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Direct Access to Enantiomerically Enriched α-Amino Phosphonic Acid Derivatives by Organocatalytic Asymmetric Hydrophosphonylation of Imines

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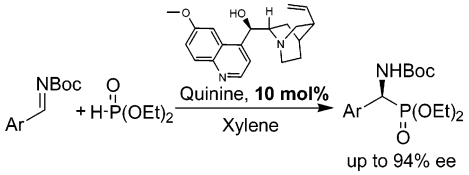

A simple and efficient organocatalytic enantioselective hydrophosphonylation of imines to enantiomerically enriched α-amino phosphonates is reported. By using 10 mol % of quinine as the catalyst in the enantioselective addition of diethyl phosphite to *N*-Boc protected imines, α-amino phosphonates are obtained in moderate to good yields and with up to 94% ee.

The addition of compounds containing phosphorus−hydrogen bonds to C−C or C−X double bonds provides an atom-economic method for the synthesis of organophosphorus derivatives. Among phosphorus compounds, α-amino phosphonic acids and their derivatives have received considerable attention in the recent years because they exhibit intriguing biological activities.[1]

Being considered as α-amino acid analogues,[2] they have found widespread use as biologically attractive peptide mimics which have been employed, for example, as inhibitors of protease[3] and as catalytic antibodies.[4] In addition, they have been used as antibacterial[5] and anti-HIV agents.[6]

Because the biological activity related to the α-amino phosphonic acid units depends on their absolute configuration, the access to optically active α-amino phosphonic acids by stereoselective synthesis has been the object of great efforts in organic chemistry.[7] Most of the strategies are based on diastereoselective hydrophosphonylation by addition of an appropriate phosphorus nucleophile, in most cases a phosphite ester, to chiral imines using stoichiometric amounts of a chiral auxiliary.[8] In contrast, only a few reports on the enantioselective catalytic hydrophosphonylations of imines are available[9] and especially those based on organocatalytic protocols have been to date scarcely investigated.[10]

We have recently reported the successful use of cinchona alkaloids as organocatalysts in the catalytic asymmetric aza-Henry reaction of imines.[11] Bearing this in mind, we were eager to investigate their potential as catalysts in the preparation of α-amino phosphonates by hydrophosphonylation of imines using dialkyl phosphites as nucleophiles.[12] At the outset of this study, an initial screening of derivatives **1a**−**d** in the addition of diethyl phosphite to *N*-tosyl protected imine **2** in toluene revealed the key role played by the free hydroxyl group in the cinchona catalysts. Therefore, using ester **1a** or carbamate **1b**, lacking the free hydroxyl group, as catalysts resulted (Table 1, entries 1 and 2) in significantly lower efficiency (conversion typically <10%). In contrast, commercially available quinine **1c** or its "pseudoenantiomer", quinidine **1d**, afforded quantitative conversion of the starting imine **2**, but only moderate enantioselectivities (entries 3 and 4, 48% and 46% ee, respectively) were achieved.[13] Further optimization revealed that the enantiose-

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(13) Several cinchona-derived catalysts with an acidic proton moiety were tested and found to be inferior to quinine and quinidine.

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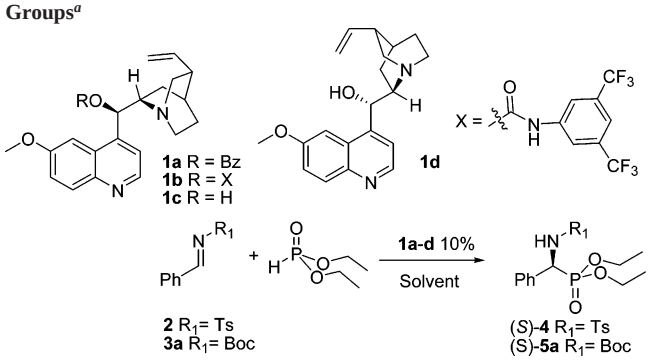
TABLE 1. Initial Screening of Catalysts, Solvents, and Protecting Groups[a]



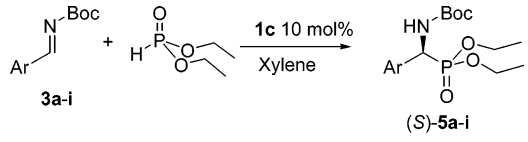
entry	R_1	catalyst	solvent	time (h)	conversion (%)[b]	ee (%)[c]
1	Ts	**1a**	toluene	42	<10	-
2	Ts	**1b**	toluene	77	0	-
3	Ts	**1c**	toluene	24	>95	48
4	Ts	**1d**	toluene	24	>95	46[d]
5	Boc	**1c**	toluene	48	>95	68
6	Boc	**1d**	toluene	48	>95	48[d]
7	Boc	**1c**	xylene	72	>95	80

[a] The reactions were carried out at 20 °C using 0.1 mmol of imine, 0.2 mmol of phosphite, and 0.01 mmol of catalyst in 1 mL of solvent. [b] Conversions were determined by ^{1}H NMR. [c] The enantiomeric excess was determined by chiral HPLC. [d] The reactions performed by quinidine **1d** gave the opposite enantiomers (*R*)-**4** and (*R*)-**5a**.

lectivity could be raised to a more satisfactory level by changing the imine **2** into *N*-Boc protected imine **3a** (entry 5, 68% ee).[14] Finally, a screening of solvents[15] suggested a significant solvent dependence with xylene affording products (*S*)-**5a**[16] with improved enantioselectivity (80% ee) and good conversion, when using quinine **1c** as the organocatalyst (entry 7).[17]

With this information in hand, we proceeded to evaluate the quinine (**1c**)-catalyzed addition of diethyl phosphite to a representative selection of substituted *N*-Boc aromatic imines. As shown in Table 2, both electron-donating (−Me, −OMe) and electron-withdrawing (−Cl) substituents on the aromatic ring were applicable and gave the corresponding products with acceptable yields within 2 or 3 reaction days at 20 °C. Some effect of the substitution pattern in the aromatic substituent of the imines could be observed in the case of imines **3b** (1-napht) and **3c** (2-napht), wherein the former afforded the corresponding α-amino phosphonate **5b** with a considerably poorer asymmetric induction (72% ee), with respect to the adduct **5c** obtained from **3c** in 85% ee (compare entries 2 and 3). Using methyl- and methoxy-substituted imines **3d**−**g** resulted in an enantiomeric excess in the range of 78−88% (entries 4−7), whereas the 3-pyridinyl- and *p*-Cl-substituted imines **3h**,**i** gave the product

TABLE 2. Enantioselective Hydrophosphonylation of Imines[a]



entry	product	Ar	time (days)	temp (°C)	yield (%)[b]	ee (%)[c]
1	**5a**	C_6H_5	3	20	83	80
2	**5b**	1-naphthyl	2	20	76	72
3	**5c**	2-naphthyl	2	20	82	85
4	**5d**	*m*-MeC_6H_4	3	20	71[d]	78
5	**5e**	*p*-MeC_6H_4	3	20	65[d]	86
6	**5f**	2,5-diMeC_6H_3	3	20	50	86
7	**5g**	*p*-$MeOC_6H_4$	2	20	50[d]	88
8	**5h**	3-pyridyl	3	20	72	48
9	**5i**	*p*-ClC_6H_4	2	20	57	77
10	**5a**	C_6H_5	3	−20	52	88
11	**5c**	2-naphthyl	4	−20	69	92
12	**5d**	*m*-MeC_6H_4	6	−20	61[d]	94
13	**5e**	*p*-MeC_6H_4	6	−20	62[d]	93
14	**5g**	*p*-$MeOC_6H_4$	7	−20	57[d]	94
15	**5i**	*p*-ClC_6H_4	4	−20	62	89

[a] The reactions were carried out using 0.1 mmol of imine, 0.2 mmol of phosphite, and 0.01 mmol of catalyst in 1 mL of solvent. [b] Yields are given for isolated products. [c] The enantiomeric excess was determined by chiral HPLC. [d] Reactions carried out on a 0.3 mmol scale.

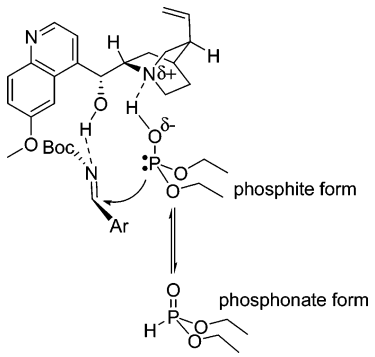


FIGURE 1. Proposed mechanism for the hydrophosphonylation of *N*-Boc imines catalyzed by quinine.

with 48% and 77% ee, respectively (entries 8 and 9), indicating that an electronic effect is also involved in the enantiodiscrimination process (compare entries 4−7 and 8−9).

Finally, an enantioselectivity/temperature profile documented that in all cases enhanced enantioselectivities were available after a prolonged reaction time (entries 10−15), by running the reactions at −20 °C. Under these conditions, α-amino phosphonates **5d** and **5g** were obtained with enantiomeric excesses up to 94% (entries 12 and 14).

A mechanistic proposal for the role of quinine **1c** as the catalyst in the hydrophosphonylation is shown in Figure 1. As the initial screening of catalysts showed the importance of the acidic hydroxyl group, we believe that the imines are activated by a hydrogen bonding from the catalyst.[11c,12] Regarding the phosphorus nucleophile, it is known that it is the phosphite and not the phosphonate form that is the actual nucleophilic species.[8d] This equilibrium, which under neutral conditions is completely shifted toward the unreactive phosphonate, can be influenced by the presence of a base.[18] Therefore, it cannot be

(14) Using a Cbz-protected imine gave a product with lower enantioselectivity compared to the analogous Boc-protected imine. This observation in combination with the more tedious preparation of Cbz imines resulted in no further consideration of Cbz imines as substrates.

(15) A screening of solvents showed that xylene gave better results than, e.g., toluene and polar protic and aprotic solvents. Use of fluorobenzene or mesitylene lowered the selectivity with respect to xylene. No difference could be observed between using a mixture of xylenes or *p*-xylene as solvent.

(16) Deprotection of the *N*-Boc moiety by treatment with TFA gave the free amine having an (*S*)-configuration with $[\alpha]^{25}_D = -15.8°$ (c = 1.0, $CHCl_3$) by comparison of the literature data [amine having an (*R*)-configuration; $[\alpha]^{25}_D = 17.2°$ (c = 1.0, $CHCl_3$): Davis, F. A.; Lee, S.; Yan, H.; Titus, D. D. *Org. Lett.* **2001**, *3*, 1757−1760].

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ruled out that the basic quinuclidinic nitrogen in the catalyst might shift the phosphite−phosphonate equilibrium toward the phosphite form and that its attack to the electrophilic azomethine carbon could be affected by the chiral environment generated by the catalyst.

In conclusion, we have provided a new straightforward organocatalytic approach for hydrophosphonylations of imines using commercially available and nonexpensive quinine as the catalyst and diethyl phosphite as the nucleophile. This simple protocol which leads to α-amino phosphonates in satisfactory yields and with up to 94% ee makes this asymmetric transformation practically important and extends the generality of catalytic enantioselective hydrophosphonylations.

Experimental Section

General Procedure for the Enantioselective Hydrophosphonylation. To a solution of imine **5a**−**i** (0.1 mmol) in xylene (900 μL) was added quinine **1c** (0.01 mmol, 100 μL, 0.1 M stock solution in xylene) followed by diethyl phosphite (0.2 mmol, 26 μL). The reaction was stirred at 20 °C or −20 °C for the time stated, after which the α-amino phosphonate (**5a**−**i**) was obtained through direct purification of the reaction mixture by column chromatography on silica gel (ethyl acetate/*n*-hexane 2:3).

(*S*)-Diethyl (*t*-Butoxycarbonylamino-phenyl-methyl) Phosphonate (5a). Following the general procedure, compound **5a** was obtained after 3 days at 20 °C as a white solid in 83% yield (28.3 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, J = 7.2 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.43 (s, 9H), 3.74 (m, 1H), 3.95 (m, 1H), 4.12 (m, 2H), 5.11 (dd, J = 9.7, 21.8 Hz, 1H), 5.51 (br s, 1H), 7.24−7.47 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 5.7 Hz), 16.6 (d, J = 5.7 Hz), 28.5, 52.1 (d, J = 154.4 Hz), 63.3 (d, J = 7.3 Hz), 63.4 (d, J = 6.9 Hz), 80.6, 128.0 (d, J = 5.8 Hz), 128.2 (d, J = 2.9 Hz), 128.8 (d, J = 2.0 Hz), 135.7, 155.1. ^{31}P NMR (161 MHz, $CDCl_3$): δ 23.0. Chiral HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane/*i*-PrOH, 0.75 mL/min, λ = 254 nm) indicated 80% ee. t_R(minor) = 31.1 min, t_R(major) = 22.4 min. $[\alpha]^{20}_D$ = −11.8 (c = 0.97, $CHCl_3$). HRMS calcd for $C_{16}H_{26}NO_5P$, m/z 343.1549; found, 343.1547.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-1-naphthyl-methyl) Phosphonate (5b). Following the general procedure, compound **5b** was obtained after 2 days at 20 °C as a white solid in 76% yield (29.9 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.83 (t, J = 7.4 Hz, 3H), 1.37 (t, J = 8.0 Hz, 3H), 1.42 (s, 9H), 3.45 (m, 1H), 3.80 (m, 1H), 4.21 (m, 2H), 5.64 (br s, 1H), 6.01 (dd, J = 9.3, 22.2 Hz, 1H), 7.45−7.60 (m, 3H), 7.70−7.76 (m, 1H), 7.79−7.89 (m, 2H), 8.19−8.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J = 5.6 Hz), 16.7 (d, J = 5.6 Hz), 28.5, 47.6 (d, J = 155.2 Hz), 63.3 (d, J = 7.8 Hz), 63.4 (d, J = 7.5 Hz), 80.6, 155.1. The aromatic carbons showed the following signals and are given without consideration of splitting: 123.7, 125.5, 126.0, 126.1, 126.8, 129.0, 131.47, 131.54, 132.3, 134.0. ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.9. Chiral HPLC analysis (Chiralpak AD-H, 90:10 *n*-hexane/*i*-PrOH, 0.75 mL/min, λ = 254 nm) indicated 72% ee. t_R(minor) = 22.6 min, t_R(major) = 15.4 min. $[\alpha]^{20}_D$ = +11.5 (c = 0.87, $CHCl_3$). HRMS calcd for $C_{20}H_{28}NO_5P$, m/z 393.1705; found, 393.1702.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-2-naphthyl-methyl) Phosphonate (5c). Following the general procedure, compound **5c** was obtained after 4 days at −20 °C as a white solid in 69% yield (27.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.10 (t, J = 6.8 Hz, 3H), 1.32 (t, J = 6.9 Hz, 3H), 1.44 (s, 9H), 3.75 (m, 1H), 3.95 (m, 1H), 4.15 (m, 2H), 5.29 (dd, J = 9.3, 22.0 Hz, 1H), 5.65 (br s, 1H), 7.43−7.60 (m, 3H), 7.78−7.93 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 5.7 Hz), 16.6 (d, J = 5.6 Hz), 28.5, 52.3 (d, J = 156.1 Hz), 63.3 (d, J = 7.3 Hz), 63.5 (d, J = 6.8 Hz), 80.7, 155.2. The aromatic carbons showed the following signals and are given without consideration of splitting: 125.8, 126.3, 126.5, 127.07, 127.12, 127.9, 128.3, 128.5, 133.0, 133.3 (d, J = 20.6 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.4. Chiral HPLC analysis (Chiralpak AD-H, 90:10 *n*-hexane/*i*-PrOH, 0.75 mL/min, λ = 254 nm) indicated 92% ee. t_R(minor) = 31.0 min, t_R(major) = 22.1 min. $[\alpha]^{20}_D$= −27.1 (c = 0.89, $CHCl_3$). HRMS calcd for $C_{20}H_{28}NO_5P$, m/z 393.1705; found, 393.1702.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-3-methylphenyl-methyl) Phosphonate (5d). Following the general procedure and performing the reaction on a 0.3 mmol scale, compound **5d** was obtained after 6 days at −20 °C as a white solid in 61% yield (57.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, J = 7.0 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H), 2.35 (s, 3H), 3.74 (m, 1H), 3.95 (m, 1H), 4.12 (m, 2H), 5.07 (dd, J = 9.9, 21.4 Hz, 1H), 5.45 (br s, 1H), 7.24−7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J = 5.8 Hz), 16.4 (d, J = 6.0 Hz), 21.4, 28.2, 51.7 (d, J = 152.8 Hz), 63.0 (d, J = 7.3 Hz), 63.2 (d, J = 7.2 Hz), 80.2, 124.8 (d, J = 6.0 Hz), 128.4, 128.5 (d, J = 5.5 Hz), 128.8 (d, J = 2.3 Hz), 135.3, 138.2, 154.8 (d, J = 11.2 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.6. Chiral HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane/*i*-PrOH, 0.75 mL/min, λ = 254 nm) indicated 94% ee. t_R(minor) = 20.9 min, t_R(major) = 16.7 min. $[\alpha]^{20}_D$ = −30.1 (c = 0.12, $CHCl_3$). HRMS calcd for $C_{17}H_{28}NO_5P$, m/z 357.1705; found, 357.1703.

(*S*)-Diethyl (*tert*-Butoxycarbonylamino-4-methylphenyl-methyl) Phosphonate (5e). Following the general procedure and performing the reaction on a 0.3 mmol scale, compound **5e** was obtained after 5 days at −20 °C as a white solid in 62% yield (58.4 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, J = 7.2 Hz, 3H), 1.29 (t, J = 7.2 Hz, 3H), 1.41 (s, 9H), 2.32 (s, 3H), 3.69−3.80 (m, 1H), 3.88−3.99 (m, 1H), 4.04−4.16 (m, 2H), 5.06 (dd, J = 9.7, 21.9 Hz, 1H), 5.48 (br s, 1H), 7.14 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J = 5.8 Hz), 16.4 (d, J = 5.8 Hz), 21.1, 28.2, 51.5 (d, J = 154.9 Hz), 62.9 (d, J = 6.7 Hz), 63.1 (d, J = 6.7 Hz), 80.2, 127.6 (d, J = 6.0 Hz), 129.2 (d, J = 2.3 Hz), 132.4, 137.7 (d, J = 2.7 Hz), 154.8 (d, J = 9.7 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 23.2. Chiral HPLC analysis (Chiralpak AD-H, 80:20 *n*-hexane/*i*-PrOH, 0.75 mL/min, λ = 254 nm) indicated 93% ee. t_R(minor) = 18.8 min, t_R(major) = 10.5 min. $[\alpha]^{20}_D$ = −1.9 (c = 1.1, $CHCl_3$). HRMS calcd for $C_{17}H_{28}NO_5P$, m/z 357.1705; found, 357.1704.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-2,5-dimethylphenyl-methyl) Phosphonate (5f). Following the general procedure, compound **5f** was obtained after 3 days at 20 °C as a pale yellow solid in 50% yield (18.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.06 (t, J = 7.3 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H), 1.42 (s, 9H), 2.31 (s, 3H), 2.41 (s, 3H), 3.56−3.67 (m, 1H), 3.83−3.94 (m, 1H), 4.09−4.20 (m, 2H), 5.36 (dd, J = 9.9, 21.8 Hz, 1H), 5.52 (br s, 1H), 6.99 (d, J = 8.0 Hz, 1H) 7.05 (d, J = 8.0 Hz, 1H), 7.20 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.1 (d, J = 5.2 Hz), 16.4 (d, J = 5.2 Hz), 19.2, 21.1, 28.3, 47.8 (d, J = 154.7 Hz), 62.9 (d, J = 7.0 Hz), 63.2 (d, J = 7.0 Hz), 80.2, 127.9, 128.7, 130.4, 133.4, 133.9, 135.7, 154.8 (d, J = 8.1 Hz). ^{31}P NMR (161 MHz, $CDCl_3$): δ 23.4. Chiral HPLC analysis (Chiralpak AD-H, 95:5 *n*-hexane/*i*-PrOH, 0.75 mL/min, λ = 254 nm) indicated 86% ee. t_R(minor) = 11.6 min, t_R(major) = 9.2 min. $[\alpha]^{20}_D$ = −18.6 (c = 1.0, $CHCl_3$). HRMS calcd for $C_{18}H_{30}NO_5P$, m/z 371.1862; found, 371.1860.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-4-methoxyphenyl-methyl) Phosphonate (5g). Following the general procedure and performing the reaction on a 0.3 mmol scale, compound **5g** was obtained after 7 days at −20 °C as a pale yellow solid in 57% yield (63.7 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.13 (t, J = 6.9 Hz, 3H), 1.31 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H), 3.77 (m + s, 1H + 3H), 3.94 (m, 1H), 4.12 (m, 2H), 5.05 (dd, J = 9.4, 21.0 Hz, 1H), 5.44 (br s, 1H), 6.83−6.91 (m, 2H), 7.29−7.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, J = 5.8 Hz), 16.6 (d, J = 5.8 Hz), 28.5, 51.4 (d, J = 153.4 Hz), 63.2 (d, J = 67.1 Hz), 63.4 (d, J = 6.5 Hz), 80. 4, 114.2, 127.8, 129.2, 129.3, 155.1 (d, J = 9.7 Hz), 159.6. ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.8. Chiral

HPLC analysis (Chiralpak AD-H, 80:20 *n*-hexane/*i*-PrOH, 0.75 mL/min, $\lambda = 254$ nm) indicated 94% ee. t_R(minor) = 21.0 min, t_R(major) = 12.0 min. $[\alpha]^{20}_D = -24.6$ ($c = 1.25$, $CHCl_3$). HRMS calcd for $C_{17}H_{28}NO_6P$, *m*/*z* 373.1654; found, 373.1652.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-pyridin-3-yl-methyl) Phosphonate (5h). Following the general procedure, compound **5h** was obtained after 3 days at 20 °C as a colorless oil in 72% yield (24.8 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.19 (t, $J = 7.0$ Hz, 3H), 1.34 (t, $J = 7.0$ Hz, 3H), 1.45 (s, 9H), 3.90 (m, 1H), 4.03 (m, 1H), 4.16 (m, 2H), 5.14 (dd, $J = 8.7$, 23.2 Hz, 1H), 5.52 (br s, 1H), 7.33 (m, 1H), 7.80 (m, 1H), 8.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, $J = 5.6$ Hz), 16.6 (d, $J = 5.5$ Hz), 28.5, 50.1 (d, $J = 155.9$ Hz), 63.57 (d, $J = 5.0$ Hz), 63.64 (d, $J = 5.0$ Hz), 80.9, 132.5, 135.6, 149.4, 155.0. ^{31}P NMR (161 MHz, $CDCl_3$): δ 21.8. Chiral HPLC analysis (Chiralpak AD-H, 55:45 *n*-hexane/*i*-PrOH, 0.5 mL/min, $\lambda = 254$ nm) indicated 48% ee. t_R(minor) = 9.4 min, t_R(major) = 10.8 min. $[\alpha]^{20}_D = -14.2$ ($c = 0.80$, $CHCl_3$). HRMS calcd for $C_{15}H_{25}N_2O_5P$, *m*/*z* 344.1501; found, 344.1503.

(*S*)-Diethyl (*t*-Butoxycarbonylamino-4-chlorophenyl-methyl) Phosphonate (5i). Following the general procedure, compound **5i** was obtained after 4 days at −20 °C as a white solid in 62% yield (26.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.15 (t, $J = 6.9$ Hz, 3H), 1.30 (t, $J = 6.9$ Hz, 3H), 1.41 (s, 9H), 3.81 (m, 1H), 3.97 (m, 1H), 4.11 (m, 2H), 5.06 (dd, $J = 9.2$, 21.6 Hz, 1H), 5.47 (br s, 1H), 7.29−7.47 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 16.4 (d, $J = 6.0$ Hz), 16.6 (d, $J = 6.0$ Hz), 28.5, 51.5 (d, $J = 155.1$ Hz), 63.4 (d, $J = 7.6$ Hz), 63.5 (d, $J = 7.3$ Hz), 80.8, 128.9, 129.3, 134.3 (d, $J = 33.0$ Hz), 155.0. ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.4. Chiral HPLC analysis (Chiralpak AD-H, 90:10 *n*-hexane/*i*-PrOH, 0.75 mL/min, $\lambda = 254$ nm) indicated 89% ee. t_R(minor) = 17.1 min, t_R(major) = 13.0 min. $[\alpha]^{20}_D = -13.9$ ($c = 1.28$, $CHCl_3$). HRMS calcd for $C_{16}H_{25}NO_5PCl$, *m*/*z* 377.1159; found, 377.1156.

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Supporting Information Available: General experimental information and ^{1}H and ^{13}C NMR spectra of products **5a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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