A Facile Synthesis of Optically Active β-Amino-β-arylethylphosphonates by Mitsunobu Reaction[‡]

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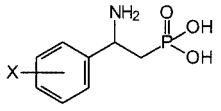
We describe a convenient and simple synthesis of optically active β-amino-β-arylethylphosphonates based on Mitsunobu reactions of chiral β-aryl-β-hydroxyethylphosphonates, prepared in turn by *Candida rugosa* lipase catalyzed kinetic resolution of the corresponding racemates.

Introduction

As phosphorus analogues of amino acids, aminophosphonic acids have attracted particular interest and have attained a position of prominence in fields of research directed towards the discovery, understanding, and modification of physiological processes in living organisms.[1,2] In the literature,[3] some racemic α-amino-β-arylethylphosphonic acids and β-amino-β-arylethylphosphonic acids are reported to be strong inhibitors of PAL and anthocyanin synthesis and are also quite active botryticides. Some compounds, such as **I**−**IV**, even gave full protection against botrytis cinerea (on apples) at levels down to 60 ppm. Another important use of β-amino-β-arylethylphosphonic acids is as potential $GABA_B$ receptor antagonists;[4] examples include compounds **I** and **V**.[4a]



I: X = H; **II**: X = 4-F; **III**: X = 4-MeO; **IV**: X = 4-Me; **V**: X = 4-Cl.

Because of their potential utilization and biological activities, the chiral synthesis of β-amino-β-arylethylphosphonic acids and their esters is of interest to organic and biological chemists.

There are a few reports on the synthesis of racemic β-amino-β-arylethylphosphonic acids and their esters. As examples, lithiated methylphosphonates have been treated with nitriles,[2a] β-oxophosphonates have been subjected to reductive amination,[2b,3b,3c,5] etc. As to the preparation of optically active β-amino-β-arylethylphosphonic acids and their esters, only Mikolajczyk et al. have reported asymmetric additions of α-phosphonate carbanions to enantiopure sulfinimines.[6] The Mitsunobu reaction[7] is one of the most effective reactions that can convert a hydroxy function into an amino group in organic molecules. To the best of our knowledge there are no reports dealing with the synthetic application of this method to the preparation of β-amino-β-arylethylphosphonic acids and their esters.[7]

In this paper we describe a convenient and simple procedure for the synthesis of optically active β-amino-β-arylethylphosphonates based on subjection of chiral β-aryl-β-hydroxyethylphosphonates[8a,8b] − conveniently prepared by enzymatic catalysis[8] − to Mitsunobu reaction conditions.

Result and Discussion

A number of (2*S*)-β-aryl-β-hydroxyethylphosphonates (**1a**−**j**) and (2*R*)-β-aryl-β-butyryloxyethylphosphonates were obtained by *Candia rugosa* lipase catalyzed (*CRL*-catalyzed) hydrolysis in diisopropyl ether pre-equilibrated with 1.2 M aqueous $MgCl_2$.[8a,8b] The (2*R*)-β-aryl-β-butyryloxyethylphosphonates were then transformed into the corresponding (2*R*)-β-aryl-β-hydroxyethylphosphonates (**2a**−**j**) by hydrolysis with use of a $NaOH/H_2O/MeOH$ system rather than a K_2CO_3/MeOH system, since longer reaction times were required in the latter case, even with no hydrolytic reaction sometimes being observed. As we have shown,

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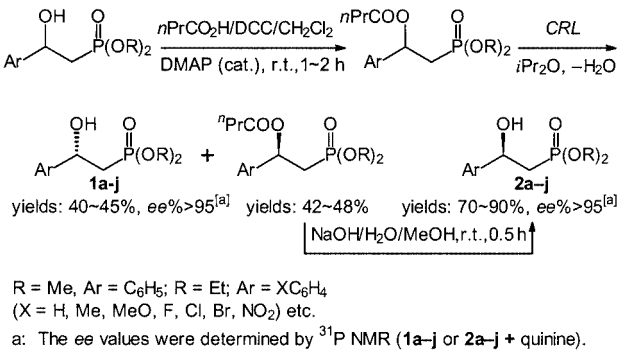
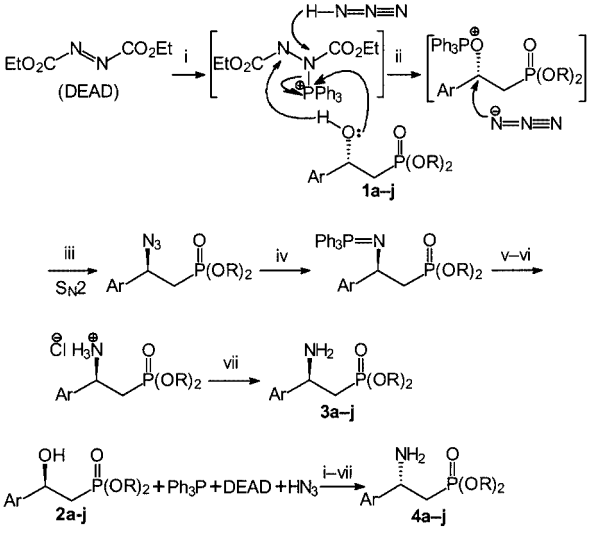
this enzyme-catalyzed process gave good chemical yields and excellent enantiomeric excesses[8a,8b] (Scheme 1).



Scheme 1

The optically active β-aryl-β-hydroxyethylphosphonates (**1a**−**j** and **2a**−**j**) were converted into the corresponding chiral β-amino-β-arylethylphosphonates with inversion of configuration by an S_N2 mechanism under Mitsunobu reaction conditions (Scheme 2 and Table 1).



Scheme 2

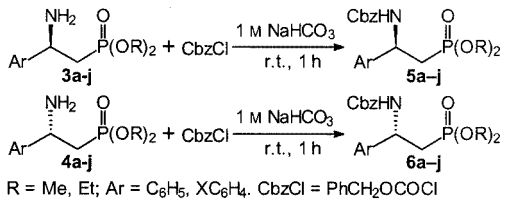
In this reaction, instead of extraction with *n*-hexane[7a−7c] to obtain the β-aryl-β-azidoethylphosphonates, the solvents were evaporated under reduced pressure, and the residue was treated directly with Ph_3P in benzene. The chiral title compounds **3a**−**j** and **4a**−**j** were finally synthesized in high yields and with good enantiomeric excesses (Table 1).

Table 1. Synthesis of title compounds **3** and **4**

Entry	R	Ar	Yield (%) 3	4	5	6	*ee* (%) 3[a]	4[b]
a	Me	C_6H_5	80	79	95	93	95.0	94.8
b	Et	C_6H_5	82	84	96	96	95.2	96.7
c	Et	4-MeC_6H_4	83	82	94	95	58.9	60.5
d	Et	4-$MeOC_6H_4$	85	88	92	97	40.5	50.9
e	Et	2-furyl	89	91	95	95	7.8	7.5
f	Et	2-BrC_6H_4	72	69	93	94	95.5	96.7
g	Et	4-FC_6H_4	93	91	96	92	97.1	98.8
h	Et	4-ClC_6H_4	91	91	90	91	95.1	95.8
i	Et	2,4-$Cl_2C_6H_3$	70	71	89	91	99.8	99.4
j	Et	4-$O_2NC_6H_4$	55	50	85	88	97.6	98.7

[a] The *ee* values were determined by chiral HPLC of their derivative **5**. [b] The *ee* values were determined by chiral HPLC of their derivative **6**.

In order to evaluate this S_N2 inversion process in the Mitsunobu reaction, the *ee* values of the title compounds **3a**−**j** and **4a**−**j** required confirmation. Since the enantiomers of the compounds **3a**−**j** or **4a**−**j** could not be resolved by chiral HPLC, enantiomeric excess values could not be obtained directly; thus, derivatization of those compounds was conducted. The conversion of amines into their corresponding benzyloxycarbonyl (Cbz) derivatives in 1 M $NaHCO_3$ was a good choice, since some literature examples[7b,9] have utilized this method to determine the *ee* values of amines (Scheme 3 and Table 1).

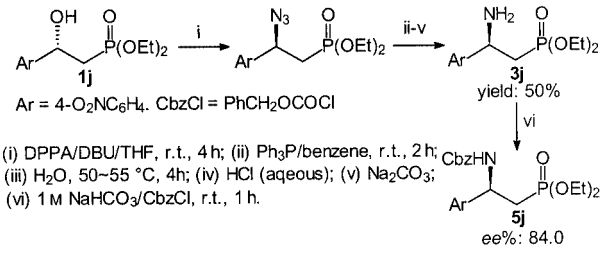


Scheme 3

From Table 1, we see that the results of the S_N2 inversion process in the Mitsunobu reaction are dependent on the nature of the aryl substituents. If there are no substituent groups (C_6H_5) or electron-withdrawing groups (F, Cl, Br, or NO_2) in the benzene ring, chiral β-aryl-β-hydroxyethylphosphonates (**1a**−**j** and **2a**−**j**) are converted into optically active β-aryl-β-azidoethylphosphonates with almost complete S_N2 inversion of configuration under Mitsunobu reaction conditions (*ee* values above 95%, even up to 99.8%). The presence of electron-donating groups (entries **c**, **d**, **e**) on the benzene ring produces a decrease in the *ee* values due to partial S_N2 reaction (*ee* values below 60%, even less than 10%).

Thompson et al. reported the use of $(PhO)_2P(O)N_3$ (DPPA)/DBU/THF to convert activated alcohols into azides.[10] We tried the this system to transform chiral β-aryl-β-hydroxyethylphosphonates (**1j**) into optically active β-am-

ino-β-arylethylphosphonates (**3j**), but the results were worse than those of the Mitsunobu reaction (Scheme 4).



Scheme 4

We finally evaluated the Mitsunobu reaction S_N2 inversion process by comparison of the optical rotations of the optically active dimethyl β-amino-β-arylethylphosphonate (**3a**). The absolute configuration of dimethyl (2*R*)-β-amino-β-arylethylphosphonate was determined by X-ray analysis of its phosphonic acid, and its optical rotation is $[\alpha]_D^{22} = -18.18$ ($c = 1.2$, $CHCl_3$),[6] while the optical rotation of the title compound (**3a**) is $[\alpha]_D^{20} = -15.3$ ($c = 1.0$, $CHCl_3$). From the above data, the absolute configuration of dimethyl β-amino-β-arylethylphosphonate (**3a**) was deduced to be (2*R*), while the absolute configuration of dimethyl β-aryl-β-hydroxyethylphosphonate (**1a**) is (2*S*). Consequently, the Mitsunobu reaction here is also an S_N2 process, as expected.

Conclusion

In summary, we describe a convenient and simple method for the synthesis of optically active β-amino-β-arylethylphosphonates in high yields and with good enantiomeric excess through the use of a Mitsunobu reaction S_N2 inversion process.

Experimental

General: IR spectra were recorded with a Shimadzu IR-440 spectrometer. EI mass spectra (MS) were run with an HP-5989A mass spectrometer. ^1H NMR spectra were recorded with a Bruker AMX 330 (300 MHz) spectrometer in $CDCl_3$, and chemical shifts are reported in ppm downfield relative to TMS (internal standard). ^{31}P NMR spectra were taken with the same spectrometer with 80% phosphoric acid as external standard. *CRL* (901 units/mg) was purchased from Sigma Chemical Co. Chiral liquid chromatography system: Waters 515 HPLC pump; UV Waters 2487 Dual λ Absorbance Detector, 254 nm; Penelson Network chromatography interface NCI 900, Turbochrom Navigator data station software; CHIRALPAK AD column and dimensions: 0.46 cm × 25 cm; flow rate: 0.7 mL/min; eluent: hexane/2-propanol = 9:1 to 8:2 (v/v).

General Procedure for the Preparation of Chiral β-Aryl-β-hydroxyethylphosphonates 1a−j and 2a−j: This was based on the literature method.[8]

General Procedure for the Preparation of Chiral β-Amino-β-arylethylphosphonates 3a−j and 4a−j: A solution of Ph_3P (0.31 g, 1.2 mmol) in CH_2Cl_2 (2 mL) was added dropwise with stirring and external cooling, at −15 to −10 °C, to a solution of DEAD (2.1 g, 1.2 mmol) in CH_2Cl_2 (0.5 mL). After 10 min, a solution of chiral β-aryl-β-hydroxyethylphosphonates (**2a−j** and **1a−j**) (1.0 mmol) was added at the same temperature. HN_3 in $CHCl_3$ (5 mL)[11] was then added dropwise. The mixture was kept at −15 to −10 °C for about 2 h and then at room temperature for another 3−6 h. After the reaction mixture had been concentrated in vacuo, the residue was dissolved in benzene (5 mL), and Ph_3P (0.28 g, 1.1 mmol) was added in one portion to the solution. After this mixture had been stirred at room temperature for 2 h, water (0.2 mL) was added, and the mixture was heated at 50−55 °C for 4 h. The reaction mixture was allowed to cool to room temperature and extracted with aqueous HCl (3×5 mL). The combined acid extracts were washed with ethyl acetate (3 × 10 mL), and the acid phase was neutralized to pH = 8−9 with Na_2CO_3 and was then extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (1 × 15 mL) and dried with Na_2SO_4, and the solvents were evaporated in vacuo to furnish the optically active products (**3a−j** and **4a−j**).

Dimethyl (2*R*)-β-Amino-β-phenylethylphosphonate (3a): Colorless oil. $[\alpha]_D^{20} = -15.3$ ($c = 1.0$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3420, 2955, 2852, 1455, 1241, 1056, 1032 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.27 (m, 5 H, Ar*H*), 4.45−4.38 (m, 1 H, ArC*H*), 3.76−3.66 (m, 6 H, OCH_3), 2.27 (s, 2 H, NH_2), 2.26−2.13 (m, 2 H, CHCH_2P) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 32.3 ppm. EI-MS: *m*/*z* (%) = 229 (4) [M^+], 214 (7), 132 (9), 124 (18), 120 (28), 106 (100), 94 (54), 79 (72), 77 (24), 47 (18). $C_{10}H_{16}NO_3P$ (229.21): calcd. C 52.40, H 7.04, N 6.11; found C 52.65, H 7.24, N 5.99.

Dimethyl (2*S*)-β-Amino-β-phenylethylphosphonate (4a): Colorless oil. $[\alpha]_D^{20} = +15.0$ ($c = 1.0$, $CHCl_3$). Compound **4a** is the enantiomer of **3a**; its spectroscopic data are identical to those of **3a**. $C_{10}H_{16}NO_3P$ (229.21): calcd. C 52.40, H 7.04, N 6.11; found C 52.69, H 7.31, N 5.89.

Diethyl (2*R*)-β-Amino-β-phenylethylphosphonate (3b): Colorless oil. $[\alpha]_D^{20} = +8.2$ ($c = 1.1$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3473, 3373, 2983, 2903, 1494, 1455, 1392, 1238, 1054, 1028, 968, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41−7.27 (m, 5 H, Ar*H*), 4.48−4.38 (m, 1 H, ArC*H*), 4.13−4.02 (m, 4 H, OCH_2CH$_3$), 2.39 (s, 2 H, NH_2), 2.23−2.13 (m, 2 H, CHCH_2P), 1.30 (t, J = 7.2 Hz, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 28.7 ppm. EI-MS: *m*/*z* (%) = 257 (5) [M^+], 228 (5), 152 (4), 125 (11), 119 (30), 106 (100), 97 (9), 79 (11), 77 (8), 65 (3). $C_{12}H_{20}NO_3P$ (257.27): calcd. C 56.02, H 7.84, N 5.44; found C 56.30, H 8.09, N 5.16.

Diethyl (2*S*)-β-Amino-β-phenylethylphosphonate (4b): Colorless oil. $[\alpha]_D^{20} = -8.5$ ($c = 1.0$, $CHCl_3$). Compound **4b** is the enantiomer of **3b**; its spectroscopic data are identical to those of **3b**. $C_{12}H_{20}NO_3P$ (257.27): calcd. C 56.02, H 7.84, N 5.44; found C 56.32, H 8.01, N 5.22.

Diethyl (2*R*)-β-Amino-β-(*p*-methylphenyl)ethylphosphonate (3c): Colorless oil. $[\alpha]_D^{20} = -3.5$ ($c = 0.7$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3373, 2983, 2908, 1515, 1240, 1054, 1029, 966, 821 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, J = 7.8 Hz, 2 H, Ar*H*), 7.15 (d, J = 7.8 Hz, 2 H, Ar*H*), 4.42−4.36 (m, 1 H, ArC*H*), 4.13−4.03 (m, 4 H, OCH_2CH$_3$), 2.33 (s, 3 H, ArCH_3), 2.17 (s, 2 H, NH_2), 2.19−2.04 (m, 2 H, CHCH_2P), 1.31 (t, J = 7.2 Hz, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 29.8 ppm. EI-MS: *m*/*z* (%) = 271 (4) [M^+], 242 (2), 152 (2), 133 (34), 120 (100),

118 (15), 97 (6), 91 (12), 80 (6), 65 (5). $C_{13}H_{22}NO_3P$ (271.30): calcd. C 57.55, H 8.17, N 5.16; found C 57.80, H 8.19, N 5.16.

Diethyl (2*S*)-β-Amino-β-(*p*-methylphenyl)ethylphosphonate (4c): Colorless oil. $[\alpha]_D^{20} = +3.5$ ($c = 1.0$, $CHCl_3$). Compound **4c** is the enantiomer of **3c**; its spectroscopic data are identical to those of **3c**. $C_{13}H_{22}NO_3P$ (271.30): calcd. C 57.55, H 8.17, N 5.16; found C 57.82, H 8.29, N, 5.36.

Diethyl (2*R*)-β-Amino-β-(*p*-methoxyphenyl)ethylphosphonate (3d): Colorless oil. $[\alpha]_D^{20} = -3.2$ ($c = 1.0$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3370, 2983, 2909, 1612, 1513, 1249, 1052, 1030, 967, 833 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, J = 6.9 Hz, 2 H, Ar*H*), 6.88 (d, J = 6.6 Hz, 2 H, Ar*H*), 4.43−4.39 (m, 1 H, ArC*H*), 4.13−4.02 (m, 4 H, O$CH_2$$CH_3$), 3.80 (s, 3 H, O$CH_3$), 2.26 (s, 2 H, N$H_2$), 2.18−2.04 (m, 2 H, CHCH_2P), 1.31 (t, J = 6.9 Hz, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 27.3 ppm. EI-MS: *m*/*z* (%) = 287 (8) [M^+], 271 (10), 149 (44), 136 (100), 134 (29), 109 (10), 93 (5), 79 (5), 77 (6), 65 (5). $C_{13}H_{22}NO_4P$ (287.29): calcd. C 54.35, H 7.72, N 4.88; found C 54.11, H 7.77, N 4.78.

Diethyl (2*S*)-β-Amino-β-(*p*-methoxyphenyl)ethylphosphonate (4d): Colorless oil. $[\alpha]_D^{20} = +3.5$ ($c = 1.0$, $CHCl_3$). Compound **4d** is the enantiomer of **3d**; its spectroscopic data are identical to those of **3d**. $C_{13}H_{22}NO_4P$ (287.29): calcd. C 54.35, H 7.72, N 4.88; found C 54.09, H 7.72, N, 4.79.

Diethyl (2*R*)-β-Amino-β-(2-furyl)ethylphosphonate (3e): Colorless oil. $[\alpha]_D^{20} = -0.5$ ($c = 0.8$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3459, 3379, 2985, 2910, 1232, 1054, 1027, 969 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.35 (1 H, m, C_4H_3O), 6.33−6.22 (m, 2 H, C_4H_3O), 4.48−4.40 (m, 1 H, ArC*H*), 4.16−4.05 (m, 4 H, O$CH_2$$CH_3$), 2.54 (s, 2 H, N$H_2$), 2.42−2.05 (m, 2 H, CHCH_2P), 1.35−1.26 (m, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 31.2 ppm. EI-MS: *m*/*z* (%) = 247 (13) [M^+], 218 (11), 172 (5), 125 (12), 109 (75), 96 (100), 80 (16), 69 (9). HR-MS calcd. for $C_{10}H_{18}NO_4P$ [M^+]: 247.0973; found 247.1014.

Diethyl (2*S*)-β-Amino-β-(2-furyl)ethylphosphonate (4e): Colorless oil. $[\alpha]_D^{20} = +1.0$ ($c = 0.9$, $CHCl_3$). Compound **4e** is the enantiomer of **3e**; its spectroscopic data are identical to those of **3e**. HR-MS calcd. for $C_{10}H_{18}NO_4P$ [M^+]: 247.0973. Found: 247.1001.

Diethyl (2*R*)-β-Amino-β-(*o*-bromophenyl)ethylphosphonate (3f): Colorless oil. $[\alpha]_D^{20} = -31.7$ ($c = 0.7$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3376, 2983, 2908, 1467, 1441, 1236, 1054, 1027, 969, 758 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.8 Hz, 1 H, Ar*H*), 7.52 (d, J = 7.8 Hz, 1 H, Ar*H*), 7.34 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.12 (d, J = 7.5 Hz, 1 H, Ar*H*), 4.79 (dt, J = 2.7, 11.4 Hz, 1 H, ArC*H*), 4.20−4.04 (m, 4 H, O$CH_2$$CH_3$), 2.33 (s, 2 H, N$H_2$), 2.30−1.98 (m, 2 H, CHCH_2P), 1.38−1.27 (m, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 26.5 ppm. EI-MS: *m*/*z* (%) = 336 (1) [M^+], 256 (62), 199 (20), 186 (91), 184 (100), 152 (15), 125 (36), 104 (14), 97 (21), 80 (15). $C_{12}H_{19}BrNO_3P$ (336.16): calcd. C 42.88, H 5.70, N 4.17; found C 42.81, H 5.90, N, 4.01.

Diethyl (2*S*)-β-Amino-β-(*o*-bromophenyl)ethylphosphonate (4f): Colorless oil. $[\alpha]_D^{20} = +31.9$ ($c = 1.0$, $CHCl_3$). Compound **4f** is the enantiomer of **3f**; its spectroscopic data are identical to those of **3f**. $C_{12}H_{19}BrNO_3P$ (336.16): calcd. C 42.88, H 5.70, N 4.17; found C 42.58, H 5.96, N 4.00.

Diethyl (2*R*)-β-Amino-β-(*p*-fluorophenyl)ethylphosphonate (3g): Colorless oil. $[\alpha]_D^{20} = -15.1$ ($c = 2.3$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3468, 3373, 3299, 2985, 2909, 1604, 1510, 1228, 1054, 1029, 967, 840 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39−7.35 (t, J = 7.5 Hz, 2 H, Ar*H*), 7.02 (t, J = 7.8 Hz, 2 H, Ar*H*), 4.46−4.38 (m, 1 H, ArC*H*), 4.13−4.03 (m, 4 H, O$CH_2$$CH_3$), 2.22 (s, 2 H, N$H_2$), 2.16−2.07 (m, 2 H, CHCH_2P), 1.31 (t, J = 7.2 Hz, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 24.4 ppm. EI-MS: *m*/*z* (%) = 275 (5) [M^+], 246 (5), 152 (8), 137 (36), 125 (28), 124 (100), 122 (20), 108 (9), 97 (21), 80 (12). $C_{12}H_{19}FNO_3P$ (275.26): calcd. C 52.36, H 6.96, N 5.09; found C 52.49, H 6.90, N 5.08.

Diethyl (2*S*)-β-Amino-β-(*p*-fluorophenyl)ethylphosphonate (4g): Colorless oil. $[\alpha]_D^{20} = +15.4$ ($c = 1.8$, $CHCl_3$). Compound **4g** is the enantiomer of **3g**; its spectroscopic data are identical to those of **3g**. $C_{12}H_{19}FNO_3P$ (275.26): calcd. C 52.36, H 6.96, N 5.09; found C 52.17, H 6.96, N, 5.28.

Diethyl (2*R*)-β-Amino-β-(*p*-chlorophenyl)ethylphosphonate (3h): Colorless oil. $[\alpha]_D^{20} = -8.2$ ($c = 1.3$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3373, 3299, 2984, 2908, 1491, 1238, 1090, 1054, 1028, 967, 828 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (dd, J = 8.7 Hz, 4 H, Ar*H*), 4.08 (dt, J = 4.2, 9.9 Hz, 1 H, ArC*H*), 4.12−4.02 (m, O4 H, C$H_2$$CH_3$), 2.77 (s, 2 H, N$H_2$), 2.22−2.05 (m, 2 H, CHCH_2P), 1.30 (t, J = 7.2 Hz, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 28.3 ppm. EI-MS: *m*/*z* (%) = 291 (10) [M^+], 262 (9), 153 (44), 140 (100), 125 (29), 108 (10), 97 (14), 80 (10), 77 (8). $C_{12}H_{19}ClNO_3P$ (291.71): calcd. C 49.41, H 6.56, N 4.80; found C 49.09, H 6.52, N 4.86.

Diethyl (2*S*)-β-Amino-β-(*p*-chlorophenyl)ethylphosphonate (4h): Colorless oil. $[\alpha]_D^{20} = +8.5$ ($c = 1.0$, $CHCl_3$). Compound **4h** is the enantiomer of **3h**; its spectroscopic data are identical to those of **3h**. $C_{12}H_{19}ClNO_3P$ (291.71): calcd. C 49.41, H 6.56, N 4.80; found C 49.27, H 6.81, N 4.71.

Diethyl (2*R*)-β-Amino-β-(*o*,*p*-dichlorophenyl)ethylphosphonate (3i): Colorless oil. $[\alpha]_D^{20} = -33.8$ ($c = 0.8$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3377, 3306, 2984, 2908, 1471, 1237, 1053, 1028, 968 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.4 Hz, 1 H, Ar*H*), 7.37−7.26 (m, 3 H, Ar*H*), 4.80 (dt, J = 3.3, 11.4 Hz, 1 H, ArC*H*), 4.19−4.03 (m, 4 H, O$CH_2$$CH_3$), 2.66 (s, 2 H, N$H_2$), 2.27−2.01 (m, 2 H, CHCH_2P), 137−1.27 (m, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 27.7 ppm. EI-MS: *m*/*z* (%) = 326 (3) [M^+ + 1], 290 (22), 187 (25), 174 (100), 152 (24), 125 (45), 108 (17), 97 (24), 80 (19). $C_{12}H_{18}Cl_2NO_3P$ (326.16): calcd. C 44.19, H 5.56, N 4.29; found C 44.17, H 5.86, N 4.00.

Diethyl (2*S*)-β-Amino-β-(*o*,*p*-dichlorophenyl)ethylphosphonate (4i): Colorless oil. $[\alpha]_D^{20} = +33.8$ ($c = 1.0$, $CHCl_3$). Compound **4i** is the enantiomer of **3i**; its spectroscopic data are identical to those of **3i**. $C_{12}H_{18}Cl_2N_2O_3P$ (326.16): calcd. C 44.19, H 5.56, N 4.29; found C 44.11, H 5.85, N 4.07.

Diethyl (2*R*)-β-Amino-β-(*p*-nitrophenyl)ethylphosphonate (3j): Colorless oil. $[\alpha]_D^{20} = +13.3$ ($c = 0.6$, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3377, 2985, 2909, 1608, 1521, 1348, 1239, 1053, 1028, 967, 857 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 7.2 Hz, 2 H, Ar*H*), 7.61 (d, J = 6.9 Hz, 2 H, Ar*H*), 4.59−4.51 (m, 1 H, ArC*H*), 4.16−4.06 (m, 4 H, O$CH_2$$CH_3$), 2.48 (s, 2 H, N$H_2$), 2.19−2.05 (m, 2 H, CHCH_2P), 1.32 (dt, J = 3.3, 6.9 Hz, 6 H, OCH$_2$CH_3) ppm. ^{31}P NMR (120 MHz, $CDCl_3$): δ = 25.5 ppm. EI-MS: *m*/*z* (%) = 302 (1) [M^+], 285 (32), 258 (6), 273 (19), 164 (46), 152 (100), 125 (92), 105 (30), 97 (42), 80 (25). $C_{12}H_{19}N_2O_5P$ (302.27): calcd. C 47.68, H 6.78, N 9.27; found C 47.48, H 6.73, N 8.99.

Diethyl (2*S*)-β-Amino-β-(*p*-nitrophenyl)ethylphosphonate (4j): Colorless oil. $[\alpha]_D^{20} = -13.8$ ($c = 1.0$, $CHCl_3$). Compound **4i** is the enantiomer of **3i**; its spectroscopic data are identical to those of **3i**. $C_{12}H_{19}N_2O_5P$ (302.27): calcd. C 47.68, H 6.78, N, 9.27; found C 47.57, H 6.67, N 9.01.

General Procedure for the Preparation of Chiral β-Aryl-β-(benzyloxycarbonylamino)ethylphosphonates 5a−j and 6a−j: Substrates **3a−j** and **4a−j** (50 mg), CbzCl (0.3 mL), and $NaHCO_3$ (1 M, 1 mL) were placed in a flask, and after the mixture had been stirred at room temperature for 1 h, ethyl acetate (5 mL) and brine (5 mL) were added. The aqueous layer was extracted with ethyl acetate (3 ×5 mL); the combined extracts were dried with anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was subjected to flash chromatography to furnish the chiral products **5a−j** and **6a−j**. The eluting solvents were ethyl acetate and *n*-hexane (1:1 to 3:1) and the yields are listed in Table 1.

Dimethyl (2*R*)-β-Benzyloxycarbonylamino-β-phenylethylphosphonate (5a): Colorless oil. $[\alpha]_D^{20} = -23.7$ (c = 1.0, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3271, 3064, 2955, 1720, 1536, 1253, 1061, 1033, 818, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.24 (m, 10 H, Ar*H*), 6.09 (s, 1 H, N*H*), 5.18−5.04 (m, 3 H, OCH_2Ph, ArC*H*), 3.63 (d, J = 11.1 Hz, 3 H, OCH_3), 3.43 (d, J = 10.5 Hz, 3 H, OCH_3), 2.50−2.28 (m, 2 H, CHCH_2P) ppm. EI-MS: m/z (%) = 363 (5) [M^+], 255 (7), 242 (12), 228 (36), 214 (30), 146 (25), 132 (30), 124 (48), 110 (39), 91 (100), 77 (18). $C_{18}H_{22}NO_5P$ (363.35): calcd. C 59.50, H 6.10, N 3.85; found C 59.37, H 6.17, N 3.74.

Dimethyl (2*S*)-β-Benzyloxycarbonylamino-β-phenylethylphosphonate (6a): Colorless oil. $[\alpha]_D^{20} = +23.8$ (c = 1.0, $CHCl_3$). Compound **6a** is the enantiomer of **5a**; its spectroscopic data are identical to those of **5a**. $C_{18}H_{22}NO_5P$ (363.35): calcd. C 59.50, H 6.10, N 3.85; found C 59.57, H 6.09, N 3.69.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-phenylethylphosphonate (5b): Colorless oil. $[\alpha]_D^{20} = -22.5$ (c = 0.8, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3267, 3034, 2984, 2909, 1722, 1537, 1249, 1025, 968, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.24 (m, 10 H, Ar*H*), 6.14 (s, 1 H, N*H*), 5.16−5.03 (m, 3 H, OCH_2Ph, ArC*H*), 4.05−3.76 (m, 4 H, OCH_2CH$_3$), 2.39−2.24 (m, 2 H, CHCH_2P), 1.24 (t, J = 7.5 Hz, 3 H, OCH$_2$CH_3), 1.10 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm. EI-MS: m/z (%) = 391 (11) [M^+], 256 (60), 242 (23), 228 (9), 196 (11), 182 (7), 138 (11), 125 (11), 104 (13), 91 (100), 77 (8). $C_{20}H_{26}NO_5P$ (391.40): calcd. C 61.37, H 6.70, N 3.58; found C 61.53, H 6.69, N 3.54.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-phenylethylphosphonate (6b): Colorless oil. $[\alpha]_D^{20} = +22.9$ (c = 1.0, $CHCl_3$). Compound **6b** is the enantiomer of **5b**; its spectroscopic data are identical to those of **5b**. $C_{20}H_{26}NO_5P$ (391.40): calcd. C 61.37, H 6.70, N 3.58; found C 61.52, H 6.67, N 3.55.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*p*-methylphenyl)ethylphosphonate (5c): Colorless oil. $[\alpha]_D^{20} = -3.2$ (c = 1.0, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3266, 3034, 2983, 2930, 1721, 1539, 1517, 1251, 1059, 1027, 967, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (s, 5 H, Ar*H*), 7.21 (d, J = 7.5 Hz, 2 H, Ar*H*), 7.13 (d, J = 7.2 Hz, 2 H, Ar*H*), 6.13 (s, 1 H, N*H*), 5.13−5.02 (m, 3 H, OCH_2Ph, ArC*H*), 4.02−3.81 (m, 4 H, OCH_2CH$_3$), 2.32 (s, 3 H, ArCH_3), 2.36−2.18 (m, 2 H, CHCH_2P), 1.35−1.11 (m, 6 H, OCH$_2$CH_3) ppm. EI-MS: m/z (%) = 405 (4) [M^+], 270 (85), 242 (10), 210 (10), 196 (7), 118 (13), 97 (7), 91 (100), 77 (6), 65 (10%). $C_{21}H_{28}NO_5P$ (405.43): calcd. C 62.21, H 6.96, N 3.45; found C 62.22, H 6.97, N 3.52.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*p*-methylphenyl)ethylphosphonate (6c): Colorless oil. $[\alpha]_D^{20} = +3.5$ (c = 1.0, $CHCl_3$). Compound **6c** is the enantiomer of **5c**; its spectroscopic data are identical to those of **5c**. $C_{21}H_{28}NO_5P$ (405.43): calcd. C 62.21, H 6.96, N 3.45; found C 62.14, H 6.96, N 3.56.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*p*-methoxyphenyl)ethylphosphonate (5d): Colorless oil. $[\alpha]_D^{20} = +17.8$ (c = 0.5, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3267, 2983, 1720, 1515, 1249, 1028, 969, 835, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33 (s, 5 H, Ar*H*), 7.26 (d, J = 8.4 Hz, 2 H, Ar*H*), 6.87 (d, J = 6.6 Hz, 2 H, Ar*H*), 6.07 (s, 1 H, N*H*), 5.14−5.02 (m, 3 H, OCH_2Ph, ArC*H*), 4.04−3.81 (m, 4 H, OCH_2CH$_3$), 3.80 (s, 3 H, OCH_3), 2.41−2.20 (m, 2 H, CHCH_2P), 1.25 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 1.15 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm. EI-MS: m/z (%) = 421 (5) [M^+], 300 (7), 286 (100), 258 (11), 230 (8), 212 (6), 192 (9), 134 (15), 91 (60), 77 (5). $C_{21}H_{28}NO_6P$ (421.43): calcd. C 59.85, H 6.70, N 3.32; found C 59.57, H 6.54, N 3.14.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*p*-methoxyphenyl)ethylphosphonate (6d): Colorless oil. $[\alpha]_D^{20} = -18.2$ (c = 0.8, $CHCl_3$). Compound **6d** is the enantiomer of **5d**; its spectroscopic data are identical to those of **5d**. $C_{21}H_{28}NO_6P$ (421.43): calcd. C 59.85, H 6.70, N 3.32; found C 59.87, H 6.73, N 3.09.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(2-furyl)ethylphosphonate (5e): Colorless oil. $[\alpha]_D^{20} = +7.2$ (c = 0.6, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3245, 3036, 2984, 2933, 1722, 1540, 1507, 1257, 1027, 969, 739, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36−7.30 (m, 6 H, Ar*H*, C_4H_3O), 6.32−6.24 (m, 2 H, C_4H_3O), 5.96 (d, J = 7.2 Hz, 1 H, N*H*), 5.29−5.12 (m, 3 H, OCH_2Ph, ArC*H*), 4.07−3.86 (m, 4 H, OCH_2CH$_3$), 2.48−2.27 (m, 2 H, CHCH_2P), 1.26 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3), 1.18 (t, J = 7.2 Hz, 3 H, OCH$_2$CH_3) ppm. EI-MS: m/z (%) = 381 (3) [M^+], 343 (65), 260 (35), 246 (100), 218 (29), 205 (34), 172 (44), 138 (39), 111 (55), 91 (53), 65 (24%). $C_{18}H_{24}NO_6P$ (381.36): calcd. C 56.69, H 6.34, N 3.67; found C 56.58, H 6.09, N 3.63.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(2-furyl)ethylphosphonate (6e): Colorless oil. $[\alpha]_D^{20} = -7.5$ (c = 0.8, $CHCl_3$). Compound **6e** is the enantiomer of **5e**; its spectroscopic data are identical to those of **5e**. $C_{18}H_{24}NO_6P$ (381.36): calcd. C 56.69, H 6.34, N 3.67; found C 56.41, H 6.39, N 3.56.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*o*-bromophenyl)ethylphosphonate (5f): Colorless oil. $[\alpha]_D^{20} = +5.6$ (c = 1.0, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3262, 3065, 2984, 1724, 1562, 1254, 1055, 1025, 969, 755, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53 (d, J = 7.8 Hz, 1 H, Ar*H*), 7.47 (d, J = 7.2 Hz, 1 H, Ar*H*), 7.34−7.27 (m, 6 H, Ar*H*), 7.13 (d, J = 7.2 Hz, 1 H, Ar*H*), 6.10 (d, J = 3.3 Hz, 1 H, N*H*), 5.41 (dd, J = 5.4, 23.1 Hz, 1 H, ArC*H*), 5.13−5.03 (m, 2 H, OCH_2Ph), 4.16−3.84 (m, 4 H, OCH_2CH$_3$), 2.44−2.32 (m, 2 H, CHCH_2P), 1.28 (t, J = 6.9 Hz, 3 H, OCH$_2$CH_3), 1.09 (t, J = 6.3 Hz, 3 H, OCH$_2$CH_3) ppm. EI-MS: m/z (%) = 471 (2) [M^+], 469 (2) [M^+], 390 (76), 347 (9), 277 (8), 257 (32), 241 (13), 211 (14), 183 (17), 125 (11), 91 (100), 65 (8). $C_{20}H_{25}BrNO_5P$ (470.30): calcd. C 51.08, H 5.36, N 2.98; found C 51.38, H 5.44, N 2.89.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*o*-bromophenyl)ethylphosphonate (6f): Colorless oil. $[\alpha]_D^{20} = -5.8$ (c = 1.0, $CHCl_3$). Compound **6f** is the enantiomer of **5f**; its spectroscopic data are identical to those of **5f**. $C_{20}H_{25}BrNO_5P$ (470.30): calcd. C 51.08, H 5.36, N 2.98; found C 51.31, H 5.28, N 2.81.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*p*-fluorophenyl)ethylphosphonate (5g): Colorless oil. $[\alpha]_D^{20} = -4.6$ (c = 2.8, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3264, 3036, 2984, 2910, 1719, 1540, 1512, 1251, 1226, 1058, 1027, 969, 840, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37−7.27 (m, 7 H, Ar*H*), 7.01 (t, J = 8.4 Hz, 2 H, Ar*H*), 6.25 (s, 1 H, N*H*), 5.12−5.02 (m, 3 H, OCH_2Ph, ArC*H*), 4.06−3.80 (m, 4 H, OCH_2CH$_3$), 2.34−2.22 (m, 2 H, CHCH_2P),

1.25 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.13 (t, J = 7.2 Hz, 3 H, OCH_2CH_3). 31P NMR (120 MHz, $CDCl_3$): δ = 24.4. EI-MS: *m*/*z* (%) = 409 (5) [M^+], 301 (14), 274 (44), 164 (13), 150 (55), 138 (48), 111 (75), 97 (80), 91 (85), 83 (83), 70 (66), 57 (100) ppm. $C_{20}H_{25}FNO_5P$ (409.39): calcd. C 58.68, H 6.16, N 3.42; found C 58.90, H 6.18, N 3.29.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*p*-fluorophenyl)ethylphosphonate (6g): Colorless oil. $[\alpha]_D^{20}$ = +5.0 (c = 1.6, $CHCl_3$). Compound **6g** is the enantiomer of **5g**; its spectroscopic data are identical to those of **5g**. $C_{20}H_{25}FNO_5P$ (409.39): calcd. C 58.68, H 6.16, N 3.42; found C 58.88, H 6.19, N 3.30.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*p*-chlorophenyl)ethylphosphonate (5h): Colorless oil. $[\alpha]_D^{20}$ = −6.3 (c = 0.8, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3263, 3035, 2984, 2932, 1719, 1539, 1494, 1249, 1025, 969, 834, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31−7.24 (m, 9 H, Ar*H*), 6.29 (s, 1 H, N*H*), 5.12−5.01 (m, 3 H, OCH_2Ph, ArC*H*), 4.06−3.82 (m, 4 H, OCH_2CH_3), 2.32−2.20 (m, 2 H, $CHCH_2P$), 1.24 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.13 (t, J = 6.9 Hz, 3 H, OCH_2CH_3). EI-MS: *m*/*z* (%) = 425 (2) [M^+], 290 (44), 276 (8), 262 (5), 234 (7), 138 (18), 125 (13), 91 (100), 65 (10) ppm. $C_{20}H_{25}ClNO_5P$ (425.85): calcd. C 56.41, H 5.92, N 3.29; found C 56.50, H 5.90, N 3.21.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*p*-chlorophenyl)ethylphosphonate (6h): Colorless oil. $[\alpha]_D^{20}$ = +6.5 (c = 1.0, $CHCl_3$). Compound **6h** is the enantiomer of **5h**; its spectroscopic data are identical to those of **5h**. $C_{20}H_{25}ClNO_5P$ (425.85): calcd. C 56.41, H 5.92, N 3.29; found C 56.56, H 5.98, N 3.15.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*o*,*p*-dichlorophenyl)ethylphosphonate (5i): Colorless oil. $[\alpha]_D^{20}$ = +6.5 (c = 1.1, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3262, 3066, 2984, 2909, 1724, 1540, 1253, 1057, 1028, 969, 865, 755, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42−7.21 (m, 8 H, Ar*H*), 6.63 (d, J = 6.6 Hz, 1 H, N*H*), 5.45−5.30 (m, 1 H, ArC*H*), 5.12−5.02 (m, 2 H, OCH_2Ph), 4.10−3.86 (m, 4 H, OCH_2CH_3), 2.45−2.21 (m, 2 H, $CHCH_2P$), 1.27 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.10 (t, J = 7.2 Hz, 3 H, OCH_2CH_3). EI-MS: *m*/*z* (%) = 459 (1) [M^+], 424 (9), 324 (7), 275 (9), 217 (4), 152 (7), 125 (12), 91 (100), 65 (10) ppm. $C_{20}H_{24}Cl_2NO_5P$ (460.29): calcd. C 52.19, H 5.26, N 3.04; found C 52.21, H 5.41, N 2.94.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*o*,*p*-dichlorophenyl)ethylphosphonate (6i): Colorless oil. $[\alpha]_D^{20}$ = −6.8 (c = 1.0, $CHCl_3$). Compound **6i** is the enantiomer of **5i**; its spectroscopic data are identical to those of **5i**. $C_{20}H_{24}Cl_2NO_5P$ (460.29): calcd. C 52.19, H 5.26, N 3.04; found C 52.33, H 5.43, N, 3.07.

Diethyl (2*R*)-β-Benzyloxycarbonylamino-β-(*p*-nitrophenyl)ethylphosphonate (5j): Colorless oil. $[\alpha]_D^{20}$ = −19.9 (c = 0.9, $CHCl_3$). IR (liquid film): $\tilde{\nu}_{max}$ = 3377, 2985, 2909, 1608, 1521, 1348, 1239, 1053, 1028, 967, 857 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 8.7 Hz, 2 H, Ar*H*), 7.51 (d, J = 8.1 Hz, 2 H, Ar*H*), 7.33 (s, 5 H, C_6H_5), 6.44 (s, 1 H, N*H*), 5.20−5.03 (m, 3 H, OCH_2Ph, ArC*H*), 4.10−3.88 (m, 4 H, OCH_2CH_3), 2.32−2.25 (m, 2 H, $CHCH_2P$), 1.27 (t, J = 6.9 Hz, 3 H, OCH_2CH_3), 1.12 (t, J = 6.9 Hz, 3 H, OCH_2CH_3) ppm. EI-MS: *m*/*z* (%) = 302 (1) [M^+], 285 (32), 258 (6), 273 (19), 164 (46), 152 (100), 125 (92), 105 (30), 97 (42), 80 (25). $C_{20}H_{25}N_2O_7P$ (436.40): calcd. C 55.05, H 5.77, N 6.42; found C 55.28, H 5.81, N 6.18.

Diethyl (2*S*)-β-Benzyloxycarbonylamino-β-(*p*-nitrophenyl)ethylphosphonate (6j): Colorless oil. $[\alpha]_D^{20}$ = +20.1 (c = 1.0, $CHCl_3$). Compound **6i** is the enantiomer of **5i**; its spectroscopic data are identical to those of **5i**. $C_{20}H_{25}N_2O_7P$ (436.40): calcd. C 55.05, H 5.77, N 6.42; found C 55.35, H 5.75, N 6.48.

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