DOI: 10.1002/ejoc.201001096

Uncatalyzed One-Pot Diastereoselective Synthesis of α-Amino Phosphonates Under Solvent-Free Conditions

Gaurao D. Tibhe,[a] Selene Lagunas-Rivera,[a] Elena Vargas-Díaz,[b] Oscar García-Barradas,[c] and Mario Ordoñez*[a]

Keywords: Diastereoselectivity / α-Amino phosphonates / Kabachnik–Fields reaction / α-Amino phosphonic acids / Phosphorus / Multicomponent reactions

Uncatalyzed one-pot, three-component reactions of aldehydes, chiral α-methylamines, and dimethyl phosphite under solvent-free conditions were used for the diastereoselective synthesis of α-amino phosphonates. The reactions proceeded with extremely high efficiency under mild conditions and gave good yields and diastereoselectivities (70:30 to 93:7 *dr*). This approach could be useful for the large-scale synthesis of several α-amino phosphonates.

Introduction

Optically active α-amino phosphonates and α-amino phosphonic acids are analogues of α-amino acids in which the planar carboxylic acid group (CO_2H) is replaced by a sterically more demanding tetrahedral phosphonic acid group ($–PO_3H_2$). Compounds of this class are currently attracting interest in organic and medicinal chemistry, as well as in agriculture, due to their important biological and pharmacological properties.[1] Thanks to the tetrahedral configuration at the phosphorus atom, α-amino phosphonic acids act as stable analogues of the unstable tetrahedral-carbon transition state in peptide hydrolysis and therefore act as enzyme inhibitors.[2] Many natural and synthetic α-amino phosphonic acids, α-amino phosphonates, and phosphonopeptides have potential applications as, for example, anti-HIV,[3] antibacterial,[4] antibiotic,[5] anticancer,[6] antitumor,[7] and antiviral agents.[8] Furthermore, in agrochemistry a number of α-amino phosphonic acids and derivatives are used as fungicidal[9] and herbicidal agents.[10]

The biological activity of an α-amino phosphonic acid or derivative depends on the absolute configuration of the stereogenic center α to the phosphorus atom.[11] As a result, routes to optically active α-aminophosphonic acids by stereoselective synthesis have been widely studied in organic chemistry.[12] A number of procedures for the stereoselective synthesis of α-amino phosphonates have been described, but there are two main pathways: (1) hydrophosphonylation of imines (Pudovik reaction),[13–15] and (2) three-component reaction in which an aldehyde, an amine, and a di- or trialkyl phosphite react in a one-pot fashion (Kabachnik–Fields reaction).[16–18]

These processes are both catalyzed either by acid or base and are the most convenient methods for the synthesis of α-amino phosphonic acids and derivatives in optically pure form. However, in spite of their potential utility, these methods typically suffer from one or more disadvantages, such as high cost, the need for a stoichiometric amount of catalyst, moisture sensitivity, the need for specialized handling techniques, tedious workup, and non-recyclability of the catalyst. The use of harmful organic solvents is also undesirable from an environmental point of view, and methods that reduce solvent use are widely sought. We aimed to develop an environmentally safe method, and here we report a diastereoselective approach to α-amino phosphonates involving one-pot, three-component reactions of alkane- and arenecarbaldehydes, chiral amines, and dimethyl phosphite [$HP(O)(OMe)_2$] under solvent-free conditions (chromatography was required for purification). This method is clean and rapid and affords the corresponding α-amino phosphonates with good to excellent yields and moderate to good diastereoselectivities, while avoiding any need for addition of any catalyst.

Results and Discussion

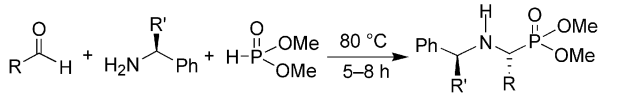
Initially, we explored one-pot, three-component reactions [the aldehydes **1**, the well-known (*S*)-α-methylbenzylamine (**2a**; R = Me, α-MBA) as the chiral source, and $HP(O)(OMe)_2$ (**3**)] under solvent-free conditions in the ab-

[a] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos,
Av. Universidad 1001, 61209 Cuernavaca, Morelos, México
Fax: +52-777-329-7997
E-mail: palacios@ciq.uaem.mx
[b] Escuela Nacional de Ciencias Biológicas del IPN, 11340, México, D. F., México
[c] Unidad de Servicios de Apoyo en Resolución Analítica, Universidad Veracruzana,
Luis Castelazo Ayala s/n, Col. Industrial Animas, 91190 Xalapa, Veracruz, México

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201001096.

sence of a catalyst. The reaction mixtures were stirred at 80 °C for 5–8 h and gave the expected α-amino phosphonates **4a**–**f**. The results are summarized in Table 1 (Entries 1–6).

Table 1. Diastereoselective three-component reactions with the chiral amines **2a** (R′ = Me) and **2b** (R′ = Et).



1 **2a–b** **3** (*R*,*S*)-**4** or (*R*,*S*)-**5**

Entry	R	R′	Product	Yield [%][a]	*dr*[b]
1	Ph	Me	**4a**	91	75:25
2	4-ClC_6H_4	Me	**4b**	80	72:28
3	4-$MeOC_6H_4$	Me	**4c**	89	76:24
4	*i*Bu	Me	**4d**	87	73.27
5	*i*Pr	Me	**4e**	79	71:29
6	*t*Bu	Me	**4f**	86	75:25
7	Ph	Et	**5a**	80	74:26
8	4-ClC_6H_4	Et	**5b**	83	76:24
9	4-$MeOC_6H_4$	Et	**5c**	82	78:22
10	*i*Bu	Et	**5d**	86	73:27
11	*i*Pr	Et	**5e**	83	72:28
12	*t*Bu	Et	**5f**	83	77:23

[a] Isolated yields. [b] Determined by ^{31}P NMR (81 and 202 MHz) examination of the crude reaction mixtures.

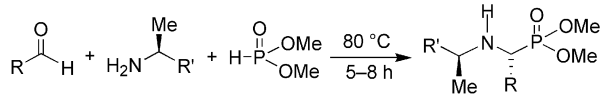
With both aliphatic and aromatic aldehydes the reactions in all cases afforded mixtures of the diastereoisomeric α-amino phosphonates, with predominance of the (*R*,*S*)-**4a**–**f** diastereoisomers. The diastereoisomeric ratios were determined by ^{31}P NMR spectroscopy at 81 and 202 MHz, and the configurations of the major and minor diastereoisomeric products were determined by analogy with results reported in the literature.[19]

In all cases the diastereoisomeric ratios were similar to those obtained in the hydrophosphonylation of imines derived from **1** (R = Ph)[20] as well as in the three-component reactions [aldehyde, **2a**, and $HP(O)(OMe)_2$] in the presence of a 5.0 M lithium perchlorate solution in diethyl ether (LPDE).[19] In addition, steric congestion was not a problem under these conditions, because the reactions with isobutyraldehyde and pivalaldehyde (Table 1, Entries 5 and 6, respectively) afforded the α-amino phosphonates in excellent yields and with moderate diastereoselectivities.

Trehan et al.[21] found that Schiff bases derived from (*R*)-α-ethylbenzylamine show C=N π-facial selectivity superior to that of Schiff bases derived from the commonly used (*R*)-α-MBA in the alkyllithium addition reaction. We therefore evaluated (*S*)-α-ethylbenzylamine as a chiral inductor in the diastereoselective synthesis of α-amino phosphonates under these one-pot, three-component reaction conditions. The one-pot reactions of both aliphatic and aromatic aldehydes **1**, (*S*)-α-ethylbenzylamine (**2b**; R′ = Et), and dimethyl phosphite under solvent-free conditions gave mixtures of the α-amino phosphonates (*R*,*S*)-**5a**–**f** in excellent yields and with diastereoselectivities identical to those obtained with (*S*)-α-MBA, so the diastereoselectivities in these reactions are not influenced by the size of the alkyl group in the α-position of the chiral amine. The results are summarized in Table 1 (Entries 7–12).

α-MBA, phenylglycinol, and esters of phenylglycine in optically pure form and in both configurations have been used as the chiral sources for diastereoselective syntheses of α-amino phosphonates under three-component catalyzed conditions, but to the best of our knowledge (*S*)-1-(1′-naphthyl)ethylamine (**2c**) had not been used in this process.[22] In order to examine the diastereoselectivity in the synthesis of α-amino phosphonates, it was of interest to evaluate the amine **2c** as a chiral source. We anticipated that the diastereoselectivity might be increased as the size of the aryl group increased from phenyl to 1-naphthyl; experimentally, however, three-component reactions of aliphatic and aromatic aldehydes, the amine **2c**, and dimethyl phosphite under solvent-free conditions and in the absence of catalyst afforded mixtures of α-amino phosphonates **6a**–**f** in excellent yields but with diastereoselectivities identical to those obtained with (*S*)-α-MBA as the chiral source. The results are summarized in Table 2 (Entries 1–6).

Table 2. Diastereoselective three-component reactions with the chiral amines **2c** (R′ = 1-naphthyl) and **2d** (R′ = *t*Bu).



1 **2c–d** **3** (*R*,*S*)-**6** or (*S*,*S*)-**7**

Entry	R	R′	Product	Yield [%][b]	*dr*[c]
1	Ph	Ar[a]	**6a**	85	71:29
2	4-ClC_6H_4	Ar[a]	**6b**	79	71:29
3	4-$MeOC_6H_4$	Ar[a]	**6c**	90	78:22
4	*i*Bu	Ar[a]	**6d**	84	69:31
5	*i*Pr	Ar[a]	**6e**	91	64:36
6	*t*Bu	Ar[a]	**6f**	88	72:28
7	Ph	*t*Bu	**7a**	91	93:07
8	4-ClC_6H_4	*t*Bu	**7b**	90	91:09
9	4-FC_6H_4	*t*Bu	**7c**	91	90:10
10	4-$MeOC_6H_4$	*t*Bu	**7d**	92	90:10
11	3,4-$Me_2OC_6H_4$	*t*Bu	**7e**	92	90:10
12	Me	*t*Bu	**7f**	92	84:16
13	Bn	*t*Bu	**7g**	52	89:11
14	*i*Bu	*t*Bu	**7h**	86	82:18
15	*i*Pr	*t*Bu	**7i**	91	80:20
16	*t*Bu	*t*Bu	**7j**	93	91:09

[a] Ar = 1-naphthyl. [b] Isolated yields. [c] Determined by ^{31}P NMR (81 and 202 MHz) examination of the crude reaction mixtures.

We next focused our attention on the evaluation of (*S*)-3,3-dimethyl-2-butylamine (**2d**) as the chiral source with the goal of obtaining α-amino phosphonates with better diastereoselectivity. In this context, benzaldehyde was initially chosen, due to its high reactivity, and it was treated with the chiral amine **2d** and $HP(O)(OMe)_2$ at 80 °C to afford the α-aminophosphonates **7a** in 91% yield and 93:7 diastereoisomeric ratio, as evidenced by ^{31}P NMR spectroscopy (Table 2, Entry 7). In order to explore the general applicability of the amine **2d** as a chiral auxiliary in the diastereoselective synthesis of α-amino phosphonates **7**, a

variety of aldehydes were studied (Table 2). In most examples, the diastereoisomeric ratios were good to excellent. Although the reactions appear to be relatively insensitive to the structure of the aldehyde component, the reaction with phenylacetaldehyde gave the phosphophenylalanine derivative in only 52% yield (Table 2, Entry 13), possibly due to isomerization of the imine prior to (or during) the reaction. The configuration of the new stereogenic center was assigned by comparison with the α-amino phosphonates containing (*S*)-α-MBA moieties. The results are summarized in Table 2 (Entries 7–16).

In an effort to explain the diastereoselectivities of these one-pot, three-component reactions for the synthesis of the α-amino phosphonates **4**–**7**, we carried out ab initio MO and DFT studies on the structures of the Schiff bases **8**–**15**. Complete optimizations were performed at the HF/3-21G level, and single-point energies were calculated at the HF/6-31+G*, MP2/6-31+G*, and B3LYP/6-31+G* levels.[21,23–25] The B3LYP/6-31+G* energies of several minima are shown in Table 3.

Table 3. Relative energies [kcal mol^{-1}] for imines **8**–**15**.

8–13 **14,15**

Entry	R	R′	Imine	Dihedral angle	B3LYP/6-31+G*
1	Ph	Ph	**8**	–3.4	0.00
2	Ph	Ph	**8**	109.6	1.60
3	Ph	Ar[a]	**9**	–3.9	0.00
4	Ph	Ar[a]	**9**	136.5	1.70
5	Ph	*t*Bu	**10**	–10.7	0.00
6	Ph	*t*Bu	**10**	–115.5	2.97
7	*i*Bu	Ph	**11**	–6.2	0.00
8	*i*Bu	Ph	**11**	108.7	1.93
9	*i*Bu	Ar[a]	**12**	–5.3	0.00
10	*i*Bu	Ar[a]	**12**	136.3	1.89
11	*i*Bu	*t*Bu	**13**	–11.1	0.00
12	*i*Bu	*t*Bu	**13**	–114.5	3.02
13	Ph	Ph	**14**	2.0	0.00
14	Ph	Ph	**14**	104.0	2.24
15	*i*Bu	Ph	**15**	0.74	0.00
16	*i*Bu	Ph	**15**	102.9	2.44

[a] Ar = 1-naphthyl.

For all Schiff bases the C–H bond of the amine in the most stable conformation was eclipsed with the N–C–H fragment, as would be expected from the 1,3-allylic strain model.[26] The conformations with C–Ph and C–Me eclipsed with N–C–H were appreciably higher in energy at all levels of calculation. The optimized geometries for the most stable conformations of imines **8**–**15** are shown in Figure 1.

For the most stable conformation, nucleophilic attack of $HP(O)(OMe)_2$ on the imines should take place at the *re* face (less hindered side) to afford the (*R*,*S*) diastereoisomers as the main products (Figure 2). Additionally, the common diastereoselectivity observed both with (*S*)-α-MBA (**2a**) and with (*S*)-1-(1′-naphthyl)ethylamine (**2c**) as the chiral auxiliaries can be explained on the basis of the Schiff base conformations, in which the phenyl and 1-naphthyl groups are oriented in a similar manner and do not lead to a difference in steric hindrance.[27]

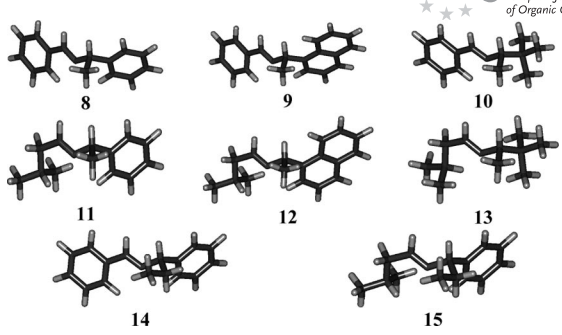


Figure 1. Optimized geometries for the most stable conformations of the imines **8**–**15**.

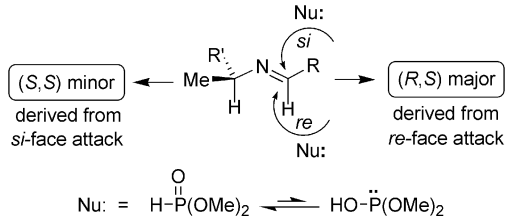


Figure 2. Proposed mechanism for nucleophilic attack of $HP(O)(OMe)_2$ onto imines.

The high diastereoselectivities obtained in the nucleophilic additions of dimethyl phosphite to imines **10** and **13** bearing the voluminous *t*Bu group can be interpreted by assuming that the *t*Bu groups block the *si* faces of the corresponding imines. In this case the nucleophilic attack proceeds stereoselectively at the *re* faces to afford the (*R*,*S*) diastereoisomers preferentially.

Conclusions

We have demonstrated highly diastereoselective one-pot, three-component reactions of aldehydes, chiral amines, and dimethyl phosphite under uncatalyzed and solvent-free conditions. We also demonstrated that Schiff bases derived from (*S*)-3,3-dimethyl-2-butylamine show C=N π-facial selectivities superior to those of Schiff bases derived from the commonly used (*S*)-α-methylbenzylamine. This procedure could be useful in the large-scale synthesis of α-amino phosphonates.

Experimental Section

General Information: All commercial materials were used as received unless otherwise noted. Flash chromatography was performed with 230–400 mesh Silica Flash 60® silica gel. Thin layer chromatography was performed with pre-coated TLC sheets of silica gel (60 F254, Merck). NMR spectra were recorded with a Varian System instrument (500 MHz for ^{1}H, 202 MHz for ^{31}P, and 125 MHz for ^{13}C) and a Mercury instrument (200 MHz for ^{1}H and 81 MHz for ^{31}P) and calibrated with $CDCl_3$ as solvent and TMS

as internal standard. High-resolution FAB$^+$ mass spectra (HRMS) were obtained with a JEOL MStation MS-700. Microanalyses were determined with an Elemental VARIO EL III machine.

General Procedure for the Synthesis of α-Amino Phosphonates: The chiral amine (1.0 equiv.) was added to the aldehyde (1.0 equiv.), and the mixture was stirred at room temperature for 15 min prior to the addition of dimethyl phosphite (1.05 equiv.). The reaction mixture was then stirred at 80 °C for 5–8 h. Progress of the reaction was monitored by TLC. The crude product was analyzed by ^{31}P NMR spectroscopy and then purified by column chromatography.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(Phenyl)[(1-phenylethyl)amino]methyl}-phosphonate (4a): Benzaldehyde (250 mg, 2.35 mmol), (*S*)-α-methylbenzylamine (MBA, 280 mg, 2.35 mmol), and dimethyl phosphite (250 mg, 2.46 mmol) were stirred at 80 °C for 5 h. The product **4a** was obtained (540 mg, 91%) as a white solid. M.p. 60 °C. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.5 Hz, 3 H, CH_3CH), 3.37* [d, J = 10.7 Hz, 3 H, $(CH_3O)_2P$], 3.43 [d, J = 10.7 Hz, 3 H, $(CH_3O)_2P$], 3.70* [d, J = 10.7 Hz, 3 H, $(CH_3O)_2P$], 3.73 [d, J = 10.7 Hz, 3 H, $(CH_3O)_2P$], 3.80 (m, 1 H, CH–N), 4.06 (d, J = 21.0 Hz, 1 H, CH–P), 7.12–7.30 (m, 20 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.2 (CH_3CH), 53.2* [d, J = 6.5 Hz, $(CH_3O)_2P$], 53.5 [d, J = 6.5 Hz, $(CH_3O)_2P$], 53.8 [d, J = 7.4 Hz, $(CH_3O)_2P$], 53.9* [d, J = 7.4 Hz, $(CH_3O)_2P$], 54.9* (d, J = 16.2 Hz, CH–N), 55.2 (d, J = 12.1 Hz, CH–N), 57.5* (d, J = 156.9 Hz, CH–P), 58.2* (d, J = 135.9 Hz, CH–P), 126.7, 127.0*, 127.1, 127.3*, 128.2*, 128.4, 128.4, 128.5, 128.6, 129.9, 132.7, 136.0, 144.9 ppm. ^{31}P NMR (81 MHz, $CDCl_3$): δ = 27.21*, 27.54 ppm. HRMS [FA]$^+$: m/z (%) = 320 (100) [M + H]$^+$, 210 (53.5), [M – 110]$^+$. $C_{17}H_{22}NO_3P$ (319.34): calcd. C 63.94, H 6.94, N 4.39; found C 63.55, H 6.94, N 4.33.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Chlorophenyl)[(1-phenylethyl)amino]-methyl}phosphonate (4b): 4-Chlorobenzaldehyde (250 mg, 1.78 mmol), (*S*)-MBA (210 mg, 1.78 mmol), and dimethyl phosphite (200 mg, 1.87 mmol) were stirred at 80 °C for 6 h. The product **4b** was obtained (500 mg, 80%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21* (d, J = 6.3 Hz, 3 H, CH_3CH), 1.25 (d, J = 6.3 Hz, 3 H, CH_3CH), 2.40–2.76 (br. s, 1 H, NH), 3.41* [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.47 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.70 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.75* [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.76 (q, J = 6.5 Hz, 1 H, CH–N), 4.05 (d, J = 21.0 Hz, 1 H, CH–P), 7.09–7.26 (m, 18 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.4 (CH_3CH), 24.7* (CH_3CH), 53.2* [d, J = 7.2 Hz, $(CH_3O)_2P$], 53.5 [d, J = 7.4 Hz, $(CH_3O)_2P$], 53.8 [d, J = 7.4 Hz, $(CH_3O)_2P$], 54.0* [d, J = 7.2 Hz, $(CH_3O)_2P$], 54.9* (d, J = 17.6 Hz, CH–N), 55.6 (d, J = 12.0 Hz, CH–N), 56.7* (d, J = 156.3 Hz, CH–P), 57.3 (d, J = 152.5 Hz, CH–P), 126.7, 126.9*, 127.2, 127.3*, 128.4, 128.6, 128.7 (J = 2.2 Hz), 128.8* (J = 2.3 Hz), 129.6 (J = 6.3 Hz), 129.8* (J = 6.4 Hz), 133.6 (J = 3.6 Hz), 133.7 (J = 3.6 Hz), 134.5*, 134.9, 143.5*, 144.7 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.60*, 26.96 ppm. HRMS [FA]$^+$: m/z (%) = 354 (25.56) [M + H]$^+$, 294 (100) [M + H – 110]$^+$, 105 (100).

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Methoxyphenyl)[(1-phenylethyl)-amino]methyl}phosphonate (4c): 4-Methoxybenzaldehyde (250 mg, 1.83 mmol), (*S*)-MBA (210 mg, 1.83 mmol), and dimethyl phosphite (200 mg, 1.92 mmol) were stirred at 80 °C for 6 h. The product **4c** was obtained (570 mg, 89%) as a yellow oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (d, J = 6.5 Hz, 3 H, CH_3CH), 3.38* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.44 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.70* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.73 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.74 (s, 3 H, CH_3O), 3.75* (s, 3 H, CH_3O), 4.00 (d, J = 20.5 Hz, 1 H, CH–P), 6.80 (AA′BB′, J = 8.3 Hz, 2 H, H_{arom}), 6.82* (AA′BB′, J = 8.3 Hz, 2 H, H_{arom}), 7.12–7.27 (m, 14 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.1 (CH_3CH), 53.4 [d, J = 7.0 Hz, $(CH_3O)_2P$], 53.7 [d, J = 7.0 Hz, $(CH_3O)_2P$], 53.8* [d, J = 7.1 Hz, $(CH_3O)_2P$], 55.0* (CH_3O), 55.2 (CH_3O), 56.7* (d, J = 153.0 Hz, CH–P), 57.1 (d, J = 154.2 Hz, CH–P), 114.0 (d, J = 2.2 Hz), 114.1* (d, J = 2.2 Hz), 126.7, 127.0*, 127.1, 127.2* 128.4, 128.5*, 129.5 (d, J = 6.5 Hz), 129.7* (d, J = 6.5 Hz), 159.4 (d, J = 2.8 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.50*, 27.79 ppm. HRMS [FA]$^+$: m/z (%) = 338 (100) [M + H]$^+$, 228 (100) [M – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{3-Methyl-1-[(1-phenylethyl)amino]-butyl}phosphonate (4d): Isovaleraldehyde (250 mg, 2.90 mmol), (*S*)-MBA (350 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **4d** was obtained (750 mg, 87%) as a yellow oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.33 [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$], 0.73 [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$], 0.74* [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$], 0.81* [d, J = 6.6 Hz, 3 H, $(CH_3)_2CH$], 1.24 (d, J = 6.3 Hz, 3 H, CH_3CH), 1.32–1.44* (m, 2 H, CH_2CH), 1.48–1.59* (m, 2 H, CH_2CH), 1.64–1.73 [m, 1 H, $CH(CH_3)_2$], 1.76–1.80* [m, 1 H, $CH(CH_3)_2$], 2.58–2.62 (m, 1 H, CH–P), 2.73–2.78* (m, 1 H, CH–P), 3.57* [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.59* [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.67 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.68 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.95* (q, J = 6.5 Hz, 1 H, CH–N), 4.06 (dq, J = 6.6, 2.9 Hz, 1 H, 1 H, CH–N), 7.10–7.26, (m, 10 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.8 (CH_3CH), 22.3*, (CH_3CH), 22.8* [$(CH_3)_2CH$], 23.5 [$(CH_3)_2CH$], 23.7 [d, J = 12.4 Hz, CH_2 $CH(CH_3)_2$], 24.0* [$(CH_3)_2CH$], 24.5 [$(CH_3)_2CH$], 24.8* [d, J = 8.5 Hz, $CH_2CH(CH_3)_2$], 39.7* [d, J = 8.5 Hz, $(CHCH_3)$], 40.1 [d, J = 2.4 Hz, $(CHCH_3)$], 49.5* (d, J = 144.6 Hz, CH–P), 49.7* (d, J = 152.3 Hz, CH–P), 52.4* [d, J = 7.4 Hz, $(CH_3O)_2P$], 52.5 [d, J = 7.4 Hz, $(CH_3O)_2P$], 52.7 [d, J = 7.4 Hz, $(CH_3O)_2P$], 53.1* [d, J = 7.3 Hz, $(CH_3O)_2P$], 55.7* (d, J = 10.5 Hz, CH–N), 56.2 (CH–N), 126.9, 127.1*, 127.2*, 127.3, 128.2, 128.3*, 144.7, 145.0* ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 32.49*, 33.54 ppm. HRMS [FA]$^+$: m/z (%) = 300 (44.61) [M + H]$^+$, 190 (100.0) [M – 110]$^+$, 105 (45.46).

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2-Methyl-1-[(1-phenylethyl)amino]-propyl}phosphonate (4e): Isobutyraldehyde (250 mg, 3.46 mmol), (*S*)-MBA (410 mg, 3.46 mmol), and dimethyl phosphite (400 mg, 3.63 mmol) were stirred at 80 °C for 8 h. The product **4e** was obtained (780 mg, 79%) as a yellow oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77* (d, J = 6.8 Hz, 3 H, CH_3), 0.87 (d, J = 6.8 Hz, 3 H, CH_3), 0.92* (d, J = 6.8 Hz, 3 H, CH_3), 1.02* (d, J = 6.8 Hz, 3 H, CH_3), 1.24* (d, J = 6.8 Hz, 3 H, CH_3), 1.26 (d, J = 6.8 Hz, 3 H, CH_3), 1.88–197 [m, 1 H, $CH(CH_3)_2$], 2.06–2.15* [m, 1 H, $CH(CH_3)_2$], 2.52 (dd, J = 12.8, 3.1 Hz, 1 H, CH–P), 2.71* (dd, J = 18.9, 3.2 Hz, 1 H, CH–P), 3.55* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.64* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.67 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.69 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.95* (q, J = 6.5 Hz, 1 H, CH–N), 4.03 (dq, J = 6.5, 3.4 Hz, 1 H, CH–N), 7.12–7.29 (m, 10 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4 (d, J = 2.6 Hz, CH_3), 18.3* (d, J = 2.6 Hz, CH_3), 20.4* (d, J = 12.3 Hz, CH_3), 20.6 (d, J = 14.3 Hz, CH_3), 23.7* (CH_3), 24.8 (CH_3), 28.6* [d, J = 5.1 Hz, $(CHCH_3)_2$], 29.8 [d, J = 5.8 Hz, $(CHCH_3)_2$], 52.1 [d, J = 7.5 Hz, $(CH_3O)_2P$], 52.2* [d, J = 7.0 Hz, $(CH_3O)_2P$], 52.4 [d, J = 7.4 Hz, $(CH_3O)_2P$], 52.6* [d, J = 7.3 Hz, $(CH_3O)_2P$], 56.2* (CH–N), 56.4 (CH–N), 56.8* (d, J = 141.2 Hz, CH–P), 57.9 (d, J = 135.0 Hz, CH–P), 127.0 (d, J = 15.2 Hz), 127.4, 128.1, 128.3*, 144.6, 145.0* ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 31.58*, 33.12 ppm. HRMS [FA]$^+$: m/z (%) = 286 (100) [M + H]$^+$, 176 (44.3) [M – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2,2-Dimethyl-1-[(1-phenylethyl)amino]-propyl}phosphonate (4f): *tert*-Butylacetaldehyde (250 mg, 2.90 mmol), (*S*)-MBA (330 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **4f** was obtained (740 mg, 86%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91 [s, 9 H, $(CH_3)_3C$], 1.11* [s, 9 H, $(CH_3)_3C$], 1.28* (d, J = 6.5 Hz, 3 H, CH_3CH), 1.35 (d, J = 6.3 Hz, 3 H, CH_3CH), 1.71 (br. s, 1 H, NH), 2.40 (d, J = 13.1 Hz, CH–P), 2.65* (d, J = 16.9 Hz, CH–P), 3.62* [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.67* [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.75 [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.81 [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 4.06–4.11* (m, 1 H, CH–N), 7.21–7.37 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.5* (CH_3), 24.4 (CH_3), 27.7 {d, J = 6.2 Hz, [$(CH_3)_3C$]}, 27.8* {d, J = 6.4 Hz, [$(CH_3)_3C$]}, 34.5 (d, J = 7.7 Hz, $CHCH_3$), 35.1* [d, J = 8.1 Hz, ($CHCH_3$)], 51.7* [d, J = 6.9 Hz, $(CH_3O)_2P$], 51.8 [d, J = 7.4 Hz, $(CH_3O)_2P$], 52.1 [d, J = 7.4 Hz, $(CH_3O)_2P$], 57.0 (CH–N), 61.0* (d, J = 140.0 Hz, CH–P), 61.5 (d, J = 132.0 Hz, CH–P), 126.9, 127.1, 127.8, 128.0, 128.2, 144.4, 145.9* ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 31.42*, 32.25 ppm. HRMS [FA]$^+$: m/z (%) = 300 (100) [M + H]$^+$, 190 (100) [M – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{Phenyl[(1-phenylpropyl)amino]methyl}-phosphonate (5a): Benzaldehyde (250 mg, 2.35 mmol), (*S*)-α-ethylbenzylamine (310 mg, 2.35 mmol), and dimethyl phosphite (250 mg, 2.46 mmol) were stirred at 80 °C for 6 h. The product **5a** was obtained (920 mg, 80%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 0.70* (t, J = 7.4 Hz, 3 H, CH_3CH_2), 1.55–1.63 (m, 2 H, CH_2), 1.72–1.78* (m, 2 H, CH_2), 3.39* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.45 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.60–3.66 (m, 1 H, CH–N), 3.71* [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.74 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 4.01 (d, J = 19.8 Hz, 1 H, CH–P), 7.10–7.31 (m, 20 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.2 (CH_3CH_2), 10.7* (CH_3CH_2), 29.0 (CH_2CH_3), 31.1* (CH_2CH_3), 53.2* [d, J = 6.8 Hz, $(CH_3O)_2P$], 53.4 [d, J = 7.1 Hz, $(CH_3O)_2P$], 53.6 [d, J = 7.1 Hz, $(CH_3O)_2P$], 53.8* [d, J = 7.1 Hz, $(CH_3O)_2P$], 57.3* (d, J = 162.5 Hz, CH–P), 57.8 (d, J = 151.2 Hz, CH–P), 61.4* (d, J = 17.4 Hz, CH–N), 62.3 (d, J = 10.7 Hz, CH–N), 127.1, 127.2*, 127.4, 127.6*, 127.7 (d, J = 2.9 Hz), 127.9* (d, J = 2.9 Hz), 128.1*, 128.2 (d, J = 6.4 Hz), 128.4*, 128.4 (d, J = 2.2 Hz), 128.5* (d, J = 2.3 Hz), 128.6* (d, J = 6.4 Hz), 129.8, 132.6*, 135.6*, 136.4, 142.4*, 143.1. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.26*, 27.70 ppm. HRMS [FA]$^+$: m/z (%) = 334 (36.50) [M + H]$^+$, 224 (100.0) [M – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Chlorophenyl)[(1-phenylpropyl)-amino]methyl}phosphonate (5b): 4-Chlorobenzaldehyde (250 mg, 1.78 mmol), (*S*)-α-ethylbenzylamine (240 mg, 1.78 mmol), and dimethyl phosphite (200 mg, 1.87 mmol) were stirred at 80 °C for 6 h. The product **5b** was obtained (500 mg, 80%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.68 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 0.69* (t, J = 7.4 Hz, 3 H, CH_3CH_2), 1.53–1.61 (m, 2 H, CH_2CH_3), 1.69–1.75* (m, 2 H, CH_2CH_3), 3.43* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.48 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.56–3.62 (m, 1 H, CH–N), 3.69* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$],3.72 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.95 (d, J = 20.2 Hz, 1 H, CH–P), 7.03–7.29 (m, 18 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0 (CH_3CH_2), 10.7* (CH_3CH_2), 29.1 (CH_2CH_3), 31.0* (CH_2CH_3), 53.3* [d, J = 6.9 Hz, $(CH_3O)_2P$], 53.4 [d, J = 7.2 Hz, $(CH_3O)_2P$], 53.6 [d, J = 7.2 Hz, $(CH_3O)_2P$], 53.8* [d, J = 6.9 Hz, $(CH_3O)_2P$], 56.7* (d, J = 153.7 Hz, CH–P), 57.3 (d, J = 151.5 Hz, CH–P), 61.4* (d, J = 16.5 Hz, CH–N), 62.4 (d, J = 10.5 Hz, CH–N), 127.1, 127.3*, 127.4, 127.5*, 128.1, 128.4*, 128.5 (d, J = 2.3 Hz), 128.7* (d, J = 2.3 Hz), 129.5 (d, J = 6.3 Hz), 129.9* (d, J = 6.4 Hz), 133.4 (d, J = 3.6 Hz), 133.6* (d, J = 3.7 Hz), 135.1, 142.1, 142.8 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 32.57, 32.65* ppm. HRMS [FA]$^+$: m/z (%) = 368 (34.67) [M + H]$^+$, 258 (100.0) [M – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Methoxyphenyl)[(1-phenylpropyl)-amino]methyl}phosphonate (5c): 4-Methoxybenzaldehyde (250 mg, 1.83 mmol), (*S*)-α-ethylbenzylamine (240 mg, 1.83 mmol), and dimethyl phosphite (200 mg, 1.92 mmol) were stirred at 80 °C for 6 h. The product **5c** was obtained (500 mg, 82%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.67 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 0.68* (t, J = 7.4 Hz, 3 H, CH_3CH_2), 1.52–1.62 (m, 2 H, CH_2CH_3), 1.68–1.76* (m, 2 H, CH_2CH_3), 3.39* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.44 [d, J = 10.4 Hz, 1 H, $(CH_3O)_2P$], 3.59–362 (m, 1 H, $CHCH_2$), 3.69* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.72 (s, 3 H, CH_3O), 3.72 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.75* (s, 3 H, CH_3O), 3.94 (d, J = 19.3 Hz, 1 H, CH–P), 6.77 (AA′BB′, J = 8.4 Hz, 2 H), 6.82* (AA′BB′, J = 8.3 Hz, 2 H), 7.10–7.21 (m, 10 H, H_{arom}), 7.23 (AA′BB′, J = 7.5 Hz, 2 H), 7.25 (AA′BB′, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.0 (CH_3CH_2), 10.8* (CH_3CH_2), 28.9 (CH_2CH_3), 31.0* (CH_2CH_3), 53.4 [$(CH_3O)_2P$], 53.5 [$(CH_3O)_2P$], 55.2 (CH_3O), 56.5* (d, J = 160.0 Hz, CH–P), 57.1 (d, J = 153.4 Hz, CH–P), 62.1 (d, J = 10.3 Hz, CH–N), 113.9 (d, J = 2.0 Hz), 114.0* (d, J = 2.0 Hz), 127.0, 127.2*, 127.5, 127.7*, 128.2, 128.3*, 129.2 (d, J = 6.5 Hz), 129.8* (d, J = 6.8 Hz), 143.2, 159.1, 159.2* ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.61*, 27.96 ppm. HRMS [FA]$^+$: m/z (%) = 364 (20.81) [M]$^+$, 254 (100.0) [M – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2-Methyl-1-[(1-phenylpropyl)amino]-propyl}phosphonate (5e): Isobutyraldehyde (250 mg, 3.46 mmol), (*S*)-α-ethylbenzylamine (410 mg, 3.46 mmol), and dimethyl phosphite (400 mg, 3.63 mmol) were stirred at 80 °C for 8 h. The product **5e** was obtained (780 mg, 79%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.69* (t, J = 6.2 Hz, 3 H, CH_3CH_2), 0.70 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 0.73 (d, J = 6.8 Hz, 3 H, CH_3CH), 0.84 (d, J = 6.9 Hz, 3 H, CH_3CH), 0.92* (d, J = 7.0 Hz, 3 H, CH_3CH), 1.01* (d, J = 7.0 Hz, 3 H, CH_3CH), 1.45–1.70 (m, 2 H, CH_2CH_3), 1.84–2.16* (m, 2 H, CH_2CH_3), 2.50 (dd, J = 12.4, 3.1 Hz, 1 H, CH–P), 2.68* (dd, J = 20.0, 3.0 Hz, 1 H, CH–P), 3.49* [d, J = 10.0 Hz, 3 H, $(CH_3O)_2P$], 3.61* [d, J = 10.0 Hz, 3 H, $(CH_3O)_2P$], 3.64 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.67 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.70–3.75 (m, 1 H, CH–N), 7.11–7.25* (m, 10 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.6* (CH_3CH_2), 10.7 (CH_3CH_2), 17.3 (d, J = 2.5 Hz, CH_3CH), 18.4* (d, J = 1.9 Hz, CH_3CH), 20.1* (d, J = 12.0 Hz, CH_3CH), 20.5 (d, J = 14.6 Hz, CH_3CH), 28 ppm. 4* (d, J = 4.9 Hz, CH_2), 29.0 (d, J = 6.0 Hz, CH_2), 30.6* [$CH(CH_3)_2$], 31.3 [$CH(CH_3)_2$], 51.8 [d, J = 7.5 Hz, $(CH_3O)_2P$], 52.1* [d, J = 7.4 Hz, $(CH_3O)_2P$], 52.3 [d, J = 7.2 Hz, $(CH_3O)_2P$], 52.7* [d, J = 7.4 Hz, $(CH_3O)_2P$], 56.4 (d, J = 133.7 Hz, CH–P), 56.5 (d, J = 147.5 Hz, CH–P), 63.0 (CH–N), 63.1* (CH–N), 127.0, 127.1*, 127.7*, 127.9, 128.0, 128.1*, 143.1, 143.2*. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 31.44*, 33.50 ppm. HRMS [FA]$^+$: m/z (%) = 300 (34.16) [M + H]$^+$, 254 (100.0) [M + H – 110]$^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2,2-Dimethyl-1-[(1-phenylpropyl)amino]-propyl}phosphonate (5f): *tert*-Butylacetaldehyde (250 mg, 2.90 mmol), (*S*)-α-ethylbenzylamine (390 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **5f** was obtained (710 mg, 79%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.60* (t, J = 7.4 Hz, 3 H, CH_3CH_2), 0.68 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 0.69 [s, 9 H, $(CH_3)_3C$], 1.01* [s, 9 H, $(CH_3)_3C$], 1.49–161 (m, 2 H,

CH_2CH_3), 2.29 (d, J = 12.6 Hz, 1 H, CH–P), 2.54* (d, J = 17.8 Hz, 1 H, CH–P), 3.43* [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.53* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.63 [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.68 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.70–3.72 (m, 1 H, CH–N), 7.11–7.22 (m, 10 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 10.5* (CH_3CH_2), 10.7 (CH_3CH_2), 27.6 [d, J = 6.1 Hz, $(CH_3)_3C$], 27.8* [d, J = 6.6 Hz, $(CH_3)_3C$], 29.1* (CH_2CH_3), 30.9 (CH_2CH_3), 34.4 [d, J = 7.8 Hz, $C(CH_3)_3$], 35.3* [d, J = 7.8 Hz, $C(CH_3)_3$], 51.6* [d, J = 7.2 Hz, $(CH_3O)_2P$], 51.7 [d, J = 7.3 Hz, $(CH_3O)_2P$], 51.9 [d, J = 7.3 Hz, $(CH_3O)_2P$] 52.1* [d, J = 7.4 Hz, $(CH_3O)_2P$], 60.8* (d, J = 135.0 Hz, CH–P), 61.1 (d, J = 130.0 Hz, CH–P), 63.5 (CH–N), 64.4* (d, J = 3.9 Hz, CH–N), 127.0*, 127.8, 128.0*, 128.4, 142.8, 143.7* ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 32.20*, 33.43 ppm. HRMS $[FA]^+$: m/z (%) = 314 (18.26) $[M + H]^+$, 204 (100.0) $[M + H - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-[{[1-(Naphthalen-1-yl)ethyl]amino}-(phenyl)methyl]phosphonate (6a): Benzaldehyde (250 mg, 2.35 mmol), (*S*)-1-(1′-naphthyl)ethylamine (420 mg, 2.35 mmol), and dimethyl phosphite (250 mg, 2.46 mmol) were stirred at 80 °C for 8 h. The product **6a** was obtained (730 mg, 85%) as an oil. Asterisk denotes minor diastereoisomer. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.42* (d, J = 6.4 Hz, 3 H, CH_3CH), 1.44 (d, J = 6.5 Hz, 3 H, CH_3CH), 3.38* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.43 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.75 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.76* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.80* (d, J = 22.7 Hz, 1 H, CH–P), 4.17 (d, J = 20.6 Hz, 1 H, CH–P), 4.40* (d, J = 6.5 Hz, 1 H, CH–N), 4.69 (dd, J = 12.7, 6.4 Hz, 1 H, CH–N), 7.17–7.83 (m, 12 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8* (CH_3), 24.8 (CH_3), 50.6 [$(CH_3O)_2P$], 52.8 [$(CH_3O)_2P$], 57.6* (d, J = 157.5 Hz, CH–P), 57.8 (d, J = 152.0 Hz, CH–P), 122.3, 123.3*, 125.3, 125.5*, 125.7, 127.5, 128.0, 128.4, 128.6, 128.8*, 128.9, 131.0, 131.4*, 133.8, 134.0* ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.29*, 26.57 ppm. HRMS $[FA]^+$: m/z (%) = 370 (100) $[M + H]^+$, 260 (100) $[M - 110]^+$, 155 (73.46).

Dimethyl (*R*,*S*)- and (*S*,*S*)-[(4-Chlorophenyl){[1-(naphthalen-1-yl)-ethyl]amino}methyl]phosphonate (6b): 4-Chlorobenzaldehyde (250 mg, 1.78 mmol), (*S*)-1-(1′-naphthyl)ethylamine (304 mg, 1.78 mmol), and dimethyl phosphite (200 mg, 1.87 mmol) were stirred at 80 °C for 6 h. The product **6a** was obtained (560 mg, 79%) as an oil. Asterisk denotes minor diastereoisomer. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.46* (d, J = 6.6 Hz, 3 H, CH_3CH), 1.49 (d, J = 6.5 Hz, 3 H, CH_3CH), 3.48* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.53 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.79 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.81* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 4.17 (d, J = 20.8 Hz, 1 H, CH–P), 4.41* (d, J = 6.3 Hz, 1 H, CH–N), 4.72 (q, J = 6.5 Hz, 1 H, CH–N), 7.17–7.96 (m, 11 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.9 (CH_3CH), 24.2* (CH_3CH), 53.4 [$(CH_3O)_2P$], 53.9 [$(CH_3O)_2P$], 56.9* (d, J = 145.0 Hz, CH–P), 57.2 (d, J = 151.9 Hz, CH–P), 122.8, 123.3*, 125.3, 125.4*, 125.6*, 125.7, 127.5, 128.6, 128.7*, 128.8, 129.6 (d, J = 6.4 Hz), 129.8* (d, J = 6.3 Hz), 130.8, 131.3*, 133.6 (d, J = 3.6 Hz), 133.7* (d, J = 3.6 Hz), 133.8, 133.9*, 134.5*, 134.8, 139.0*, 140.2 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.34*, 26.68 ppm. HRMS $[FA]^+$: m/z (%) = 404 (18.62) $[M + H]^+$, 294 (34.94) $[M - 110]^+$, 155 (100).

Dimethyl (*R*,*S*)- and (*S*,*S*)-[(4-Methoxyphenyl){[1-(naphthalen-1-yl)-ethyl]amino}methyl]phosphonate (6c): 4-Methoxybenzaldehyde (250 mg, 1.83 mmol), (*S*)-1-(1′-naphthyl)ethylamine (310 mg, 1.83 mmol), and dimethyl phosphite (200 mg, 1.92 mmol) were stirred at 80 °C for 6 h. The product **6c** was obtained (560 mg, 76%) as an oil. Asterisk denotes minor diastereoisomer. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.46* (d, J = 6.4 Hz, 3 H, CH_3CH), 1.49 (d, J = 6.5 Hz, 3 H, CH_3CH), 3.45* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.50 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.80 [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.81* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.82 (s, 3 H, CH_3O), 4.17 (d, J = 20.2 Hz, 1 H, CH–P), 4.73 (d, J = 6.3 Hz, 1 H, CH–N), 6.78–7.90 (m, 11 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7 (CH_3CH), 53.4 [$(CH_3O)_2P$], 53.7 [$(CH_3O)_2P$], 55.2 (CH_3O), 57.0 (d, J = 154.4 Hz, CH–P), 114.0, 123.0, 123.3*, 125.3, 125.5, 125.7, 127.5*, 128.8, 129.6 (d, J = 6.7 Hz), 130.9, 131.4*, 133.8, 133.9*, 159.3 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.14*, 27.37 ppm. HRMS $[FA]^+$: m/z (%) = 400 (20.05) $[M + H]^+$, 290 (77.85) $[M - 110]^+$, 155 (100).

Dimethyl (*R*,*S*)- and (*S*,*S*)-(3-Methyl-1-{[1-(naphthalen-1-yl)ethyl]-amino}butyl)phosphonate (6d): Isovaleraldehyde (250 mg, 2.90 mmol), (*S*)-1-(1′-naphthyl)ethylamine (496 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **6d** was obtained (850 mg, 84%) as an oil. Asterisk denotes minor diastereoisomer. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.47 [d, J = 6.5 Hz, 6 H, (CH_3CH)], 0.76 [d, J = 6.6 Hz, 3 H, $(CH_3)_2CH$], 0.84 [d, J = 6.7 Hz, 3 H, $(CH_3)_2CH$], 0.88* [d, J = 6.6 Hz, 6 H, $(CH_3)_2CH$], 1.44–1.50 (m, 2 H, CH_2CH), 1.60–1.70* [m, 1 H, $CH(CH_3)_2$], 1.83–1.96 [m, 1 H, $CH(CH_3)_2$], 2.73–2.80 (m, 1 H, CH–P), 3.00 (ddd, J = 14.8, 7.9, 5.6 Hz, 1 H, CH–P), 3.69* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.70 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.72 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.75* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 4.97* (q, J = 6.5 Hz, 1 H, CH–N), 5.15* (m, 1 H, CH–N), 7.43–7.52 (m, 4 H, H_{arom}), 7.69–7.75* (m, 4 H, H_{arom}), 7.82–7.87 (m, 3 H, H_{arom}), 8.28* (dd, J = 12.4, 8.6 Hz, 3 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0 (CH_3CH), 22.1* (CH_3CH), 22.9 [$(CH_3)_2CH$], 23.1* [$(CH_3)_2CH$], 23.5 [$(CH_3)_2CH$], 23.9 (d, J = 12.1 Hz, CH_2CH_3), 24.5* [$(CH_3)_2$-CH], 24.8* (d, J = 9.1 Hz, CH_2CH_3), 39.8* (d, J = 2.5 Hz, CH–N), 40.4 (d, J = 2.5 Hz, CH–N), 50.0 (d, J = 142.1 Hz, CH–P), 52.5 [d, J = 7.5 Hz, $(CH_3O)_2P$], 52.7 [d, J = 7.4 Hz, $(CH_3O)_2P$], 53.0* [$(CH_3O)_2P$], 123.1, 123.2*, 123.5, 123.7*, 125.2, 125.3*, 125.5, 125.6*, 125.7, 125.8*, 127.3, 127.4*, 128.8, 128.9*, 131.1*, 131.6, 133.8, 133.9*, 140.8*, 140.9 ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 32.60*, 33.52 ppm. HRMS $[FA]^+$: m/z (%) = 350 (100) $[M + H]^+$, 240 (100) $[M + H - 110]^+$, 155 (75.6). $C_{19}H_{28}NO_3P$ (349.41): calcd. C 65.31, H 8.08, N 4.01; found C 65.09, H 8.87, N 4.40.

Diethyl (*R*,*S*)- and (*S*,*S*)-(2-Methyl-1-{[1-(naphthalen-1-yl)ethyl]-amino}propyl)phosphonate (6e): Isobutyraldehyde (250 mg, 3.46 mmol), (*S*)-1-(1′-naphthyl)ethylamine (590 mg, 3.46 mmol), and dimethyl phosphite (400 mg, 3.63 mmol) were stirred at 80 °C for 8 h. The product **6e** was obtained (950 mg, 82%) as an oil. Asterisk denotes minor diastereoisomer. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 [d, J = 6.9 Hz, 6 H, $(CH_3)_2CH$], 1.13, (dd, J = 6.9, 0.8 Hz, 3 H, CH_3CH), 1.50 (br. s, NH), 2.72 (d, J = 12.0 Hz, 1 H, CH_3CH), 2.92 (dd, J = 18.0, 3.2 Hz, 1 H, CH–P), 3.65 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.68* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.72* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.73 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 4.90–4.94 (m, 1 H, CH–N), 5.08–5.15 (m, 1 H, CH–N), 7.41–7.53 (m, 6 H, H_{arom}), 7.73–7.78 (m, 1 H, H_{arom}), 7.83–7.89* (m, 5 H, H_{arom}), 8.26 (d, J = 5.4 Hz, 2 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6 (CH_3CH), 18.2* (CH_3CH), 20.5* [d, J = 12.5 Hz, $(CH_3)_2CH$], 20.8 [d, J = 14.4 Hz, $(CH_3)_2CH$], 23.0* [$(CH_3)_2CH$], 24.5 [$(CH_3)_2CH$], 28.7* (d, J = 5.2 Hz), 29.2 (d, J = 5.7 Hz), 52.0 [$(CH_3O)_2P$], 52 ppm. 5 [$(CH_3O)_2P$], 56.8* (d, J = 140.2 Hz, CH–P), 57.0 (d, J = 133.3 Hz, CH–P), 123.1, 123.7, 124.1, 125.2, 125.3*, 125.5, 125.6*, 125.7*, 127.3, 127.4*, 128.8, 128.9*, 131.1*, 131.5, 134.0*, 140.5, 140.9*. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.96*, 32.27 ppm. HRMS $[FA]^+$: m/z (%) = 336 (100) $[M + H]^+$, 226 (72.74) $[M + H - 110]^+$, 155 (37.4).

Dimethyl (*R*,*S*)- and (*S*,*S*)-(2,2-Dimethyl-1-{[1-(naphthalen-1-yl)-ethyl]amino}propyl)phosphonate (6f): *tert*-Butylacetaldehyde (250 mg, 2.90 mmol), (*S*)-1-(1′-naphthyl)ethylamine (490 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **6f** was obtained (890 mg, 88%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.97 [s, 9 H, $(CH_3)_3C$], 1.16* [s, 9 H, $(CH_3)_3C$], 1.42* (d, J = 6.5, Hz, 3 H, CH_3CH), 1.48 (d, J = 6.6, Hz, 3 H, CH_3CH), 2.49 (d, J = 12.5 Hz, 1 H, CH–N), 2.79* (d, J = 16.0 Hz, 1 H, CH–N), 3.62* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.68* [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 3.69 [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.81 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 4.95 (m, 1 H, CH–N), 5.05 (m, 1 H, CH–N), 7.43–7.50 (m, 5 H, H_{arom}), 7.71–7.77 (m, 2 H, H_{arom}), 7.84–7.87* (m, 5 H, H_{arom}), 8.30* (d, J = 8.3 Hz, 2 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.0 (CH_3CH), 24.5* (CH_3CH), 27.8 [$(CH_3)_3C$], 27.9* [$(CH_3)_3C$], 34.7 [d, J = 7.4 Hz, $C(CH_3)_3$], 35.0* 7 [d, J = 8.2 Hz, $C(CH_3)_3$], 52.0 [$(CH_3O)_2P$], 52.3 [$(CH_3O)_2P$], 61.2* (d, J = 132.4 Hz, CH–P), 62.4 (d, J = 131.2 Hz, CH–P), 123.3, 123.7*, 125.0, 125.1, 125.3*, 125.4, 125.5*, 125.6, 125.8*, 127.3, 127.4*, 128.8, 128.9*, 130.8*, 131.6, 133.8 (d, J = 2.5 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 31.65*, 32.09 ppm. HRMS $[FA]^+$: m/z (%) = 350 (100) $[M + H]^+$, 240 (100) $[M - 110]^+$, 155 (96.9).

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(Phenyl)[(1,2,2-trimethylpropyl)amino]-methyl}phosphonate (7a): Benzaldehyde (250 mg, 2.35 mmol), (*S*)-1,2,2-trimethylpropylamine (237 mg, 2.35 mmol), and dimethyl phosphite (250 mg, 2.46 mmol) were stirred at 80 °C for 8 h. The product **7a** was obtained (640 mg, 91%) as a solid. M.p. 66 °C. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.79 [s, 9 H, $(CH_3)_3C$], 0.83* [s, 9 H, $(CH_3)_3C$], 0.86 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.09 (br, 1 H, CH–N), 3.50 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.70 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.77* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 4.13 (d, J = 21.4 Hz, 1 H, CH–P), 7.29–7.39 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2 (CH_3CH), 17.4* (CH_3CH), 26.3 [$(CH_3)_3C$], 34.0 [$C(CH_3)_3$], 35.5* [$C(CH_3)_3$], 53.4 [d, J = 6.9 Hz, $(CH_3O)_2P$], 54.0 [d, J = 6.9 Hz, $(CH_3O)_2P$], 57.8 (d, J = 15.9 Hz, CH–N), 57.9 (d, J = 152.5 Hz, CH–P), 127.8 (d, J = 3.2 Hz), 128.3 (d, J = 2.5 Hz), 128.8 (d, J = 6.4 Hz), 135.7 (d, J = 4.1 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.26*, 27.54 ppm. HRMS $[FA]^+$: m/z (%) = 300 (100) $[M + H]^+$, 190 (16.3) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Chlorophenyl)[(1,2,2-trimethylpropyl)amino]methyl}phosphonate (7b): 4-Chlorobenzaldehyde (250 mg, 1.78 mmol), (*S*)-1,2,2-trimethylpropylamine (179 mg, 1.78 mmol), and dimethyl phosphite (200 mg, 1.87 mmol) were stirred at 80 °C for 6 h. The product **7b** was obtained (530 mg, 90%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 [s, 9 H, $(CH_3)_3C$], 0.89* [s, 9 H, $(CH_3)_3C$], 0.92 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.08 (q, J = 6.4 Hz, 1 H, CH–N), 2.23* (q, J = 6.4 Hz, 1 H, CH–N), 3.51* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.61 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.76 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.97* (d, J = 22.6 Hz, 1 H, CH–P), 4.16 (d, J = 21.0 Hz, 1 H, CH–P), 7.30–7.36 (m, 4 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.1 (CH_3CH), 26.3 [$(CH_3)_3C$], 34.0 [$C(CH_3)_3$], 53.5 [$(CH_3O)_2P$], 53.9 [$(CH_3O)_2P$], 57.4 (d, J = 158.7 Hz, CH–P), 57.8 (d, J = 15.6 Hz, CH–N), 128.4 (d, J = 2.4 Hz), 130.0 (d, J = 6.2 Hz), 133.5 (d, J = 4.0 Hz), 134.4 (d, J = 4.6 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.65*, 25.90 ppm. HRMS $[FA]^+$: m/z (%) = 334 (100) $[M + H]^+$, 244 (20.25) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Fluorophenyl)[(1,2,2-trimethylpropyl)amino]methyl}phosphonate (7c): 4-Fluorobenzaldehyde (250 mg, 2.01 mmol), (*S*)-1,2,2-trimethylpropylamine (200 mg, 2.01 mmol), and dimethyl phosphite (230 mg, 2.11 mmol) were stirred at 80 °C for 6 h. The product **7c** was obtained (570 mg, 91%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 [s, 9 H, $(CH_3)_3C$], 0.89* [s, 9 H, $(CH_3)_3C$], 0.92 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.08 (q, J = 6.4 Hz, 1 H, CH–N), 3.49* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.59 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.76 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.83* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.97* (d, J = 22.6 Hz, 1 H, CH–P), 4.16 (d, J = 21.0 Hz, 1 H, CH–P), 7.01–7.10 (m, 2 H, H_{arom}), 7.34–7.41 (m, 2 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2 (CH_3CH), 17.3* (CH_3CH), 26.3* [$(CH_3)_3C$], 26.4 [$(CH_3)_3C$], 34.0 [$C(CH_3)_3$], 35.4* [$C(CH_3)_3$], 53.4 [d, J = 6.9 Hz, $(CH_3O)_2P$], 54.0 [d, J = 6.9 Hz, $(CH_3O)_2P$], 57.5 (d, J = 153.7 Hz, CH–P), 58.0 (d, J = 15.7 Hz, CH–N), 115.2 (dd, J = 21.5, 2.5 Hz), 130.3 (dd, J = 8.1, 6.4 Hz), 131.5* (dd, J = 4.4, 3.2 Hz), 161.4 (d, J = 3.4 Hz), 163.4 (d, J = 3.5 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.00* (d, J = 4.8 Hz), 26.23 (d, J = 5.2 Hz) ppm. HRMS $[FA]^+$: m/z (%) = 318 (100) $[M + H]^+$, 208 (100) $[M + H - 110]^+$. $C_{15}H_{25}FNO_3P$ (317.34): calcd. C 56.77, H 7.94, N 4.41; found C 57.01, H 7.80, N 4.52.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(4-Methoxyphenyl)[(1,2,2-trimethylpropyl)amino]methyl}phosphonate (7d): 4-Methoxybenzaldehyde (250 mg, 1.83 mmol), (*S*)-1,2,2-trimethylpropylamine (180 mg, 1.83 mmol), and dimethyl phosphite (200 mg, 1.92 mmol) were stirred at 80 °C for 6 h. The product **7d** was obtained (500 mg, 92%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.82 [s, 9 H, $(CH_3)_3C$], 0.86* [s, 9 H, $(CH_3)_3C$], 0.89 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.10 (q, J = 6.4, Hz, 1 H, CH–N), 2.26* (q, J = 6.4, Hz, 1 H, CH–N), 3.44* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.55 [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 3.74 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.78 (s, 3 H, CH_3O), 3.81* [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 4.11 (d, J = 20.9 Hz, 1 H, CH–P), 6.87 (AA′BB′, J = 8.8 Hz, 2 H, H_{arom}), 7.29 (AA′BB′, J = 8.8 Hz, 2 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.1 (CH_3CH), 17.3* (CH_3CH), 26.3 $(CH_3)_3C$, 33.0 [$C(CH_3)_3$], 35.4* [$C(CH_3)_3$], 53.4 [$(CH_3O)_2P$], 53.9 [$(CH_3O)_2P$], 55.1 [(CH_3O)], 57.3 (d, J = 152.5 Hz, CH–P), 57.5 (d, J = 16.0 Hz, CH–N), 113.6, 127.4 (d, J = 4.3 Hz), 129.8 (d, J = 6.4 Hz), 159.1 (d, J = 3.0 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.49*, 26.84 ppm. HRMS $[FA]^+$: m/z (%) = 330 (100) $[M + H]^+$, 272 (3.10) $[M - 58]^+$, 220 (100) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{(3,4-Dimethoxyphenyl)[(1,2,2-trimethylpropyl)amino]methyl}phosphonate (7e): 3,4-Dimethoxybenzaldehyde (250 mg, 1.50 mmol), (*S*)-1,2,2-trimethylpropylamine (150 mg, 1.50 mmol), and dimethyl phosphite (170 mg, 1.57 mmol) were stirred at 80 °C for 6 h. The product **7e** was obtained (500 mg, 91%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 [s, 9 H, $(CH_3)_3C$], 0.86* [s, 9 H, $(CH_3)_3C$], 0.90 (d, J = 6.4 Hz, 3 H, CH_3CH), 2.06–2.17 (m, 1 H, CH–N), 3.55 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.73 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.85 (s, 6 H, CH_3O), 4.10 (d, J = 20.7 Hz, 1 H, CH–P), 6.80 (d, J = 8.2 Hz, 1 H, H_{arom}), 6.87 (d, J = 5.2 Hz, 1 H, H_{arom}), 6.99 (s, 1 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2 (CH_3CH), 26.3* $(CH_3)_3C$, 26.4 $(CH_3)_3C$, 34.0 [$C(CH_3)_3$], 35.5* [$C(CH_3)_3$], 53.4 [d, J = 6.9 Hz, $(CH_3O)_2P$], 54.0 [d, J = 7.0 Hz, $(CH_3O)_2P$], 55.7 (CH_3O), 55.8 (CH_3O), 57.5 (d, J = 155.0 Hz, CH–P), 57.6 (d, J = 16.0 Hz, CH–N), 110.6 (d, J = 2.4 Hz), 111.5 (d, J = 5.3 Hz), 121.3 (d, J = 7.7 Hz), 128.0 (d, J = 4.7 Hz), 148.6 (d, J = 3.2 Hz), 148.8 (d, J = 2.6 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.42*, 26.72 ppm. HRMS $[FA]^+$: m/z (%) = 360 (100) $[M + H]^+$, 302 (1.17) $[M - 58]^+$, 250 (100) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{1-[(1,2,2-trimethylpropyl)amino]-ethyl}phosphonate (7f): Acetaldehyde (250 mg, 5.68 mmol), (*S*)-1,2,2-trimethylpropylamine (570 mg, 5.68 mmol), and dimethyl phosphite (650 mg, 5.97 mmol) were stirred at 80 °C for 6 h. The product **7f** was obtained (1.30 g, 92%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.83 [s, 9 H, $(CH_3)_3C$], 0.83* [s, 9 H, $(CH_3)_3C$], 0.90 (d, J = 6.4 Hz, 3 H, CH_3CH), 0.94* (d, J = 6.6 Hz, 3 H, CH_3CH), 1.20 (dd, J = 18.1, 7.0 Hz, 1 H, CH_3CH–P), 1.27* (dd, J = 17.7, 7.1 Hz, 1 H, CH_3CH–P), 2.33–2.41 (m, 1 H, CH_3CH–N), 2.95* (dq, J = 15.0, 7.0 Hz, 1 H, CH–P), 3.01 (dq, J = 15.0, 7.0 Hz, 1 H, CH–P), 3.72* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.74 [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 3.76* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.77 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5 (CH_3CH–N), 14.7 (CH_3CH–P), 16.4* (CH_3CH–N), *16.8 (CH_3CH–P), 26.2* [$(CH_3)_3C$], 26.3 [$(CH_3)_3C$], 33.1* [$C(CH_3)_3$], 34.2 [$C(CH_3)_3$], 48.1 (d, J = 157.5 Hz, CH–P), 50.3* (d, J = 157.9 Hz, CH–P), 52.6* [$(CH_3O)_2P$], 52.8 [d, J = 7.1 Hz, $(CH_3O)_2P$], 53.2* [$(CH_3O)_2P$], 53.6 [$(CH_3O)_2P$], 58.9 [d, J = 13.6 Hz, (CH–N)], 61.3* [d, J = 9.9 Hz, (CH–N)] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.75*, 31.24 ppm. HRMS $[FA]^+$: m/z (%) = 338 (100) $[M + H]^+$, 180 (53.5) $[M - 58]^+$, 128 (23.81) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2-Phenyl-1-[(1,2,2-trimethylpropyl)amino]-ethyl}phosphonate (7 g): Phenylacetaldehyde (250 mg, 2.08 mmol), (*S*)-1,2,2-trimethylpropylamine (210 mg, 2.08 mmol), and dimethyl phosphite (240 mg, 5.18 mmol) were stirred at 80 °C for 6 h. The product **7g** was obtained (330 g, 52%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.45* (d, J = 6.4 Hz, 1 H, CH_3CH), 0.69 [s, 9 H, $(CH_3)_3C$], 0.81* [s, 9 H, $(CH_3)_3C$], 0.93 (d, J = 6.5, Hz, 3 H, CH_3CH), 2.26 (q, J = 6.5, Hz, 1 H, CH–N), 2.80 (dt, J = 14.1, 8.2, Hz, 2 H, CH–P), 3.08–3.16 (m, 1 H, CH-CH_2Ph), 3.23 (dd, J = 14.3, 8.2 Hz, 1 H, CH_2Ph), 3.70 [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.75 [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 7.18–7.32 (m, 5 H, H_{arom}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3* (CH_3CH), 15.1 (CH_3CH), 25.8* [$(CH_3)_3C$], 26.1 [$(CH_3)_3C$], 34.4* (CH_2Ph), 34.6 (CH_2Ph), 37.1* [$C(CH_3)_3$], 37.2 [$C(CH_3)_3$], 52.5 [d, J = 7.5 Hz, $(CH_3O)_2P$], 53.6 [d, J = 7.3 Hz, $(CH_3O)_2P$], 55.2* (d, J = 154.0 Hz, CH–P), 55.5 (d, J = 154.8 Hz, CH–P), 60.1* (CH–N), 60.4 (d, J = 8.8 Hz, CH–N), 126.4, 126.6*, 128.1, 128.2*, 129.6, 129.8*, 138.2 (d, J = 11.3 Hz) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 29.71, 29.85* ppm. HRMS $[FA]^+$: m/z (%) = 314 (100) $[M + H]^+$, 256 (40.85) $[M - 58]^+$, 204 (87.17) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{3-Methyl-1-[(1,2,2-trimethylpropyl)amino]-butyl}phosphonate (7h): Isovaleraldehyde (250 mg, 2.90 mmol), (*S*)-1,2,2-trimethylpropylamine (290 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **7h** was obtained (700 g, 86%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.85 [s, 9 H, $(CH_3)_3C$], 0.87* [s, 9 H, $(CH_3)_3C$], 0.89 [d, J = 6.8 Hz, 3 H, $(CH_3)_2CH$], 0.91* [d, J = 6.9 Hz, 3 H, $(CH_3)_2CH$], 0.92 [d, J = 6.7 Hz, 3 H, $(CH_3)_2CH$], 0.97 (d, J = 6.4 Hz, 3 H, CH_3CH–N), 1.31–1.43 [m, 1 H, $CH(CH_3)_2$], 1.57–1.65* [m, 1 H, $CH_2(CH_3)_2$], 1.89 (dt, J = 20.1, 6.7 Hz, 2 H, CH–P), 2.43 (q, J = 6.4 Hz, 1 H, CH–NH), 2.62* (dq, J = 6.4, 2.2 Hz, 1 H, CH–N), 2.89–2.97 (m, 1 H, CH_2CH), 3.74 [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 3.75* [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$], 3.76* [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$], 3.80 [d, J = 10.2 Hz, 3 H, $(CH_3O)_2P$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8* (CH_3CH), 15.3 (CH_3CH), 21.5* [$(CH_3)_2CH$], 22.5 [$(CH_3)_2CH$], 22.8 [$(CH_3)_2CH$], 23.4* [$(CH_3)_2CH$], 24.0* [d, J = 11.6 Hz, $CH(CH_3)_2$], 24.6 [d, J = 8.7 Hz, $CH(CH_3)_2$], 26.3* [$(CH_3)_3C$], 26.4 [$(CH_3)_3C$], 34.4 (CH_2), 34.6* (CH_2), 40.3* [$C(CH_3)_3$], 40.8 [$(CH_3)_3C$], 50.6* (d, J = 152.0 Hz, CH–P), 51.6 (d, J = 152.0 Hz, CH–P), 52.4 [d, J = 5.1 Hz, $(CH_3O)_2P$], 52.6* [d, J = 6.9 Hz, $(CH_3O)_2P$], 53.7 [d, J = 7.3 Hz, $(CH_3O)_2P$], 59.8* (CH–N), 60.4 (d, J = 9.6 Hz, CH–N) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 31.41, 31.84* ppm. HRMS $[FA]^+$: m/z (%) = 280 (100) $[M + H]^+$; 222 (51.98) $[M - 58]^+$, 170 (100) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2-Methyl-1-[(1,2,2-trimethylpropyl)-amino]propyl}phosphonate (7i): Isobutyraldehyde (250 mg, 3.46 mmol), (*S*)-1,2,2-trimethylpropylamine (350 mg, 3.46 mmol), and dimethyl phosphite (400 mg, 3.53 mmol) were stirred at 80 °C for 8 h. The product **7i** was obtained (820 g, 91%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 [s, 9 H, $(CH_3)_3C$], 0.98 (d, J = 6.4 Hz, 6 H, CH_3CH), 1.04 [d, J = 6.9 Hz, 3 H, $(CH_3)_2CH$], 1.07 [d, J = 6.9 Hz, 3 H, $(CH_3)_2$-CH], 2.01–2.21 [m, 1 H, $CH(CH_3)_2$], 2.46 (q, J = 6.4 Hz, 1 H, CH–N), 2.51–2.58* (m, 1 H, CH–N), 2.80* (d, J = 14.9 Hz, 1 H, CH–P), 2.90 (d, J = 18.3 Hz, 1 H, CH–P), 3.75 [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.76* [d, J = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.80 [d, J = 10.3 Hz, 3 H, $(CH_3O)_2P$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.8* (CH_3CH), 15.0 (CH_3CH), 17.7* [$(CH_3)_2CH$], 18.5 [$(CH_3)_2$-CH], 20.2 [$(CH_3)_2CH$], 20.4* [$(CH_3)_2CH$], 26.3* [$(CH_3)_3C$], 26.4 [$(CH_3)_3C$], 29.3* [d, J = 6.2 Hz, $CH(CH_3)_2$], 29.4 [d, J = 5.3 Hz, $CH(CH_3)_2$], 34.4* [$C(CH_3)_3$], 34.8 [$C(CH_3)_3$], 52.2 [d, J = 6.7 Hz, $(CH_3O)_2P$], 53.3 [d, J = 6.2 Hz, $(CH_3O)_2P$], 57.4* (d, J = 138.4 Hz, CH–P), 58.7 (d, J = 146.5 Hz, CH–P), 61.1 (d, J = 9.1 Hz, CH–N) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.45*, 31.95 ppm. HRMS $[FA]^+$: m/z (%) = 266 (100) $[M + H]^+$, 208 (45.64) $[M - 58]^+$, 156 (100) $[M - 110]^+$.

Dimethyl (*R*,*S*)- and (*S*,*S*)-{2,2-Dimethyl-1-[(1,2,2-trimethylpropyl)-amino]propyl}phosphonate (7j): *tert*-Butylacetaldehyde (250 mg, 2.90 mmol), (*S*)-1,2,2-trimethylpropylamine (490 mg, 2.90 mmol), and dimethyl phosphite (330 mg, 3.04 mmol) were stirred at 80 °C for 8 h. The product **7j** was obtained (750 g, 93%) as an oil. Asterisk denotes minor diastereoisomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89* [s, 9 H, $(CH_3)_3C$], 0.91 [s, 9 H, $(CH_3)_3C$], 0.97 (d, J = 6.4 Hz, 1 H, CH_3CH), 1.05* [s, 9 H, $(CH_3)_3C$], 1.08 [s, 9 H, $(CH_3)_3$-C], 2.53–2.60 (m, 1 H, CH–N), 2.70 (d, J = 18.1 Hz, CH–P), 3.71 [d, J = 10.6 Hz, 3 H, $(CH_3O)_2P$], 3.73* [d, J = 10.5 Hz, 3 H, $(CH_3O)_2P$], 3.74* [d, J = 10.3 Hz, $(CH_3O)_2P$], 3.79 [d, J = 10.3 Hz, $(CH_3O)_2P$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.4* (CH_3), 14.6 (CH_3), 26.2* [$(CH_3)_3C$], 26.6 [$(CH_3)_3C$], 27.7* [d, J = 6.1 Hz, $(CH_3)_3C$], 28.0 [d, J = 7.0 Hz, $(CH_3)_3C$], 35.0 [d, J = 1.4 Hz, $C(CH_3)_3$], 36.3 [d, J = 7.8 Hz, $C(CH_3)_3$], 51.8* [$(CH_3O)_2P$], 53.5 [d, J = 7.4 Hz, $(CH_3O)_2P$], 62.3 (d, J = 7.6 Hz, CH–N), 62.4 (d, J = 145.0 Hz, CH–P) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 30.16, 32.67* ppm. HRMS $[FA]^+$: m/z (%) = 280 (100) $[M + H]^+$, 222 (35.98) $[M - 58]^+$, 170 (100) $[M - 110]^+$.

Supporting Information (see footnote on the first page of this article): ^{31}P NMR spectra of all diastereoisomeric mixtures.

Acknowledgments

We thank the Consejo Nacional de Ciencia y Tecnología (CONACYT) of México (project 62271) for financial support. We also thank Victoria Labastida for the HRMS analysis.

[1] a) V. P. Kukhar, H. R. Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids – Chemistry and Biological Activity* (Ed.: V. P. Kukhar), John Wiley & Sons, Chichester, **2000**; b) P. Kafarski, B. Lejczak, *Phosphorus Sulfur Relat. Elem.* **1991**, *63*, 193–215; c) B. Dhawan, D. Redmore, *Phosphorus Sulfur Relat. Elem.* **1987**, *32*, 119–144; d) M. Sieńczyk, J. Oleksyszyn, *Curr. Med. Chem.* **2009**, *16*, 1673–1687.

[2] a) R. Rozenfeld, X. Iturrioz, M. Okada, B. Maigret, C. Llorents-Cortes, *Biochemistry* **2003**, *42*, 14785–14793; b) R. Hirschmann, A. B. Smith III, C. M. Taylor, P. A. Benkovic, S. D. Taylor, K. M. Yager, P. A. Sprengler, S. J. Benkovic, *Science* **1994**, *265*, 234–237; c) M. C. Allen, W. Fuhrer, B. Tuck, R. Wade, J. M. Wood, *J. Med. Chem.* **1989**, *32*, 1652–1661; d) P. P. Giannousis, P. A. Bartlett, *J. Med. Chem.* **1987**, *30*, 1603–1609.
[3] a) E. Alonso, A. Solis, C. del Pozo, *Synlett* **2000**, 698–700; b) B. Stowasser, K.-H. Budt, L. Jian-Qi, A. Peyman, D. Ruppert, *Tetrahedron Lett.* **1992**, *33*, 6625–6628; c) N. P. Camp, P. C. D. Hawkins, P. B. Hitchcock, D. Gani, *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1047–1052.
[4] a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet, P. S. Ringrose, *Nature* **1978**, *272*, 56–58; b) F. R. Atherton, C. H. Hassall, R. W. Lambert, *J. Med. Chem.* **1986**, *29*, 29–40.
[5] a) T. Kametani, K. Kigasawa, M. Hiiragi, K. Wakisaka, S. Haga, H. Sugi, K. Tanigawa, Y. Suzuki, K. Fukawa, O. Irino, O. Saita, S. Yamabe, *Heterocycles* **1981**, *16*, 1205–1242; b) B. Lejczak, P. Kafarski, H. Sztajer, P. Mastalerz, *J. Med. Chem.* **1986**, *29*, 2212–2217.
[6] Y. Feng, J. K. Coward, *J. Med. Chem.* **2006**, *49*, 770–788.
[7] a) P. Kafarski, B. Lejczak, *Curr. Med. Chem.* **2001**, *1*, 301–312; b) G. Lavielle, P. Hautefaye, C. Schaeffer, J. A. Boutin, C. A. Cudennec, A. Pierré, *J. Med. Chem.* **1991**, *34*, 1998–2003.
[8] J. Huang, R. Chen, *Heteroat. Chem.* **2000**, *11*, 480–492.
[9] L. Maier, P. J. Diel, *Phosphorus Sulfur Relat. Elem.* **1991**, *57*, 57–64.
[10] a) H. Kozlowski, A. Pusino, J. Swiatek, J. Spychala, T. Gloweiak, G. Micera, C. Gessa, *J. Agric. Food Chem.* **1990**, *38*, 1989–1992; b) H. Nska, D. Bonarska, K. Bielecki, J. Sarapuk, *Cell. Mol. Biol. Lett.* **2002**, *7*, 929–935.
[11] a) M. Drag, M. Pawelczak, P. Kafarski, *Chirality* **2003**, *15*, S104–S107; b) E. K. Baylis, C. D. Campbell, J. G. Dingwall, *J. Chem. Soc. Perkin Trans. 1* **1984**, 2845–2853; c) F. R. Atherton, M. J. Hall, C. H. Hassall, R. W. Lambert, W. J. Lloyd, P. S. Ringrose, *Antimicrob. Agents Chemother.* **1979**, *15*, 696–705.
[12] a) M. Ordóñez, H. Rojas-Cabrera, C. Cativiela, *Tetrahedron* **2009**, *65*, 17–49; b) P. S. Bhadury, B.-A. Song, S. Yang, Y. Zhang, S. Zhang, *Curr. Org. Synth.* **2008**, *5*, 134–150; c) P. Merino, E. Marqués-López, R. P. Herrera, *Adv. Synth. Catal.* **2008**, *350*, 1195–1208; d) J.-A. Ma, *Chem. Soc. Rev.* **2006**, *35*, 630–636; e) J. Uziel, J. P. Genêt, *Russ. J. Org. Chem.* **1997**, *33*, 1521–1542; f) V. P. Kukhar, V. A. Soloshonok, V. A. Solodenko, *Phosphorus Sulfur Relat. Elem.* **1994**, *92*, 239–264.
[13] A. N. Pudovik, *Dokl. Akad. Nauk SSSR* **1952**, *83*, 865.
[14] For the diastereoselective Pudovik reaction, see: a) S. Cherenok, A. Vovk, I. Muravyova, A. Shivanyuk, V. Kukhar, J. Lipkowski, V. Kalchenko, *Org. Lett.* **2006**, *8*, 549–552; b) G. A. Kachkovskii, N. V. Andrushko, S. Y. Sheiko, O. I. Kolodiazhnyi, *Russ. J. Gen. Chem.* **2005**, *75*, 1735–1743, and references therein.
[15] For the enantioselective Pudovik reaction, see: a) J. Abell, H. Yamamoto, *J. Am. Chem. Soc.* **2008**, *130*, 10521–10523; b) B. Saito, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986; c) D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani, A. Ricci, *J. Org. Chem.* **2006**, *71*, 6269–6272; d) T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett.* **2005**, *7*, 2583–2585, and references therein.
[16] a) M. I. Kabachnik, T. Y. Medved, *Dokl. Akad. Nauk SSSR* **1952**, *83*, 689; b) M. I. Kabachnik, T. Ya. Medved, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1953**, 1126; c) M. I. Kabachnik, T. Ya. Medved, *Izv. Akad. Nauk SSSR, Ser. Khim.* **1954**, 1024; d) E. Fields, *J. Am. Chem. Soc.* **1952**, *74*, 1528–1531; e) R. A. Cherkasov, V. I. Galkin, *Russ. Chem. Rev.* **1998**, *67*, 857–882; f) N. S. Zefirov, E. D. Matveeva, *ARKIVOC* **2008**, *(i)*, 1–17.
[17] For the diastereoselective Kabachnik–Fields reaction, see: a) A. Satish-Kumar, S. C. Taneja, M. S. Hundal, K. K. Kapoor, *Tetrahedron Lett.* **2008**, *49*, 2208–2212; b) H. Liu, S. Cai, J. Xu, *J. Pept. Sci.* **2006**, *12*, 337–340; c) K. C. K. Swamy, S. Kumaraswamy, K. S. Kumar, C. Muthiah, *Tetrahedron Lett.* **2005**, *46*, 3347–3351, and references therein.
[18] For the enantioselective Kabachnik–Fields reaction, see: a) X. Zhou, D. Shang, Q. Zhang, *Org. Lett.* **2009**, *11*, 1401–1404; b) B. Saito, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986; c) B. Kaboudin, M. Sorbiun, *Tetrahedron Lett.* **2007**, *48*, 9015–9017.
[19] a) A. Heydari, A. Karimian, J. Ipaktschi, *Tetrahedron Lett.* **1998**, *39*, 6729–6732; b) M. R. Saidi, N. Azizi, *Synlett* **2002**, 1347–1349.
[20] a) W. F. Gilmore, H. A. McBride, *J. Am. Chem. Soc.* **1972**, *94*, 4361–4361; b) T. Glowiak, W. Sawka-Dobrowolska, J. Kowalik, P. Mastalerz, M. Soroka, J. Zoń, *Tetrahedron Lett.* **1977**, *18*, 3965–3968.
[21] N. Soma Ghosh, N. Singh, G. Kaur Nanda, P. Venugopalan, P. V. Bharatam, S. Trehan, *Chem. Commun.* **2003**, 1420–1421.
[22] For the application of (*S*)-1-(1′-naphthyl)ethylamine as chiral auxiliary, see: a) A. N. Chernega, S. G. Davies, A. M. Fletcher, C. J. Goodwin, D. Hepworth, R. S. Prasad, P. M. Roberts, E. D. Savory, A. D. Smith, J. E. Thomson, *Tetrahedron* **2010**, *66*, 4167–4194; b) A. N. Chernega, S. G. Davies, C. J. Goodwin, D. Hepworth, W. Kurosawa, P. M. Roberts, J. E. Thomson, *Org. Lett.* **2009**, *11*, 3254–3257.
[23] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, Revision C.02, Gaussian, Inc., Pittsburgh, PA, **2003**.
[24] a) A. D. Becke, *J. Chem. Phys.* **1988**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[25] a) P. C. Hariharan, J. A. Pople, *Chem. Phys. Lett.* **1972**, *66*, 217–219; b) A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100.
[26] a) R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860; b) M. J. Lucero, K. N. Houk, *J. Am. Chem. Soc.* **1997**, *119*, 826–827.
[27] Addition of cyanide to the Schiff bases of (*S*)-1-(1′-naphthyl)-ethylamine or (*S*)-α-methylbenzylamine gave identical diastereoselectivities: T. Lee, Y. Ahn, *Bull. Korean Chem. Soc.* **2002**, *23*, 1490–1492.

Received: August 4, 2010
Published Online: October 20, 2010

