mmol, 1.5 equiv) were added, and the mixture was stirred for 36 h at the same temperature. The resulting mixture was directly filtered through a short pad of neutral alumina and Na_2SO_4. The filtrate was evaporated in vacuo and purified by silica gel (60 N, spherical neutral, Kanto Chemical Co.) column chromatography with hexane/ethyl acetate to give hydroaminated product **3**. In some cases, additional purification was performed by GPC to obtain the pure product. The diastereomeric ratio was determined by ^1H NMR, and the enantiomeric ratio of each diastereomer was determined by chiral HPLC analysis on a chiral stationary phase.

1.0 mmol Scale Synthesis of 3ra. $Cu(OAc)_2•H_2O$ (6.0 mg, 0.030 mmol), (*R*)-DM-SEGPHOS (88 mg, 0.12 mmol), and CsOPiv (704 mg, 3.0 mmol) were placed in a 20 mL Schlenk tube, which was filled with nitrogen by the standard Schlenk technique. 1,4-Dioxane (4.0 mL) was added, and the mixture was stirred for 15 min at room temperature. $(EtO)_3SiH$ (0.42 mL, 3.0 mmol) was then added, and the suspension was stirred for an additional 5 min. Finally, diisopropyl (*E*)-(2-phenylprop-1-en-1-yl)phosphonate (**1r**; 284 mg, 1.0 mmol) and *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**; 476 mg, 1.5

mmol) were added, and the mixture was stirred for 36 h at the same temperature. The resulting mixture was directly filtered through a short pad of neutral alumina and Na_2SO_4. The filtrate was evaporated in vacuo and purified by silica gel (60 N, spherical neutral, Kanto Chemical Co.) column chromatography with hexane/ethyl acetate (4/1, v/v) and then GPC (ethyl acetate and then $CHCl_3$) to give diisopropyl [(1*S*,2*S*)-1-(dibenzylamino)-2-phenylpropyl]phosphonate (*syn*-**3ra**, 132 mg, 0.27 mmol) and diisopropyl [(1*R*,2*S*)-1-(dibenzylamino)-2-phenylpropyl]phosphonate (*anti*-**3ra**, 198 mg, 0.41 mmol) in 27% and 41% yields, respectively. The enantiomeric ratio of each diastereomer was determined to be 99/1 by chiral HPLC analysis on a chiral stationary phase.

A 41/59 Diastereomixture of Diisopropyl [(1*S*,2*S*)-1-(dibenzylamino)-2-phenylpropyl]phosphonate (*syn*-3ra) and Diisopropyl [(1*R*,2*S*)-1-(dibenzylamino)-2-phenylpropyl]phosphonate (*anti*-3ra). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 84 mg (70%, 0.25 mmol scale), 329.6 mg (69%, 1.0 mmol scale); colorless gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* = 7.3 Hz, 0.59 × 4H for ***anti*-3ra**), 7.33 (d, *J* = 7.1 Hz, 0.59 × 4H for ***anti*-3ra**), 7.28-7.17 (m, 0.41 × 9H for ***syn*-3ra** and 0.59 × 2H for ***anti*-3ra**), 7.13-7.10 (m, 0.59 × 3H for ***anti*-3ra**), 6.93-6.91 (m, 0.41 × 4H for ***syn*-3ra** and 0.59 × 2H for ***anti*-3ra**), 6.78 (d, *J* = 6.6 Hz, 0.41 × 2H for ***syn*-3ra**), 4.96-4.82 (m, 0.41 × 2H for ***syn*-3ra**), 4.64-4.56 (m, 0.59H for ***anti*-3ra**), 4.50-4.42 (m, 0.59H for ***anti*-3ra**), 4.11 (dd, *J* = 13.4, 4.7 Hz, 0.59 × 2H for ***anti*-3ra**), 4.04 (d, *J* = 13.7 Hz, 0.59 × 2H for ***anti*-3ra**), 3.98 (dd, *J* = 13.4, 5.2 Hz, 0.41 × 2H for ***syn*-3ra**), 3.80 (br, 0.41 × 2H for ***syn*-3ra**), 3.28-3.19 [(m, 0.41H for ***syn*-3ra** and 0.59H for ***anti*-3ra**)], 3.10 (dd, *J* = 12.8, 10.8 Hz, 0.41H for ***syn*-3ra**), 3.04 (dd, *J* = 14.8, 10.0 Hz, 0.59H for ***anti*-3ra**), 1.45 (d, *J* = 6.2 Hz, 0.41 × 3H for ***syn*-3ra**), 1.403 (d, *J* = 6.2 Hz, 0.41 × 3H for ***syn*-3ra**), 1.395 (d, *J* = 6.2 Hz, 0.41 × 3H for ***syn*-3ra**), 1.35 (d, *J* = 7.0 Hz, 0.59 × 3H for ***anti*-3ra**), 1.321 (d, *J* = 6.2 Hz, 0.59 × 3H for ***anti*-3ra**), 1.319 (d, *J* = 6.2 Hz, 0.41 × 3H for ***syn*-3ra**), 1.25 (d, *J* = 6.2 Hz, 0.59 × 3H for ***anti*-3ra**), 1.23 (d, *J* = 7.0 Hz, 0.41 × 3H for ***syn*-3ra**), 0.96 (d, *J* = 6.2 Hz, 0.59 × 3H for ***anti*-3ra**), 0.90 (d, *J* = 6.2 Hz, 0.59 × 3H for ***anti*-3ra**);

$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 145.8 (d, *J* = 14.6 Hz), 145.0 (d, *J* = 2.0 Hz), 139.8, 139.3, 129.6, 129.4, 128.5, 128.23, 128.16, 128.0, 127.9, 127.8, 126.9, 126.8, 126.1, 125.9, 70.1 (d, *J* = 7.3 Hz), 69.5 (d, *J* = 7.4 Hz), 69.3 (d, *J* = 8.2 Hz), 69.1 (d, *J* = 8.1 Hz), 62.2 (d, *J* = 128.1 Hz), 61.7 (d, *J* = 124.0 Hz), 55.1, 54.3, 40.6 (d, *J* = 7.5 Hz), 39.8 (d, *J* = 6.6 Hz), 24.54 (d, *J* = 3.2 Hz), 24.53 (d, *J* = 4.0 Hz), 24.49 (d, *J* = 5.1 Hz), 24.16 (d, *J* = 4.3 Hz), 24.15 (d, *J* = 2.9 Hz), 24.08 (d, *J* = 3.0 Hz), 23.8 (d, *J* = 4.2 Hz), 23.6 (d, *J* = 3.8 Hz), 21.7, 21.0 (d, *J* = 10.1 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.31, 24.89; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{39}NO_3P$ 480.2662, found 480.2650. CHIRALCEL OD-H column, 98/2 hexane/isopropyl alcohol, 0.5 mL/min, major isomers: t_R = 11.2, 12.1 min, minor isomers: t_R = 10.0, 17.0 min.

Diisopropyl [(1*S*,2*S*)-1-(Dibenzylamino)-2-phenylpropyl]phosphonate (*syn*-3ra). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC (ethyl acetate and then $CHCl_3$): 132 mg (27%, 1.0 mmol scale); white solid; mp 74.9-75.9 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.18 (m, 9H), 6.93-6.92 (m, 4H), 6.79 (d, *J* = 7.6 Hz, 2H), 4.96-4.83 (m, 2H), 3.99 (dd, *J* = 13.4, 5.0 Hz, 2H), 3.81 (br, 2H), 3.29-3.19 (m, 1H), 3.11 (dd, *J* = 12.2, 10.8 Hz, 1H), 1.46 (d, *J* = 6.2 Hz, 3H), 1.41 (d, *J* = 6.1 Hz, 3H), 1.40 (d, *J* = 6.1 Hz, 3H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.24 (d, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 145.8 (d, *J* = 14.6 Hz), 139.3, 129.6, 128.2, 128.0, 127.9, 126.8, 126.0, 70.1 (d, *J* = 7.2 Hz), 69.4 (d, *J* = 8.2 Hz), 61.8 (d, *J* = 124.0 Hz), 54.4, 40.7 (d, *J* = 7.5 Hz), 24.6 (d, *J* = 3.0 Hz), 24.5 (d, *J* = 5.8 Hz), 24.17 (d, *J* = 4.2 Hz), 24.16 (d, *J* = 2.9 Hz), 21.7; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.31; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{39}NO_3P$ 480.2662, found 480.2665. CHIRALCEL OD-H column, 98/2 hexane/isopropyl alcohol, 0.5 mL/min, major isomer t_R = 11.0 min, minor isomer t_R = 14.4 min.

Diisopropyl [(1*R*,2*S*)-1-(Dibenzylamino)-2-phenylpropyl]phosphonate (*anti*-3ra). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC (ethyl acetate and then $CHCl_3$): 198 mg (41%, 1.0 mmol scale); white solid; mp 104.8-105.8 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ

7.44 (d, *J* = 7.4 Hz, 4H), 7.33 (t, *J* = 7.3 Hz, 4H), 7.26 (t, J = 7.4 Hz, 2H), 7.15-7.10 (m, 3H), 6.92 (d, *J* = 7.4 Hz, 2H), 4.65-4.57 (m, 1H), 4.51-4.43 (m, 1H), 4.11 (dd, *J* = 13.4, 4.4 Hz, 2H), 4.05 (d, *J* = 13.6 Hz, 2H), 3.29-3.19 (m, 1H), 3.04 (dd, *J* = 14.6, 9.8 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 1.33 (d, *J* = 6.2 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 0.97 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 145.0 (d, *J* = 1.8 Hz), 139.8, 129.4, 128.5, 128.3, 127.8, 127.0, 126.1, 69.5 (d, *J* = 7.4 Hz), 69.1 (d, *J* = 8.1 Hz), 61.8 (d, *J* = 127.9 Hz), 55.1, 39.9 (d, *J* = 6.7 Hz), 24.5 (d, *J* = 4.9 Hz), 24.1 (d, *J* = 3.0 Hz), 23.9 (d, *J* = 4.1 Hz), 23.6 (d, *J* = 3.8 Hz), 21.1 (d, *J* = 10.2 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 24.89; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{39}NO_3P$ 480.2662, found 480.2667. CHIRALCEL OD-H column, 98/2 hexane/isopropyl alcohol, 0.5 mL/min, major isomer t_R = 10.7 min, minor isomer t_R = 9.7 min.

A 40/60 Diastereomixture of Diisopropyl {(1*S*,2*S*)-1-(Dibenzylamino)-2-(4-methoxyphenyl)propyl} phosphonate (*syn*-3sa) and Diisopropyl ((1*R*,2*S*)-1-(Dibenzylamino)-2-(4-methoxyphenyl)propyl) phosphonate (*anti*-3sa). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 92.8 mg (73%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42 (d, *J* = 7.3 Hz, 0.60 × 4H for ***anti*-3sa**), 7.32 (d, *J* = 7.1 Hz, 0.60 × 4H for ***anti*-3sa**), 7.27-7.23 (m, 0.60 × 2H for ***anti*-3sa**), 7.19-7.18 (m, 0.40 × 6H for ***syn*-3sa**), 7.00-6.94 (m, 0.40 × 4H for ***syn*-3sa**), 6.84 (d, *J* = 8.7 Hz, 0.60 × 2H for ***anti*-3sa**), 6.76-6.67 (m, 0.40 × 4H for ***syn*-3sa** and 0.60 × 2H for ***anti*-3sa**), 4.95-4.81 (m, 0.40 × 2H for ***syn*-3sa**), 4.65-4.57 (m, 0.60H for ***anti*-3sa**), 4.53-4.45 (m, 0.60H for ***anti*-3sa**), 4.09 (dd, *J* = 13.5, 4.7 Hz, 0.60 × 2H for ***anti*-3sa**), 4.03 (d, *J* = 13.5 Hz, 0.60 × 2H for ***anti*-3sa**), 3.99 (dd, *J* = 13.4, 5.1 Hz, 0.40 × 2H for ***syn*-3sa**), 3.85 (s, 0.40 × 3H for ***syn*-3sa**), 3.80 (br, 0.40 × 2H for ***syn*-3sa**), 3.75 (s, 0.60 × 3H for ***anti*-3sa**), 3.24-3.14 (m, 0.40H for ***syn*-3sa** and 0.60H for ***anti*-3sa**), 3.04 (dd, *J* = 12.9, 10.8 Hz, 0.40H for ***syn*-3sa**), 2.99 (dd, *J* = 14.7, 9.7 Hz, 0.60H for ***anti*-3sa**), 1.44 (d, *J* = 6.2 Hz, 0.40 × 3H for ***syn*-3sa**), 1.40 (d, *J* = 6.2 Hz, 0.40 × 3H for ***syn*-3sa**), 1.39 (d, *J* = 6.2 Hz, 0.40 × 3H for ***syn*-3sa**), 1.33-1.30 (m, 0.40 × 3H for ***syn*-3sa** and 0.60 × 6H for ***anti*-3sa**), 1.26 (d, *J*

= 6.2 Hz, 0.60 × 3H for ***anti*-3sa**), 1.20 (d, *J* = 6.8 Hz, 0.40 × 3H for ***syn*-3sa**), 1.01 (d, *J* = 6.2 Hz, 0.60 × 3H for ***anti*-3sa**), 0.95 (d, *J* = 6.2 Hz, 0.60 × 3H for ***anti*-3sa**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 158.0, 157.9, 139.8, 139.4, 138.1 (d, *J* = 14.8 Hz), 137.1 (d, *J* = 2.8 Hz), 129.6, 129.3 (2C), 129.0, 128.2, 127.9, 126.9, 126.8, 113.4, 113.2, 70.1 (d, *J* = 7.3 Hz), 69.5 (d, *J* = 7.6 Hz), 69.4 (d, *J* = 8.2 Hz), 69.1 (d, *J* = 8.2 Hz), 62.5 (d, *J* = 127.5 Hz), 61.9 (d, *J* = 123.9 Hz), 55.4, 55.3, 55.1, 54.3, 39.8 (d, *J* = 7.6 Hz), 39.0 (d, *J* = 6.7 Hz), 24.53 (d, *J* = 3.2 Hz), 24.52 (d, *J* = 4.2 Hz), 24.48 (d, *J* = 5.2 Hz), 24.2-24.1 (3C), 23.9 (d, *J* = 4.1 Hz), 23.7 (d, *J* = 4.0 Hz), 21.8, 21.0 (d, *J* = 10.2 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.42, 25.19; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{30}H_{41}NO_4P$: 510.2768, found: 510.2749. CHIRALPAK AD-H column, 97/3 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 27.8, 41.1 min, minor isomers t_R = 23.2, 34.7 min.

A 52/48 Diastereomixture of Diisopropyl {(1*S*,2*S*)-1-(Dibenzylamino)-2-[4-(trifluoromethyl)phenyl]propyl} phosphonate (*syn*-3ta) and Diisopropyl {(1*R*,2*S*)-1-(Dibenzylamino)-2-[4-(trifluoromethyl)phenyl]propyl} phosphonate (*anti*-3ta). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 108 mg (79%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42-7.37 (m, 4H), 7.33 (t, *J* = 7.1 Hz, 2H), 7.28-7.25 (m, 1H), 7.21-7.16 (m, 3H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.88-6.86 (m, 2H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.97-4.86 (m, 0.52 × 2H for ***syn*-3ta**), 4.70-4.62 (m, 0.48H for ***anti*-3ta**), 4.55-4.47 (m, 0.48H for ***anti*-3ta**), 4.08 (dd, *J* = 13.1, 5.1 Hz, 0.48 × 4H for ***anti*-3ta**), 3.98 (dd, *J* = 13.4, 5.2 Hz, 0.52 × 2H for ***syn*-3ta**), 3.80 (br, 0.52 × 2H for ***syn*-3ta**), 3.34-3.23 (m, 0.52H for ***syn*-3ta** and 0.48 × 1H for ***anti*-3ta**), 3.12 (dd, *J* = 13.3, 10.9 Hz, 0.52H for ***syn*-3ta**), 3.02 (dd, *J* = 15.2, 9.4 Hz, 0.48H for ***anti*-3ta**), 1.46 (d, *J* = 6.2 Hz, 0.52 × 3H for ***syn*-3ta**), 1.41 [(d, *J* = 6.2 Hz, 0.52 × 3H for ***syn*-3ta** and 0.48 × 3H for ***anti*-3ta**)], 1.36 (d, *J* = 6.4 Hz, 0.48 × 6H for ***anti*-3ta**), 1.35 (d, *J* = 6.1 Hz, 0.52 × 3H for ***syn*-3ta**), 1.26 (d, *J* = 6.2 Hz, 0.52 × 3H for ***syn*-3ta**), 1.23 (d, *J* = 6.8 Hz, 0.52 × 3H for ***syn*-3ta**), 0.96 (d, *J* = 6.2 Hz, 0.48 × 3H for ***anti*-3ta**), 0.93 (d, *J* = 6.2 Hz, 0.48 × 3H for ***anti*-3sa**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 150.1 (d, *J* = 14.5 Hz), 149.2,

139.5, 139.0, 129.5, 129.3, 128.8, 128.41 (q, J = 32.0 Hz), 128.37, 128.3, 128.2 (q, J = 31.9 Hz), 128.0, 127.1, 127.0, 124.9 (q, J = 3.8 Hz), 124.7 (q, J = 3.8 Hz), 124.5 (q, J = 269.9 Hz), 124.4 (q, J = 269.9 Hz), 70.3 (d, J = 7.3 Hz), 69.8 (d, J = 7.5 Hz), 69.6 (d, J = 8.2 Hz), 69.3 (d, J = 8.2 Hz), 62.0 (d, J = 128.9 Hz), 61.5 (d, J = 125.1 Hz), 55.2, 54.3, 40.7 (d, J = 7.9 Hz), 39.7 (d, J = 6.8 Hz), 24.5-24.4 (m, 3C), 24.2-24.1 (m, 3C), 23.7 (d, J = 4.0 Hz), 23.6 (d, J = 3.7 Hz), 21.4, 20.2 (d, J = 9.3 Hz); $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz) δ -62.13 (s), -62.36 (s); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 25.53, 24.29; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{30}H_{38}F_3NO_3P$ 548.2536, found 548.2546. CHIRALPAK AD-H column, 97/3 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 21.9, 27.7 min, minor isomers t_R = 14.7, 19.8 min.

A 48/52 Diastereomixture of Diisopropyl [(1*S*,2*S*)-2-(4-Bromophenyl)-1-(dibenzylamino)propyl]phosphonate (*syn*-3ua) and Diisopropyl [(1*R*,2*S*)-2-(4-Bromophenyl)-1-(dibenzylamino)propyl]phosphonate (*anti*-3ua). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC (ethyl acetate and then $CHCl_3$): 112 mg (82%, 0.25 mmol scale); colorless gum; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, J = 7.1 Hz, 0.52 × 4H for ***anti*-3ua**), 7.33 (t, J = 7.1 Hz, 0.52 × 4H for ***anti*-3ua**), 7.29 (d, J = 8.5 Hz, 0.48 × 2H for ***syn*-3ua**), 7.26-7.20 [(m, 0.48 × 6H for ***syn*-3ua** and 0.52 × 4H for ***anti*-3ua**)], 6.94-6.93 (m, 0.48 × 4H for ***syn*-3ua**), 6.79 (d, J = 8.4 Hz, 0.52 × 2H for ***anti*-3ua**), 6.63 (d, J = 8.3 Hz, 0.48 × 2H for ***syn*-3ua**), 4.97-4.82 (m, 0.48 × 2H for ***syn*-3ua**), 4.72-4.60 (m, 0.52H for ***anti*-3ua**), 4.56-4.47 (m, 0.52H for ***anti*-3ua**), 4.07 (dd, J = 13.3, 4.6 Hz, 0.52 × 4H for ***anti*-3ua**), 3.98 (dd, J = 13.4, 5.1 Hz, 0.48 × 2H for ***syn*-3ua**), 3.80 (br, 0.48 × 2H for ***syn*-3ua**), 3.24-3.13 (m, 0.48H for ***syn*-3ua** and 0.52H for ***anti*-3ua**), 3.05 (dd, J = 13.1, 11.1 Hz, 0.48H for ***syn*-3ua**), 2.97 (dd, J = 15.2, 9.4 Hz, 0.52H for ***anti*-3ua**), 1.45 (d, J = 6.2 Hz, 0.48 × 3H for ***syn*-3ua**), 1.40 (d, J = 6.2 Hz, 0.48 × 6H for ***syn*-3ua**), 1.35-1.32 (m, 0.48 × 3H for ***syn*-3ua** and 0.52 × 6H for ***anti*-3ua**), 1.26 (d, J = 6.2 Hz, 0.52 × 3H for ***anti*-3ua**), 1.19 (d, J = 6.8 Hz, 0.48 × 3H for ***syn*-3ua**), 1.03 (d, J = 6.2 Hz, 0.52 × 3H for ***anti*-3ua**), 0.97 (d, J = 6.2 Hz, 0.52 × 3H for ***anti*-3ua**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$,

100 MHz) δ 145.0 (d, J = 14.7 Hz), 144.0 (d, J = 3.0 Hz), 139.6, 139.1, 131.0, 130.8, 130.2, 129.9, 129.5, 129.3, 128.3, 128.0, 127.0, 126.9, 119.8, 119.4, 70.2 (d, J = 7.3 Hz), 69.8 (d, J = 7.6 Hz), 69.5 (d, J = 8.2 Hz), 69.1 (d, J = 8.2 Hz), 62.2 (d, J = 128.4 Hz), 61.6 (d, J = 124.8 Hz), 55.2, 54.4, 40.3 (d, J = 7.8 Hz), 39.4 (d, J = 6.9 Hz), 24.6-24.5 (m, 3C), 24.2-24.1 (m, 3C), 23.9 (d, J = 4.1 Hz), 23.7 (d, J = 3.9 Hz), 21.5, 20.4 (d, J = 9.5 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 25.76, 24.59; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{38}BrNO_3P$ 558.1767, found 558.1744. CHIRALCEL OD-H column, 98.5/1.5 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 12.0, 12.8 min, minor isomers t_R = 11.0, 19.0 min.

Diisopropyl [(1*S*,2*S*)-2-(4-Bromophenyl)-1-(dibenzylamino)propyl]phosphonate (*syn*-3ua). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC (ethyl acetate and then $CHCl_3$): 54 mg (39%, 0.25 mmol scale); white solid; mp 124.6-125.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28 (d, J = 8.4 Hz, 2H), 7.22-7.20 (m, 6H), 6.94-6.92 (m, 4H), 6.62 (d, J = 8.4 Hz, 2H), 4.95-4.83 (m, 2H), 3.98 (dd, J = 13.4, 5.2 Hz, 2H), 3.79 (br, 2H), 3.22-3.13 (m, 1H), 3.04 (dd, J = 13.2, 10.8 Hz, 1H), 1.44 (d, J = 6.2 Hz, 3H), 1.40 (d, J = 6.2 Hz, 6H), 1.33 (d, J = 6.2 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H) ; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 145.0 (d, J = 14.7 Hz), 139.1, 131.0, 129.9, 129.5, 128.0, 126.9, 119.4, 70.2 (d, J = 7.3 Hz), 69.5 (d, J = 8.1 Hz), 61.5 (d, J = 124.8 Hz), 54.4, 40.3 (d, J = 7.8 Hz), 24.53 (d, J = 3.2 Hz), 24.52 (d, J = 5.4 Hz), 24.2 (d, J = 4.5 Hz), 24.1 (d, J = 3.2 Hz), 21.5; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 25.77; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{38}BrNO_3P$ 558.1767, found 558.1740. CHIRALCEL OD-H column, 98.5/1.5 hexane/isopropyl alcohol, 0.5 mL/min, major isomer t_R = 13.0 min, minor isomer t_R = 21.9 min.

Diisopropyl [(1*R*,2*S*)-2-(4-Bromophenyl)-1-(dibenzylamino)propyl]phosphonate (*anti*-3ua). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC (ethyl acetate and then $CHCl_3$): 60 mg (43%, 0.25 mmol scale); white solid; mp 102.6-103.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (d, J = 7.4 Hz, 4H), 7.32 (t, J = 7.4 Hz, 4H), 7.28-7.23 (m, 4H), 6.78 (d, J = 8.4 Hz, 2H), 4.70-4.61 (m, 1H), 4.56-4.48 (m, 1H), 4.05 (dd, J = 13.3, 5.2 Hz, 4H), 3.23-3.14 (m, 1H), 2.96 (dd, J =

15.2, 9.4 Hz, 1H), 1.34 (d, *J* = 7.1 Hz, 3H), 1.32 (d, *J* = 7.8 Hz, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.2 Hz, 3H), 0.96 (d, *J* = 6.2 Hz, 3H) ; $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 144.0 (d, *J* = 2.9 Hz), 139.6, 130.8, 130.2, 129.3, 128.3, 127.0, 119.7, 69.8 (d, *J* = 7.5 Hz), 69.3 (d, *J* = 8.1 Hz), 62.2 (d, *J* = 128.4 Hz), 55.2, 39.3 (d, *J* = 7.0 Hz), 24.5 (d, *J* = 4.9 Hz), 24.1 (d, *J* = 3.2 Hz), 23.9 (d, *J* = 4.1 Hz), 23.7 (d, *J* = 4.0 Hz), 20.4 (d, *J* = 9.5 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 24.61; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{38}BrNO_3P$ 558.1767, found 558.1741. CHIRALCEL OD-H column, 98.5/1.5 hexane/isopropyl alcohol, 0.5 mL/min, major isomer t_R = 14.7 min, minor isomer t_R = 12.1 min.

A 44/56 diisopropyl [(1*S*,2*S*)-1-(Dibenzylamino)-2-(naphthalen-2-yl)propyl]phosphonate (*syn*-3va) and Diisopropyl [(1*R*,2*S*)-1-(Dibenzylamino)-2-(naphthalen-2-yl)propyl]phosphonate (*anti*-3va). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC ($CHCl_3$): 89 mg (67%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87-7.84 (m, 0.44H for ***syn*-3va**), 7.75-7.72 (m, 0.56H for ***anti*-3va**), 7.68-7.63 (m, 0.44 × 2H for ***syn*-3va** and 0.56H for ***anti*-3va**), 7.60 (d, *J* = 8.5 Hz, 0.56H for ***anti*-3va**), 7.47-7.36 (m, 0.44 × 2H for ***syn*-3va** and 0.56 × 7H for ***anti*-3va**), 7.33-7.29 (m, 0.44H for ***syn*-3va** and 0.56 × 4H for ***anti*-3va**), 7.27-7.23 (m, 0.56 × 2H for ***anti*-3va**), 7.15-7.11 (m, 0.44 × 2H for ***syn*-3va**), 7.06-7.03 (m, 0.44 × 4H for ***syn*-3va**), 6.99-6.96 (m, 0.56H for ***anti*-3va**), 6.88-6.83 (m, 0.44 × 5H for ***syn*-3va**), 4.98-4.85 (m, 0.44 × 2H for ***syn*-3va**), 4.63-4.55 (m, 0.56H for ***anti*-3va**), 4.46-4.38 (m, 0.56H for ***anti*-3va**), 4.14-4.06 (m, 0.56 × 4H for ***anti*-3va**), 4.00 (dd, *J* = 13.4, 5.2 Hz, 0.44 × 2H for ***syn*-3va**), 3.85 (br, 0.44 × 2H for ***syn*-3va**), 3.46-3.36 (m, 0.44H for ***syn*-3va** and 0.56H for ***anti*-3va**), 3.20 (dd, *J* = 13.0, 10.8 Hz, 0.44H for ***syn*-3va**), 3.15 (dd, *J* = 15.1, 9.6 Hz, 0.56H for ***anti*-3va**), 1.48 (d, *J* = 6.2 Hz, 0.44 × 3H for ***syn*-3va**), 1.44 (d, *J* = 7.0 Hz, 0.56 × 3H for ***anti*-3va**), 1.42 (d, *J* = 6.1 Hz, 0.44 × 3H for ***syn*-3va**), 1.41 (d, *J* = 6.2 Hz, 0.44 × 3H for ***syn*-3va**), 1.35 (d, *J* = 6.2 Hz, 0.44 × 3H for ***syn*-3va**), 1.31-1.30 [(m, 0.44 × 3H for ***syn*-3va** and 0.56 × 3H for ***anti*-3va**)], 1.23 (d, *J* = 6.2 Hz, 0.56 × 3H for ***anti*-3va**), 0.83 (d, *J* = 6.2 Hz, 0.56 × 3H for ***anti*-3va**), 0.75 (d, *J* = 6.2 Hz, 0.56 × 3H for ***anti*-3va**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 143.4 (d, *J* = 14.7 Hz), 142.3 (d,

J = 2.8 Hz), 139.8, 139.2, 133.4, 133.3, 132.4 (2C), 129.5, 129.4, 128.2, 127.9, 127.7, 127.6, 127.54, 127.47, 127.43, 127.33, 127.29, 127.0, 126.73 (2C), 126.69 (2C), 126.5, 125.6, 125.1 (2C), 70.2 (d, *J* = 7.3 Hz), 69.5 (d, *J* = 7.4 Hz), 69.4 (d, *J* = 8.0 Hz), 69.1 (d, *J* = 8.2 Hz), 62.2 (d, *J* = 128.2 Hz), 62.0 (d, *J* = 124.0 Hz), 55.2, 54.4, 40.8 (d, *J* = 7.5 Hz), 40.0 (d, *J* = 6.9 Hz), 24.59- 24.55 (2C), 24.5 (d, *J* = 5.0 Hz), 24.22 (d, *J* = 4.0 Hz), 24.18 (d, *J* = 2.9 Hz), 24.1 (d, *J* = 3.2 Hz), 23.64 (d, *J* = 4.2 Hz), 23.58 (d, *J* = 3.8 Hz), 21.5, 20.6 (d, *J* = 9.7 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.14, 24.83; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{33}H_{41}NO_3P$ 530.2819, found 530.2805. CHIRALPAK AD-H column, 97/3 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 22.9, 35.0 min, minor isomers t_R = 18.2, 30.8 min.

A 51/49 Diastereomixture of Diisopropyl [(1*S*,2*S*)-1-(Dibenzylamino)-2-(6-methoxypyridin-3-yl)propyl]phosphonate (*syn*-3wa) and Diisopropyl [(1*R*,2*S*)-1-(Dibenzylamino)-2-(6-methoxypyridin-3-yl)propyl]phosphonate (*anti*-3wa). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 102 mg (80%, 0.25 mmol scale); colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 2.3 Hz, 0.51H for ***syn*-3wa**), 7.76 (d, *J* = 2.3 Hz, 0.49H for ***anti*-3sa**), 7.42 (s, 0.49 × 2H for ***anti*-3wa**), 7.40 (s, 0.51 × 2H for ***syn*-3wa**), 7.34-7.30 (m, 0.49 × 5H for ***anti*-3wa**), 7.27-7.24 (m, 0.49 × 2H for ***anti*-3wa**), 7.21-7.18 (m, 0.51 × 5H for ***syn*-3wa**), 7.05 (dd, *J* = 8.5, 2.4 Hz, 0.49H for ***anti*-3wa**), 6.96-6.94 (m, 0.51 × 4H for ***syn*-3wa**), 6.76 (dd, *J* = 8.5, 2.5 Hz, 0.49H for ***anti*-3wa**), 6.56 (d, *J* = 8.5 Hz, 0.51H for ***syn*-3wa**), 6.53 (d, *J* = 8.5 Hz, 0.49H for ***anti*-3wa**), 4.96-4.83 (m, 0.51 × 2H for ***syn*-3wa**), 4.73-4.65 (m, 0.49H for ***anti*-3wa**), 4.56-4.48 (m, 0.49H for ***anti*-3wa**), 4.08 (dd, *J* = 13.0, 4.6 Hz, 0.49 × 4H for ***anti*-3wa**), 3.98 (dd, *J* = 13.4, 5.0 Hz, 0.51 × 2H for ***syn*-3wa**), 3.97 (s, 0.51 × 3H for ***syn*-3wa**), 3.86 (s, 0.49 × 3H for ***anti*-3wa**), 3.81 (br, 0.51 × 2H for ***syn*-3wa**), 3.23-3.13 (m, 0.51H for ***syn*-3wa** and 0.49H for ***anti*-3wa**), 3.00 (dd, *J* = 13.7, 10.6 Hz, 0.51H for ***syn*-3wa**), 2.93 (dd, *J* = 14.8, 9.7 Hz, 0.49H for ***anti*-3wa**), 1.45 (d, *J* = 6.2 Hz, 0.51 × 3H for ***syn*-3wa**), 1.401 (d, *J* = 6.2 Hz, 0.40 × 3H for ***syn*-3ta**), 1.396 (d, *J* = 6.2 Hz, 0.40 × 3H for ***syn*-3ta**), 1.36 (d, *J* = 6.2 Hz, 0.48 × 3H for ***anti*-3wa**), 1.323 (d, *J* = 7.2 Hz, 0.49 × 3H for ***anti*-3wa**), 1.318 (d, *J* = 6.1 Hz, 0.51 × 3H for ***syn*-**

3wa), 1.27 (d, *J* = 6.2 Hz, 0.49 × 3H for ***syn*-3wa**), 1.20 (d, *J* = 6.8 Hz, 0.49 × 3H for ***anti*-3wa**), 1.00 (d, *J* = 6.4 Hz, 0.49 × 3H for ***anti*-3wa**), 0.98 (d, *J* = 6.4 Hz, 0.49 × 3H for ***anti*-3wa**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7 (2C), 146.5, 145.7, 139.6, 139.1, 138.5, 138.0, 133.9 (d, *J* = 14.5 Hz), 132.8 (d, *J* = 2.6 Hz), 129.44, 129.35, 128.3, 128.0, 127.0, 126.9, 110.2, 109.9, 70.2 (d, *J* = 7.2 Hz), 69.7 (d, *J* = 7.5 Hz), 69.5 (d, *J* = 8.2 Hz), 69.3 (d, *J* = 8.1 Hz), 62.3 (d, *J* = 128.3 Hz), 61.5 (d, *J* = 125.1 Hz), 55.0, 54.0, 53.4, 53.3, 37.2 (d, *J* = 8.0 Hz), 36.5 (d, *J* = 6.4 Hz), 24.52 (d, *J* = 3.4 Hz), 24.51 (d, *J* = 4.6 Hz), 24.47 (d, *J* = 5.0 Hz), 24.1 (3C), 23.9 (d, *J* = 4.0 Hz), 23.8 (d, *J* = 3.9 Hz), 21.4, 20.5 (d, *J* = 9.9 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 25.73, 24.51; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{40}N_2O_4P$ 511.2720, found 511.2742. CHIRALPAK AD-H column, 97/3 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 32.9, 41.6 min, minor isomers t_R = 23.5, 38.3 min.

A 47/53 Diastereomixture of Diisopropyl [(1*S*,2*S*)-1-(Dibenzylamino)-2-phenylbutyl]phosphonate (*syn*-3xa) and Diisopropyl [(1*R*,2*S*)-1-(Dibenzylamino)-2-phenylbutyl]phosphonate (*anti*-3xa). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 81 mg (63%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, *J* = 7.1 Hz, 0.53 × 4H for ***anti*-3xa**), 7.34 (t, *J* = 7.2 Hz, 0.53 × 4H for ***anti*-3ra**), 7.28-7.24 (m, 0.53 × 2H for ***anti*-3xa**), 7.23-7.18 (m, 0.47 × 9H for ***syn*-3xa**), 7.13-7.10 (m, 0.53 × 3H for ***anti*-3xa**), 6.89-6.86 (m, 0.47 × 4H for ***syn*-3xa** and 0.53 × 2H for ***anti*-3xa**), 6.76 (d, *J* = 6.8 Hz, 0.47 × 2H for ***syn*-3xa**), 4.94-4.83 (m, 0.47 × 2H for ***syn*-3xa**), 4.61-4.52 (m, 0.53H for ***anti*-3xa**), 4.49-4.41 (m, 0.53H for ***anti*-3xa**), 4.11 (dd, *J* = 13.4, 4.8 Hz, 0.53 × 2H for ***anti*-3xa**), 4.04 (d, *J* = 12.3 Hz, 0.53 × 2H for ***anti*-3xa**), 3.96 (dd, *J* = 13.4, 5.4 Hz, 0.47 × 2H for ***syn*-3xa**), 3.74 (br, 0.47 × 2H for ***syn*-3xa**), 3.17 (dd, *J* = 12.6, 10.7 Hz, 0.47 × 1H for ***syn*-3xa**), 3.09 (dd, *J* = 14.6, 10.3 Hz, 0.53H for ***anti*-3xa**), 3.02-3.87 (m, 0.47 × 1H for ***syn*-3xa** and 0.53 × 1H for ***anti*-3xa**), 2.57-2.49 (m, 0.53H for ***anti*-3xa**), 2.12-2.02 (m, 0.53H for ***anti*-3xa**), 1.44 (d, *J* = 6.2 Hz, 0.47 × 3H for ***syn*-3xa**), 1.41-1.39 (m, 0.47 × 3H for ***syn*-3xa** and 0.53 × 3H for ***anti*-3xa**), 1.33 (d, *J* = 5.9 Hz, 0.47 × 3H for ***syn*-3xa**), 1.31 (d, *J* = 5.9 Hz, 0.53 × 3H for ***anti*-3xa**), 1.26-1.15 (m, 0.47 × 2H for

***syn*-3xa**), 1.23 (d, J = 6.2 Hz, 0.47 × 3H for ***syn*-3xa**), 0.93 (d, J = 6.2 Hz, 0.53 × 3H for ***anti*-3xa**), 0.90 (d, J = 6.2 Hz, 0.53 × 3H for ***anti*-3xa**), 0.56 (t, J = 7.4 Hz, 0.47 × 3H for ***syn*-3xa**), 0.55 (t, J = 7.2 Hz, 0.53 × 3H for ***anti*-3xa**); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.8 (d, J = 13.8 Hz), 142.3 (d, J = 1.1 Hz), 139.9, 139.3, 129.7, 129.5, 129.4, 129.3, 128.2, 127.81, 127.76, 127.6, 126.9, 126.8, 126.1, 125.9, 70.0 (d, J = 7.3 Hz), 69.41 (d, J = 6.9 Hz), 69.42 (d, J = 8.7 Hz), 69.0 (d, J = 8.1 Hz), 62.1 (d, J = 128.1 Hz), 61.0 (d, J = 123.8 Hz), 55.0, 54.3, 48.4 (d, J = 8.0 Hz), 47.6 (d, J = 5.6 Hz), 27.1, 26.3 (d, J = 9.8 Hz), 24.6-24.5 (m, 3C), 24.54 (d, J = 3.2 Hz), 24.53 (d, J = 4.0 Hz), 24.20 (d, J = 2.6 Hz), 24.17 (d, J = 4.0 Hz), 24.0 (d, J = 3.3 Hz), 23.8 (d, J = 4.2 Hz), 23.6 (d, J = 3.8 Hz), 12.3, 12.0; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.87, 24.80; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{30}H_{41}NO_3P$ 494.2819, found 494.2805. CHIRALPAK AD-H column, 99/1 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 48.1, 70.9 min, minor isomers t_R = 37.9, 65.1 min.

A 38/62 Diastereomixture of Diisopropyl [(1*S*,2*S*)-1-(Dibenzylamino)-2-methyl-4-phenylbutyl]phosphonate (*syn*-3ya) and Diisopropyl [(1*R*,2*S*)-1-(Dibenzylamino)-2-methyl-4-phenylbutyl]phosphonate (*anti*-3ya). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 119 mg (94%, 0.25 mmol scale); colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 7.8 Hz, 0.62 × 4H for ***anti*-3ya**), 7.33-7.12 (m, 0.38 × 15H for ***syn*-3ya** and 0.62 × 9H for ***anti*-3ya**), 7.03 (d, J = 7.7 Hz, 0.62 × 2H for ***anti*-3ya**), 4.85-4.74 (m, 0.38 × 2H for ***syn*-3ya** and 0.62 × 2H for ***anti*-3ya**), 4.04-3.88 (m, 0.38 × 4H for ***syn*-3ya** and 0.62 × 4H for ***anti*-3ya**), 2.82 (dd, J = 17.6, 6.4 Hz, 0.62 × 1H for ***anti*-3ya**), 2.65 (dd, J = 15.9, 8.72 Hz, 0.38 × 1H for ***syn*-3ya**), 2.56-2.48 (m, 0.38H for ***syn*-3ya**), 2.43-2.29 (m, 0.38 × 2H for ***syn*-3ya** and 0.62 × 2H for ***anti*-3ya**), 2.26-2.19 (m, 0.62H for ***anti*-3ya**), 1.98-1.88 (m, 0.62 × 2H for ***anti*-3ya**), 1.82-1.73 (m, 0.38 × 2H for ***syn*-3ya**), 1.36-1.33 (m, 0.38 × 9H for ***syn*-3ya** and 0.62 × 6H for ***anti*-3ya**), 1.31 (d, J = 6.2 Hz, 0.62 × 3H for ***anti*-3ya**), 1.26-1.25 (m, 0.38 × 3H for ***syn*-3ya** and 0.62 × 3H for ***anti*-3ya**), 1.13 (d, J = 6.8 Hz, 0.62 × 3H for ***anti*-3ya**), 1.00 (d, J = 6.6 Hz, 0.38 × 3H for ***syn*-3ya**); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.8, 142.5, 140.1,

140.0, 130.0, 129.4, 128.5, 128.4, 128.3 (2C), 128.20, 128.17, 127.04, 126.99, 125.63, 125.57, 69.9-69.8 (m, 2C), 69.6 (d, J = 8.1 Hz), 69.4 (d, J = 8.2 Hz), 61.8 (d, J = 127.2 Hz), 60.3 (d, J = 127.1 Hz), 56.2, 55.5, 35.9 (d, J = 7.3 Hz), 35.4 (d, J = 9.4 Hz), 33.3 (d, J = 7.5 Hz), 33.1, 33.0 (d, J = 6.3 Hz), 32.9, 24.6-24.1 (m, 8C), 17.49, 17.47 (d, J = 8.6 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.94, 26.55; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{31}H_{43}NO_3P$ 508.2975, found 508.2954. CHIRALPAK AD-H column, 98/2 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 25.5, 28.1 min, minor isomers t_R = 20.4, 32.9 min.

A 49/51 Diastereomixture of Diisopropyl [(1*S*,2*S*)-1-(Benzyl(methyl)amino)-2-phenylpropyl]phosphonate (*syn*-3rb) and Diisopropyl [(1*R*,2*S*)-1-(Benzyl(methyl)amino)-2-phenylpropyl]phosphonate (*anti*-3rb). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 56 mg (56%, 0.25 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (d, J = 7.1 Hz, 0.51 × 2H for ***anti*-3rb**), 7.34-7.04 (m, 0.49 × 8H for ***syn*-3rb** and 0.51 × 8H for ***anti*-3rb**), 6.63 (d, J = 6.2 Hz, 0.49 × 2H for ***syn*-3rb**), 4.90-4.79 (m, 0.49 × 2H for ***syn*-3rb**), 4.58-4.44 (m, 0.51 × 2H for for ***anti*-3rb**), 4.08 (dd, J = 13.6, 1.8 Hz, 0.51 × 2H for ***anti*-3rb**), 3.99 (dd, J = 13.8, 2.8 Hz, 0.49 × 2H for ***syn*-3rb**), 3.28-3.16 (m, 0.49H for ***syn*-3rb** and 0.59H for ***anti*-3rb**), 3.09 (dd, J = 13.5, 10.8 Hz, 0.41H for ***syn*-3rb**), 3.02 (dd, J = 14.3, 9.6 Hz, 0.51H for ***anti*-3rb**), 2.48 (d, J = 2.4 Hz, 0.51 × 3H for ***anti*-3rb**), 2.25 (d, J = 2.5 Hz, 0.49 × 3H for ***syn*-3rb**), 1.41-1.37 (m, 0.49 × 12H for ***syn*-3rb** and 0.51 × 6H for ***anti*-3rb**), 1.25 (d, J = 6.2 Hz, 0.51 × 3H for ***anti*-3rb**), 1.24 (d, J = 6.2 Hz, 0.49 × 3H for ***syn*-3rb**), 1.02 (d, J = 6.2 Hz, 0.51 × 3H for ***anti*-3rb**), 1.01 (d, J = 6.2 Hz, 0.51 × 3H for ***anti*-3rb**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 146.6 (d, J = 14.7 Hz), 145.1 (d, J = 11.64 Hz), 140.2, 139.8 (d, J = 1.6 Hz), 128.9, 128.5 (2C), 128.19, 128.16, 128.0, 127.8, 127.5, 126.8, 126.4, 126.2, 125.9, 70.0 (d, J = 7.5 Hz), 69.5 (d, J = 7.7 Hz), 69.4 (d, J = 6.5 Hz), 69.1, 68.5 (d, J = 136.0 Hz), 61.5 (d, J = 128.8 Hz), 60.6, 60.2, 40.6 (d, J = 9.0 Hz), 40.3 (d, J = 7.6 Hz), 38.0, 36.9, 24.5 (d, J = 3.3 Hz), 24.4 (d, J = 4.7 Hz), 24.32 (d, J = 5.1 Hz), 24.27-24.19 (m, 3C), 23.9 (d, J = 3.8 Hz), 23.8 (d, J = 4.1 Hz), 20.8, 20.7 (d, J = 9.8 Hz); $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 26.48, 25.18; HRMS (APCI) m/z $(M + H)^+$ calcd

for $C_{23}H_{35}NO_3P$ 404.2349, found 404.2341. CHIRALCEL OD-H column, 99/1 hexane/isopropyl alcohol, 0.5 mL/min, major isomers t_R = 14.3, 47.4 min, minor isomers t_R = 16.1, 19.0 min.

Diisopropyl [1-(Dibenzylamino)-4-phenylbutyl]phosphonate (3za). It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v): 82 mg (66%, 0.25 mmol scale); white solid; mp 81.8-82.8 °C ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, *J* = 7.0 Hz, 4H), 7.29 (t, *J* = 7.1 Hz, 4H), 7.25-7.21 (m, 4H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 4.80-4.68 (m, 2H), 3.90 (d, *J* = 2.5 Hz, 4H), 2.90 (ddd, *J* = 14.9, 10.3, 3.0 Hz, 1H), 2.41-2.30 (m, 2H), 1.92-1.82 (m, 1H), 1.80-1.70 (m, 1H), 1.64-1.52 (m, 2H), 1.333 (d, *J* = 6.2 Hz, 3H), 1.326 (d, *J* = 6.1 Hz, 3H) 1.31 (d, *J* = 6.1 Hz, 3H) 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 142.2, 140.0, 129.3, 128.4, 128.22, 128.21, 127.0, 125.7, 70.0 (d, *J* = 7.3 Hz), 69.7 (d, *J* = 7.3 Hz), 55.5 (d, *J* = 131.4 Hz), 54.8, 35.1, 28.0 (d, *J* = 12.4 Hz), 27.2 (d, *J* = 6.1 Hz), 24.4 (d, *J* = 3.4 Hz), 24.31 (d, *J* = 5.1 Hz), 24.27 (d, *J* = 3.0 Hz), 24.2 (d, *J* = 4.3 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 26.93; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{30}H_{41}NO_3P$ 494.2819, found 494.2797.

General Procedure for the Cu-Catalyzed Silylamination of α,β-Unsaturated Phosphonates with Silylboranes and Hydroxylamine. $Cu(OPiv)_2$ (10.0 mg, 0.038 mmol, 15 mol %), TMS-dppbz (38 mg, 0.038 mmol, 15 mol %), and CsOPiv (176 mg, 0.75 mmol, 3.0 equiv) were placed in a 20 mL Schlenk tube, which was filled with nitrogen by the standard Schlenk technique. 1,4-Dioxane (0.60 mL) was added, and the mixture was stirred for 15 min at room temperature. A solution of pinB–$SiMe_2$Ph (230 mg, 0.88 mmol, 3.5 equiv) in 1,4-dioxane (0.60 mL) was then added, and the suspension was stirred for an additional 3 min. α,β-Unsaturated phosphonate **1** (0.25 mmol, 1.0 equiv) was subsequently added. After the mixture had been stirred for 5 min, *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine (**2a**; 119 mg, 0.38 mmol, 1.5 equiv) was finally added, and the mixture was stirred for 18 h at the same temperature. The resulting mixture was directly filtered through a short pad of neutral alumina and Na_2SO_4. The filtrate was evaporated in vacuo and purified by silica gel (60 N, spherical neutral, Kanto Chemical Co.) column

chromatography with hexane/ethyl acetate and GPC ($CHCl_3$) to give silylaminated product **7**. The *syn/anti* ratio was estimated by ^1H NMR analysis.

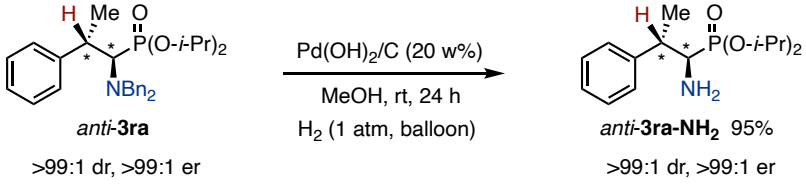
A 12/88 Diastereomixture of Diethyl {(1*S,2*S**)-1-(Dibenzylamino)-2-[dimethyl(phenyl)silyl]-4-phenylbutyl} phosphonate (*syn*-7aa) and Diethyl {(1*R**,2*S**)-1-(Dibenzylamino)-2-[dimethyl(phenyl)silyl]-4-phenylbutyl} phosphonate (*anti*-7aa).** It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC ($CHCl_3$): 78 mg (51%, 0.25 mmol scale); colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59-7.57 (m, 0.12× 2H for ***syn*-7aa**), 7.45 (d, J = 6.5 Hz, 0.88 × 2H for ***anti*-7aa**), 7.39-7.08 (m, 0.12 × 16H for ***syn*-7aa** and 0.88 × 16H for ***anti*-7aa**), 6.90 (d, J = 7.5 Hz, 0.12 × 2H for ***syn*-7aa**), 6.79 (d, J = 7.7 Hz, 0.88 × 2H for ***anti*-7aa**), 4.18-3.96 (m, 0.12 × 4H for ***syn*-7aa** and 0.88 × 8H for ***anti*-7aa**), 3.85-3.75 (m, 0.12 × 2H for ***syn*-7aa**), 3.43-3.26 (m, 0.12H for ***syn*-7aa** and 0.88H for ***anti*-7aa**), 3.30 (d, J = 13.6 Hz, 0.12 × 2H for ***syn*-7aa**), 2.57-2.49 (m, 0.12H for ***syn*-7aa**), 2.42-2.30 (m, 0.12 × 2H for ***syn*-7aa** and 0.88H for ***anti*-7aa**), 2.20-2.10 (m, 0.12H for ***syn*-7aa** and 0.88× 2H for ***anti*-7aa**), 1.84-1.77 (m, 0.88H for ***anti*-7aa**), 1.71-1.64 (m, 0.12H for ***syn*-7aa**), 1.60-1.52 (m, 0.88H for ***anti*-7aa**), 1.34 (t, J = 7.1 Hz, 0.88 × 3H for ***anti*-7aa**), 1.32 (t, J = 7.0 Hz, 0.88 × 3H for ***anti*-7aa**), 1.29 (t, J = 7.1 Hz, 0.12 × 3H for ***syn*-7aa**), 1.28 (t, J = 7.0 Hz, 0.12 × 3H for ***syn*-7aa**), 0.43 (s, 0.12 × 3H for ***syn*-7aa**), 0.32 (s, 0.88 × 3H for ***anti*-7aa**), 0.17 (s, 0.88 × 3H for ***anti*-7aa**), 0.15 (s, 0.12 × 3H for ***syn*-7aa**); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.7, 142.2, 140.4, 140.2, 139.8, 139.5, 134.1, 134.0, 129.5, 129.1, 129.0, 128.7, 128.34 (2C), 128.31 (2C), 128.2, 128.1, 128.0, 127.7, 127.1, 127.0, 125.8, 125.5, 61.9 (d, J = 7.3 Hz), 61.3 (d, J = 7.4 Hz), 61.0 (d, J = 6.8 Hz), 60.8 (d, J = 7.8 Hz), 56.8 (d, J = 153.4 Hz), 56.7 (d, J = 132.0 Hz), 56.0, 55.4 (d, J = 7.1 Hz), 36.3 (2C), 31.2 (d, J = 7.5 Hz), 29.7 (d, J = 6.1 Hz), 26.2 (d, J = 7.1 Hz), 22.2 (d, J = 7.9 Hz), 16.8-16.6 (m, 4C), -1.37, -1.89, -3.20, -3.46; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 28.47, 26.40; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{36}H_{47}NO_3PSi$ 600.3057, found 600.3058.

An 11/89 Diastereomixture of Diethyl {(1*S,2*S**)-1-(Dibenzylamino)-2-[dimethyl(phenyl)silyl]propyl}phosphonate (*syn*-7ba) and Diethyl {(1*S**,2*R**)-1-(Dibenzylamino)-2-[dimethyl(phenyl)silyl]propyl}phosphonate (*anti*-7ba).** It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC ($CHCl_3$): 68 mg (54%, 0.25 mmol scale); colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.22 (m, 0.11 × 15H for ***syn*-7ba** and 0.89 × 15H for ***anti*-7ba**), 4.19-3.95 (m, 0.11 × 4H for ***syn*-7ba** and 0.89 × 6H for ***anti*-7ba**), 3.92 (dd, *J* = 13.7, 4.7 Hz, 0.89 × 2H for ***anti*-7ba**), 3.83-3.75 (m, 0.11 × 2H for ***syn*-7ba**), 3.50 (d, *J* = 13.5 Hz, 0.11 × 2H for ***syn*-7ba)**, 3.36-3.29 (m, 0.11H for ***syn*-7ba** and 0.89H for ***anti*-7ba**), 1.53-1.44 (m, 0.11H for ***syn*-7ba** and 0.89H for ***anti*-7ba**), 1.39-1.29 (m, 0.11 × 6H for ***syn*-7ba** and 0.89 × 6H for ***anti*-7ba**), 1.26 (td, *J* = 7.1, 2.1 Hz, 0.11 × 3H for ***syn*-7ba**), 1.19 (d, *J* = 7.6 Hz, 0.89 × 3H for ***anti*-7ba**), 0.29 (s, 0.11 × 3H for ***syn*-7ba**), 0.21 (s, 0.89 × 3H for ***anti*-7ba**), 0.15 (s, 0.11 × 3H for ***syn*-7ba**), -0.12 (s, 0.89 × 3H for ***anti*-7ba**); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.9, 139.6, 139.3, 139.2, 134.0, 133.8, 129.6, 129.1, 128.9, 128.6, 128.3, 128.1, 127.8, 127.6, 127.1, 126.9, 61.7 (d, *J* = 7.3 Hz), 61.1 (d, *J* = 7.2 Hz), 60.9 (d, *J* = 7.9 Hz), 60.8 (d, *J* = 7.1 Hz), 56.7 (d, *J* = 2.6 Hz), 56.4 (d, *J* = 152.1 Hz), 55.85 (d, *J* = 124.9 Hz), 55.82 (d, *J* = 6.6 Hz), 21.4 (d, *J* = 4.7 Hz), 18.2 (d, *J* = 7.7 Hz) 16.71 (d, *J* = 5.1 Hz), 16.66 (d, *J* = 5.5 Hz), 16.6 (d, *J* = 7.2 Hz), 16.5 (d, *J* = 7.5 Hz), 13.5 (d, *J* = 6.5 Hz), 12.2 (d, *J* = 4.3 Hz), -3.5, -3.7, -4.0, -4.2; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ 29.25, 26.52; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{29}H_{41}NO_3PSi$ 510.2588, found 510.2613.

A 26/74 Diastereomixture of Diethyl {(1*S,2*S**)-1-(dibenzylamino)-2-[dimethyl(phenyl)silyl]-2-phenylethyl}phosphonate (*syn*-7ka) and Diethyl {(1*S**,2*R**)-1-(dibenzylamino)-2-[dimethyl(phenyl)silyl]-2-phenylethyl}phosphonate (*anti*-7ka).** It was purified by silica gel column chromatography with hexane/ethyl acetate (4/1, v/v) and GPC ($CHCl_3$): 49 mg (35%, 0.25 mmol scale); colorless oil; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.07 (m, 0.26 × 20H for ***syn*-7ka** and 0.74 × 12H for ***anti*-7ka**), 7.02 (t, *J* = 7.9 Hz, 0.74 × 2H for ***anti*-7ka**), 6.80 (br, 0.74 × 4H for ***anti*-7ka**), 6.50 (br, 0.74 × 2H for ***anti*-7ka**), 4.12-3.88 (m, 0.26 × 2H for ***syn*-7ka** and 0.74 × 4H for ***anti*-7ka**), 3.85-3.78 (m,

0.26 × 2H for ***syn*-7ka** and 0.74 × 2H for ***anti*-7ka**), 3.75-3.44 (m, 0.26 × 3H for ***syn*-7ka** and 0.74 × 3H for ***anti*-7ka**), 3.28-3.18 (m, 0.26 × 2H for ***syn*-7ka**), 3.12 (d, J = 4.8 Hz, 0.26H for ***syn*-7ka**), 3.07 (dd, J = 11.3, 11.3 Hz, 0.74H for ***anti*-7ka**), 1.33 (t, J = 7.0 Hz, 0.74 × 3H for ***anti*-7ka**), 1.30 (t, J = 7.0 Hz, 0.74 × 3H for ***anti*-7ka**), 1.14 (t, J = 7.0 Hz, 0.26 × 6H for ***syn*-7ka**), 0.28 (s, 0.26 × 3H for ***syn*-7ka**), 0.17 (s, 0.74 × 3H for ***anti*-7ka**), 0.080 (s, 0.26 × 3H for ***syn*-7ka**), -0.058 (s, 0.74 × 3H for ***anti*-7ka**); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.3 (d, J = 14.2 Hz), 141.7 (d, J = 2.8 Hz), 140.9, 140.0 (2C), 139.8, 135.2, 135.1, 132.0, 131.1 (2C), 130.4, 129.9, 129.4, 129.1 (2C), 128.9, 128.8 (d, J = 4.2 Hz), 128.6, 128.2, 127.9 (2C), 126.3, 125.6, 62.2-62.0 (m, 3C), 61.6 (d, J = 7.5 Hz), 59.2 (d, J = 150.4 Hz), 57.5 (d, J = 5.3 Hz), 56.9 (d, J = 130.7 Hz), 54.9, 37.9 (d, J = 8.6 Hz), 37.2 (d, J = 9.6 Hz), 17.73 (d, J = 5.5 Hz), 17.72 (d, J = 5.8 Hz), 17.6 (d, J = 5.6 Hz), 17.3 (d, J = 6.3 Hz), 0.0, -1.2, -2.2, -2.6; $^{31}P\{^{1}H\}$ NMR ($CDCl_3$, 162 MHz) δ 27.75, 27.12; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{34}H_{43}NO_3PSi$ 572.2744, found 572.2772.

Procedure for Hydrogenolysis of 3ra. A 20 mL two-neck reaction flask equipped with a stir bar was charged with diisopropyl [(1*R*,2*S*)-1-(dibenzylamino)-2-phenylpropyl]phosphonate (*anti*-**3ra**, 48.0 mg, 0.10 mmol, >1/99 *syn*/*anti*, >99/1 er), $Pd(OH)_2$ on carbon (20 wt%, 9.6 mg), and MeOH (1.0 mL). The flask was evacuated and backfilled with hydrogen (this process was repeated a total of three times), and the suspension was stirred at room temperature for 24 h under a hydrogen atmosphere (1 atm, balloon). The reaction flask was then evacuated and backfilled with N_2. The resulting mixture was filtered through a pad of Celite and then evaporated in vacuo to give diisopropyl [(1*R*,2*S*)-1-amino-2-phenylpropyl]phosphonate (*anti*-**3ra-NH$_2$**, 28.4 mg, 0.095 mmol) in 95% yield with a >1/99 *anti/syn* ratio. The enantiomeric ratio (er) was determined to be >99/1 by chiral HPLC analysis on a chiral stationary phase.



Diisopropyl [(1*R*,2S)-1-Amino-2-phenylpropyl]phosphonate (*anti*-3ra-NH_2). It was purified by filtration with Celite: 28.4 mg (95%, 0.1 mmol scale); colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33-7.28 (m, 4H), 7.24-7.20 (m, 1H), 4.75 (sep, *J* = 6.2 Hz, 1H), 4.72 (sep, *J* = 6.3 Hz, 1H), 3.39-3.31 (m, 1H), 3.10 (dd, *J* = 16.2, 3.5 Hz, 1H), 1.38 (d, *J* = 7.2 Hz, 3H), 1.34 (d, *J* = 6.2 Hz, 3H), 1.32-1.29 (m, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz: δ 144.7 (d, *J* = 15.0 Hz), 128.3, 127.7, 126.5, 70.6 (d, *J* = 6.8 Hz), 70.5 (d, *J* = 6.4 Hz), 55.1 (d, *J* = 147.8 Hz), 39.7, 24.2-24.0 (m, 4C), 14.2; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ 25.80 ; HRMS (APCI) m/z $(M + H)^+$ calcd for $C_{15}H_{27}NO_3P$ 300.1723, found 300.1710. CHIRALPAK AD-H column, 96/4 hexane/isopropyl alcohol, 0.5 mL/min, major isomer t_R = 23.3 min, minor isomer t_R = 20.6 min.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are openly available in the published article and its online Supporting Information.

Supporting Information

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

^{1}H, ^{13}C{^{1}H}, ^{19}F{^{1}H}, and ^{31}P{^{1}H} NMR spectra, detailed optimization studies, epimerization test, and chiral HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by JSPS KAKENHI Grants. JP 22J10951 (Grant-in-Aid for JSPS Research Fellow to Soshi Nishino) and JP 22H02077 [Grant-in-Aid for Scientific Research(B) to K.H.] as well as by the JST FOREST Program (Grant JPMJFR211X to K.H.).

References

(1) Mucha, A.; Kafarski, P.; Berlicki, Ł. Remarkable Potential of the α-Aminophosphonate/Phosphinate Structural Motif in Medicinal Chemistry. *J. Med. Chem*. **2011**, *54*, 5955–5980.

(2) (a) Keglevich, G.; Balint, E. The Kabachnik–Fields Reaction: Mechanism and Synthetic Use. *Molecules* **2012**, *17*, 12821–12835. (b) Denmark, S. E.; Chatani, N.; Pansare, S. V. Asymmetric electrophilic amination of chiral phosphorus-stabilized anions. *Tetrahedron* **1992**, *48*, 2191–2208. (c) Hanessian, S.; Bennani, Y. L. Electrophilic Amination and Azidation of Chiral α-Alkyl Phosphonamides: Asymmetric Syntheses of α-Amino α-Alkyl Phosphonic Acids. *Synthesis* **1994**, *199*4, 1272–1274. (d) Pagliarin, R.; Papeo, G.; Sello, G.; Sisti, M.; Paleari, L. Design of β-amino alcohols as chiral auxiliaries

in the electrophilic amination of 1,3,2-oxazaphospholanes. *Tetrahedron* **1996**, *52*, 13783–13794. (e) Bernardi, L.; Zhuang, W.; Jørgensen, K. A. An Easy Approach to Optically Active α-Amino Phosphonic Acid Derivatives by Chiral Zn(II)-Catalyzed Enantioselective Amination of Phosphonates. *J. Am. Chem. Soc.* **2005**, *127*, 5772–5773. (f) McDonald, S. L.; Wang, Q. Copper-Catalyzed α-Amination of Phosphonates and Phosphine Oxides: A Direct Approach to α-Amino Phosphonic Acids and Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 1867–1871.

(3) (a) Burger, A.; Shelver, W. H. Dialkylaminoalkyl Diphenylphosphine Oxides. *J. Med. Chem*. **1961**, *4*, 225–230. (b) Venugopalan, B.; Hamlet, A. B.; Durst, T. A short synthesis of the Δ-carbopenem ring system. *Tetrahedron Lett.* **1981**, *22*, 191–194. (c) Palacios, F.; Alonso, C.; de los Santos, J. M. Synthesis of β-Aminophosphonates and -Phosphinates. *Chem. Rev*. **2005**, *105*, 899–931. (d) Matveeva, E. V.; Petrovskii, P. V.; Odinets, I. L. Efficient synthesis of racemic β-aminophosphonates via aza-Michael reaction in water. *Tetrahedron Lett.* **2008**, *49*, 6129–6133.

(4) For selected reviews of hydroamination, see: (a) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. Hydroamination: Direct Addition of Amines to Alkenes and Alkynes. *Chem. Rev.* **2008**, *108*, 3795–3892. (b) Hesp, K. D.; Stradiotto, M. Rhodium- and Iridium-Catalyzed Hydroamination of Alkenes. *ChemCatChem* **2010**, *2*, 1192–1207. (c) Huang, L.; Arndt, M.; Gooβen, K.; Heydt, H.; Gooβen, L. Late Transition Metal-Catalyzed Hydroamination and Hydroamidation. *Chem. Rev.* **2015**, *115*, 2596–2697. (d) Coman, S. M.; Parvulescu, V. I. Nonprecious Metals Catalyzing Hydroamination and C–N Coupling Reactions. *Org. Process Res. Dev.* **2015**, *19*, 1327–1355.

(5) Nishino, S.; Miura, M.; Hirano, K. An umpolung-enabled copper-catalysed regioselective hydroamination approach to α-amino acids. *Chem. Sci.* **2021**, *12*, 11525–11537.

(6) (a) Seebach, D.; Corey, E. J. Generation and Synthetic Applications of 2-Lithio-1,3-dithianes. *J. Org. Chem.* **1975**, *40*, 231–237. (b) Seebach, D. Methods of Reactivity Umpolung. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258.

(7) For related seminal work on electrophilic amination with hydroxylamines, see: (a) Tsutsui, H.; Hayashi, Y.; Narasaka, K. Preparation of Primary Amines by the Copper(I) Catalyzed Reaction of 4,4'-Bis(trifluoromethyl)benzophenone *O*-Methylsulfonyloxime and Alkyl Grignard Reagents. *Chem. Lett.* **1997**, *26*, 317-318. (b) Berman, A. M.; Johnson, J. S. Copper-Catalyzed Electrophilic Amination of Diorganozinc Reagents. *J. Am. Chem. Soc.* **2004**, *126*, 5680-5681. For a unique organocatalytic approach with the hydroxylamine, see: (c) MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem.–Eur. J.* **2013**, *19*, 2597–2601. For recent reviews, accounts, and perspectives, see: (d) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L. Copper Hydride Catalyzed Hydroamination of Alkenes and Alkynes. *Angew. Chem., Int. Ed*. **2016**, *55*, 48–57. (e) Dong, X.; Liu, Q.; Dong, Y.; Liu, H. Transition-Metal-Catalyzed Electrophilic Amination: Application of *O*-Benzoylhydroxylamines in the Construction of the C−N Bond. *Chem.–Eur. J.* **2017**, *23*, 2481–2511. (f) Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Olefin Functionalization: From Hydroamination to Carbonyl Addition. *Acc. Chem. Res.* **2020**, *53*, 1229–1243. (g) Hirano, K.; Miura, M. Hydroamination, Aminoboration, and Carboamination with Electrophilic Amination Reagents: Umpolung-Enabled Regio- and Stereoselective Synthesis of N-Containing Molecules from Alkenes and Alkynes. *J. Am. Chem. Soc.* **2022**, *144*, 648–661.

(8) Kobayashi, T.; Nishino, S.; Miura, M.; Hirano, K. Synthesis of β-Silyl-α-amino Acid Derivatives by Cu-Catalyzed Regio- and Enantioselective Silylamination of α,β-Unsaturated Esters. *Org. Lett.* **2022**, *24*, 1418–1422.

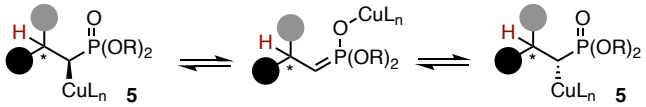
(9) Duan, Z.-C.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Zheng, Z. Cu-catalyzed asymmetric conjugate reduction of β-substituted α,β-unsaturated phosphonates: an efficient synthesis of optically active β-stereogenic alkylphosphonates . *Tetrahedron Lett.* **2009**, *50*, 6720–6722.

(10) A similar poor stereocontrol at the α-position was observed in the related reaction of α,β-unsaturated esters. See refs 5 and 8. We also confirmed no epimerization of the product under reaction conditions. See the Supporting Information for details.

(11) For a review of copper hydride chemistry, see: Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916–2927.

(12) Zhang, L.; Fang, Y.; Jin, X.; Guo, T.; Li, R.; Li, Y.; Li, X.; Yang, Y.; Yuan, M.; Tian, Z. Efficient synthesis of a-substituted ethylphosphonates via CuH- catalyzed conjugate reduction of terminal alkenylphosphonate. *Tetrahedron Lett.* **2017**, *58*, 4538–4541.

(13) One possibility is the tautomerization between intermediate **5** and its ylide with the *O*-bound Cu moiety (see the following scheme). For a related tautomerization-like process between the phosphonate and ylide, see: Kadyrov, A. A.; Röschenthaler, G.-V. 1,1,3,3,3-Pentafluoro-2-pentafluorophenylpropene Oxide. Precursor for Novel Phosphonates and Ylides. *Heteroatom Chem.* **1997**, *8*, 59–61.



(14) Xie, L.-H.; Suh, M. P. Flexible Metal-Organic Framework with Hydrophobic Pores. *Chem.—Eur. J.* **2011**, *17*, 13653–13656.

(15) Ito, S.; Itoh, T.; Nakamura, M. Diastereoselective Carbometalation of Oxa- and Azabicyclic Alkenes under Iron Catalysis. *Angew. Chem., Int. Ed.* **2011**, *50*, 454–457.

(16) (a) Duhamel, T.; Martínez, M. D.; Sideri, I. K.; Muñiz, K. 1,3-Diamine Formation from an Interrupted Hofmann–Löffler Reaction: Iodine Catalyst Turnover through Ritter-Type Amination. *ACS Catal.* **2019**, *9*, 7741–7745. (b) Winterton, S. E.; Ready, J. M. [3 + 2]-Cycloadditions of Azomethine Imines and Ynolates. *Org. Lett.* **2016**, *18*, 2608–2611. (c) Hurtak, J. A.; McDonald, F. E. Synthesis of the ABC Substructure of Brevenal by Sequential exo-Mode Oxacyclizations of Acyclic Polyene Precursors. *Org. Lett.* **2017**, *19*, 6036–6039. (d) Sabitha, G.; Reddy, S. S. S.; Raju, A.; Yadav, J. S. A Concise Stereoselective Total Synthesis of Synargentolide A from 3,4,6-Tri-O-acetyl-D-glucal. *Synthesis* **2011**, *2011*, 1279. (e) Nieto, C. T.; Salgado, M. M.; Dominguez, S, H.; Diez, D.; Garrido, N. M. Rapid access with diversity to enantiopure flexible PNA monomers following asymmetric orthogonal strategies. *Tetrahedron: Asymmetry* **2014**, *25*, 1046.

(17) Berman, A. M.; Johnson, J. S. Copper-Catalyzed Electrophilic Amination of Organozinc Nucleophiles: Documentation of *O*-Benzoyl Hydroxylamines as Broadly Useful $R_2N(+)$ and $RHN(+)$ Synthons. *J. Org. Chem*. **2006**, *71*, 219–224, and ref 7b.