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Asymmetric synthesis of optically active α-substituted α-amino-*H*-phosphinates through resolution of 1,1-diethoxyethyl(aminomethyl)phosphinates

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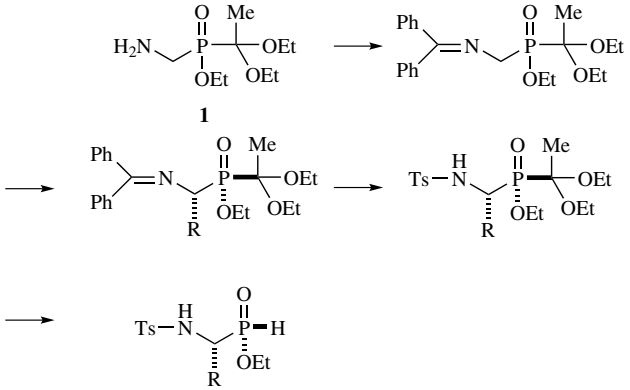
Abstract—Both enantiomers of 1,1-diethoxyethyl(aminomethyl)phosphinates were prepared through chromatographic separation of a diastereomeric mixture derived from (*S*)-phenylethylamine and 1,1-diethoxyethyl-*H*-phosphinate. The individual enantiomer was transformed into α-substituted α-amino-*H*-phosphinate with high enantiomeric purity by a highly diastereoselective alkylation at the α-carbon on the basis of our previously developed method.

1. Introduction

α-Aminophosphinic acid derivatives are of much interest due to their usefulness both in the development of catalytic antibodies[1] and pharmacologically active substances.[2] Some peptides incorporating these molecules have been shown to be effective inhibitors against aspartic acid proteases and Zn-metalloproteases.[3] For the preparation of various α-aminophosphinic acid derivatives, α-substituted α-amino-*H*-phosphinic acids have been utilized as versatile synthetic intermediates.[4] Inspection of the literature revealed that the asymmetric synthesis of this class of compounds has been attained relying upon resolution[5] or kinetic resolution with enzymes.[6] An alternative synthesis involves the alkylation at the α-carbon of imines derived from optically active 2-hydroxypinan-3-one and aminomethylphosphinate which has a diethoxymethyl functionality as a protecting group at the phosphorus atom.[7] However, in this methodology, the diastereoselectivity for the alkylation induced by the chiral auxiliary on the nitrogen was reported to be modest and the enantiomeric purity of target α-substituted α-amino-*H*-phosphinic acids resulted in low yields. The modest selectivity might be associated with the diastereomeric purity of the substrate imine; a 1:1 mixture of a diastereomeric isomer arising from the chirality of the phosphorus atom was utilized without separation.

We recently succeeded in the diastereoselective synthesis of racemic α-substituted α-amino-*H*-phosphinates showing a defined stereochemistry at both the phosphorus atom and the α-carbon starting from ethyl 1,1-diethoxyethyl(aminomethyl)phosphinate **1** (Scheme 1).[8] In our methodology, the alkylation of the phosphorus-stabilized carbanion is controlled by the chirality of the phosphorus atom. The protecting group on the phosphorus atom could be removed under mild conditions without a loss of the phosphorus chirality.



Scheme 1.

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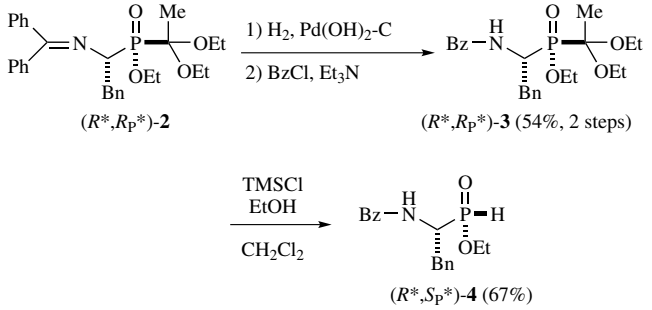
Based upon our methodology, the preparation of optically active forms of α-substituted α-amino-*H*-phosphinates in high optical purity would be feasible, if an optically active form of ethyl 1,1-diethoxyethyl(aminomethyl)phosphinate **1** was used as a starting material. Herein, we report the experimental results on the preparation of both the enantiomer of ethyl 1,1-diethoxyethyl(aminomethyl)phosphinate through resolution and then conversion into α-substituted α-amino-*H*-phosphinates.

2. Results and discussion

2.1. Determination of stereochemistry of α-substituted α-amino-*H*-phosphinates

As described in our previous paper,[8] the deprotection step of a 1,1-diethoxyethyl moiety for α-substituted *N*-Ts-α-aminophosphinates into the corresponding α-amino-*H*-phosphinates proceeded in a highly diastereoselective manner (Scheme 1). The relative stereochemistry of the product was estimated on the hypothesis that this deprotection step proceeded with retention of the phosphorus chirality. To confirm the stereochemistry of α-substituted *N*-Ts-α-amino-*H*-phosphinates, we attempted to obtain a single crystal suitable for X-ray crystallographic analysis. However, this attempt failed. Therefore, in this study, we first surveyed other derivatives suitable for X-ray crystallographic analysis to verify the stereochemistry of α-substituted α-amino-*H*-phosphinates. Via these efforts, racemic imine (R^*,R_P^*)-**2** was transformed into *N*-benzoyl derivative (R^*,R_P^*)-**3** through sequential hydrogenolysis and benzoylation (Scheme 2). Deprotection of a 1,1-diethoxyethyl moiety in (R^*,R_P^*)-**3** was conducted with TMSCl and EtOH to furnish α-substituted *N*-Bz-α-amino-*H*-phosphinate (R^*,S_P^*)-**4** without detecting the (R^*,R_P^*)-isomer. The relative configuration of (R^*,S_P^*)-**4** was determined unambiguously by X-ray crystallographic analysis (Fig. 1). Thus, we confirmed that the deprotection step proceeded in a retentive manner of phosphorus chirality as predicted.



Scheme 2.

2.2. Preparation of optically active 1,1-diethoxyethyl-(aminomethyl)phosphinate

After the unambiguous establishment of the stereochemical outcome in our synthesis of α-substituted α-amino-*H*-phosphinates, our attention next centered on the preparation of both the enantiomer of 1,1-diethoxyethyl(aminomethyl)-phosphinate **1**, necessary for extending our methodology to the enantio-divergent synthesis of α-substituted α-amino-*H*-phosphinates. Racemic **1** has previously been synthesized through the reductive debenzylation of (benzylamino)methyl(1,1-diethoxyethyl)phosphinate **7**, prepared via the addition of 1,1-diethoxyethyl-*H*-phosphinate **6**[9] to 1,3,5-tribenzyl-1,3,5-triazinane **5** (Scheme 3). We applied this method for the preparation of both enantiomers of **1**. Thus, optically active triazinane **9** was prepared from paraformaldehyde and (*S*)-phenylethylamine **8** according to a literature procedure (Scheme 4).[10] Subsequently, **9** was treated with *H*-phosphinate **6** to give aminophosphinate **10** as a 1:1 mixture of diastereoisomers. The separation of the individual diastereomer of **10** on column chromatography under a variety of conditions failed due to the high polarity of **10**. Therefore, amine **10** was converted into several secondary amine derivatives by introducing a functionality, which was readily removed after separation. For this purpose, α-picolineborane (α-pic-BH_3)-mediated reductive amination[11] of several aromatic aldehydes including benzaldehyde, 4-bromobenzaldehyde, 4-anisaldehyde, 1-naphthaldehyde, and 2-naphthaldehyde with amine **10** was examined. We were pleased to find that (S,R_P)-**11** and (S,S_P)-**11**, derived from 2-naphthaldehyde, proved to be optimum derivatives, which were provided in relatively good yields (67%) and easily isolated by silica gel column chromatography. Although the exact reason for the facile separation of (S,R_P)-**11** and (S,S_P)-**11** is unclear, it might be attributed to an increased hydrophobic property. Hydrogenolysis of (S,R_P)-**11** over $Pd(OH)_2$–C and the subsequent transformation of the resulting amine to imine furnished the desired optically active 1,1-diethoxy-

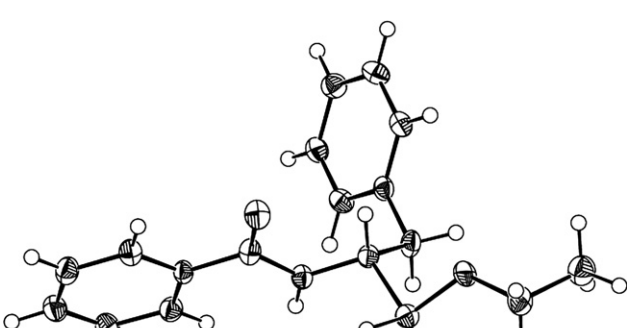
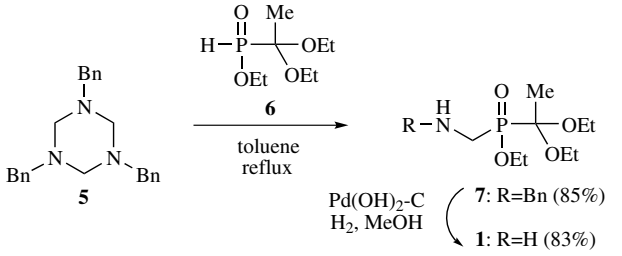
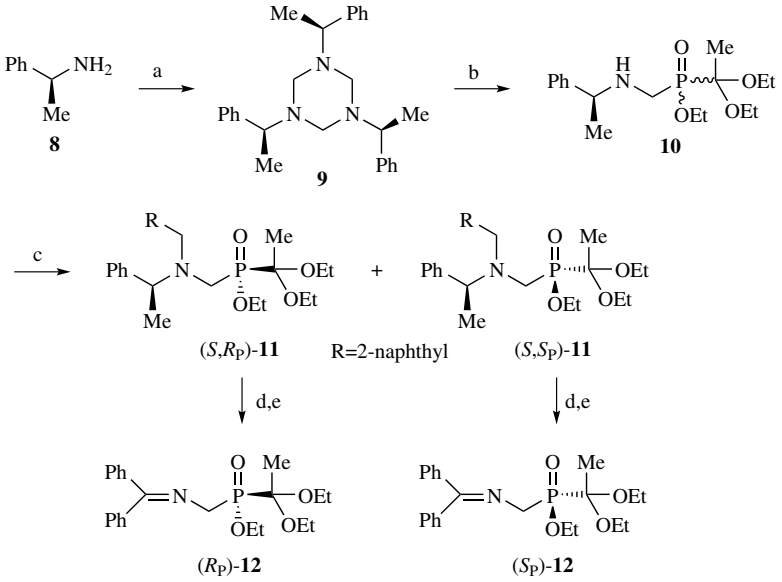


Figure 1. ORTEP drawing of the X-ray crystal structure of (R^*,S_P^*)-**4**.



Scheme 3.

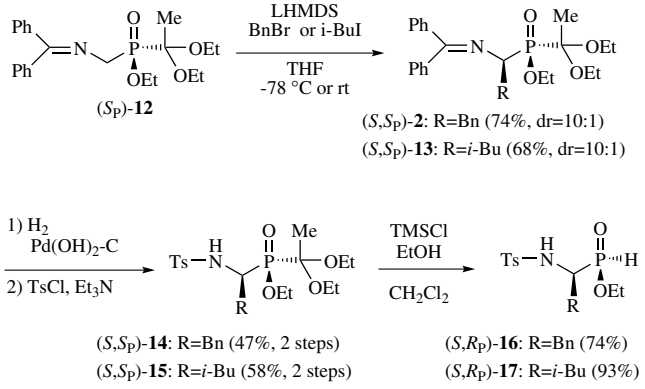


Scheme 4. Reagents and conditions: (a) $(CH_2O)_n$, $TsOH{\cdot}H_2O$, MeOH, reflux; (b) **6**, toluene, reflux, 61% (2 steps); (c) α-pic-BH_3, 2-naphthaldehyde, MeOH/AcOH (10:1), rt, 67%; (d) H_2, $Pd(OH)_2$–C, MeOH; (e) benzophenone, toluene, reflux, (R_P)-**12**: 51% (2 steps), (S_P)-**12**: 45% (2 steps).

ethyl(aminomethyl)phosphinate (R_P)-**12**. Enantiomer (S_P)-**12** was also prepared from (S,S_P)-**11**.

2.3. Diastereoselective synthesis of optically active α-substituted α-amino-*H*-phosphinates

With optically active 1,1-diethoxyethyl(aminomethyl)phosphinates in hand, we next directed our efforts toward their conversion into α-amino-*H*-phosphinates (Scheme 5). According to our previous procedure, treatment of the anion, generated from (S_P)-**12** and LHMDS, with benzyl bromide at −78 °C gave (S,S_P)-**2** and (R,S_P)-**2** in a 10:1 ratio. The reaction with *i*-BuI proceeded at room temperature providing (S,S_P)-**13** and (R,S_P)-**13** in a ratio of 10:1. After sequential hydrogenolysis and tosylation of (S,S_P)-**2**, deprotection of the ketal moiety in tosylamide (S,S_P)-**14** provided α-amino-*H*-phosphinate (S,R_P)-**16**. Moreover, (S,S_P)-**13** was converted into (S,R_P)-**17**.



(S_P)-**12**

(S,S_P)-**2**: R=Bn (74%, dr=10:1)

(S,S_P)-**13**: R=*i*-Bu (68%, dr=10:1)

(S,S_P)-**14**: R=Bn (47%, 2 steps)

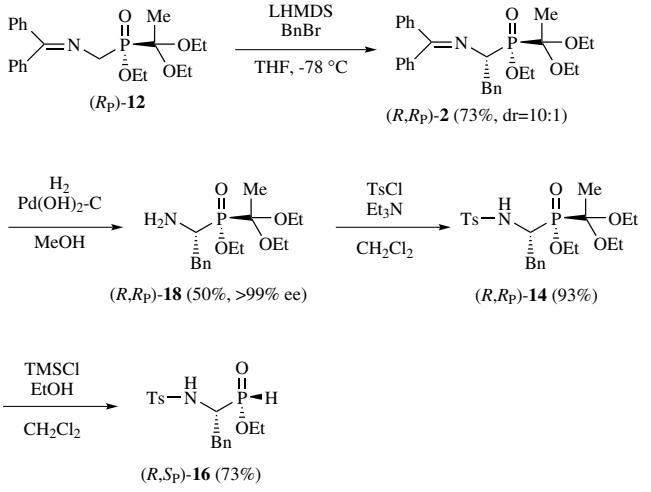
(S,S_P)-**15**: R=*i*-Bu (58%, 2 steps)

(S,R_P)-**16**: R=Bn (74%)

(S,R_P)-**17**: R=*i*-Bu (93%)

Scheme 5.

The optically active α-amino-*H*-phosphinates (R,S_P)-**16**, enantiomer of (S,R_P)-**16**, was prepared starting from (R_P)-**12** through the same sequence (Scheme 6). The intermediary free amine (R,R_P)-**18** was found to be almost enantiomerically pure by ^{31}P NMR analysis of the corresponding (*R*)-MTPA and (*S*)-MTPA-amides, indicating that no racemization occurred in this sequence.



(R_P)-**12**

(R,R_P)-**2** (73%, dr=10:1)

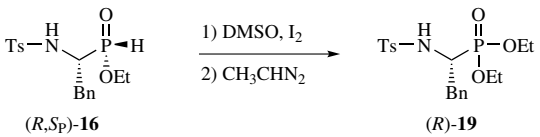
(R,R_P)-**18** (50%, >99% ee)

(R,R_P)-**14** (93%)

(R,S_P)-**16** (73%)

Scheme 6.

The absolute configuration of (R,S_P)-**16** was determined after conversion into the α-amino phosphonate (*R*)-**19** through oxidation with DMSO and I_2,[12] followed by esterification with diazoethane (Scheme 7). The negative sign of



(R,S_P)-**16**

(*R*)-**19**

Scheme 7.

the optical rotation $\{[\alpha]_D^{24} = -27.5$ (c 0.2, $CHCl_3$)$\}$ was opposite to that of known compound (S)-**19** with 65% ee $\{[\alpha]_D^{20} = +20.0$ (c 0.1, CH_2Cl_2)$\}$.[13]

3. Conclusion

In conclusion, we have developed a method for preparing optically active aminomethylphosphinates via resolution starting from (*S*)-phenylethylamine. These compounds were converted into α-amino-*H*-phosphinates in a diastereoselective manner via alkylation and deprotection of the ketal moiety. Application of the synthesis of peptide derivatives is currently ongoing.

4. Experimental

All melting points were taken on a Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FTIR-620. Mass spectra were measured on Micromass LCT and Micromass Autospec by electrospray ionization. NMR spectra were obtained on a Bruker DPX400 NMR spectrometer operated at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ ($\delta = 7.26$) for $CDCl_3$ solution. For ^{13}C NMR spectra, the chemical shifts in $CDCl_3$ are recorded relative to the $CDCl_3$ resonance ($\delta = 77.0$). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 ($\delta = 0$) with broad-band ^{1}H decoupling. Flash column chromatography was performed on 40–100 μm Silica Gel 60 (Kanto Chemical Co., Inc.). Column chromatography was carried out using 63–210 μm Silica Gel 60N (Kanto Chemical Co., Inc.).

4.1. (1R^*,R_P^*)-1,1-diethoxyethyl(1-benzoylamino-2-phenylethyl)phosphinate (1R^*,R_P^*)-3

To a solution of (R^*,R_P^*)-**2** (1.34 g, 2.72 mmol) in MeOH (27.2 mL) was added 20% $Pd(OH)_2$–C (163 mg) and stirred for 23 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue. To a solution of the residue in CH_2Cl_2 (29.2 mL) were added Et_3N (0.76 mL, 5.5 mmol) and BzCl (0.32 mL, 3.8 mmol) and stirred for 30 min at room temperature. After the mixture was concentrated, the residue was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give (R^*,R_P^*)-**3** (637 mg, 54%). Colorless plates; mp 152–154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.16 (10H, m), 5.14–5.04 (1H, m), 4.30–4.17 (2H, m), 3.87–3.70 (4H, m), 3.39–3.29 (1H, m), 3.20–3.03 (1H, m), 1.58 (3H, d, $J = 12.1$ Hz), 1.37 (3H, t, $J = 7.0$ Hz), 1.26 (3H, t, $J = 7.1$ Hz), 1.24 (3H, t, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 137.5–126.6 (aromatic), 102.3 (d, $J_{CP} = 138.7$ Hz), 62.3 (d, $J_{CP} = 7.5$ Hz), 58.8 (d, $J_{CP} = 4.3$ Hz), 57.7 (d, $J_{CP} = 7.7$ Hz), 47.3 (d, $J_{CP} = 93.3$ Hz), 35.1, 19.9 (d, $J_{CP} = 13.1$ Hz), 16.5 (d, $J_{CP} = 4.9$ Hz), 15.4, 14.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.44; IR (KBr) 3296, 1649, 1159, 1034 cm^{-1}; MS m/z 434 (MH^+); HRMS: (MH^+) calcd for $C_{23}H_{33}NO_5P$, 434.2096; found, 434.2114.

4.2. (1R^*,S_P^*)-Ethyl 1-benzoylamino-2-phenylethylphosphinate (R^*,S_P^*)-4

To a solution of (R^*,R_P^*)-**3** (380 mg, 0.88 mmol) in CH_2Cl_2 (18.3 mL) were added EtOH (103 μL), and TMSCl (223 μL, 1.76 mmol) at room temperature. After stirring for 2 h at the same temperature, the mixture was concentrated to give a residue, which was purified by column chromatography ($CHCl_3$) to give (R^*,S_P^*)-**4** (188 mg, 67%). Colorless plates; mp 196–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.21 (10H, m), 7.20 (1H, d, $J = 560.5$ Hz), 4.80–4.74 (1H, m), 4.22–4.12 (2H, m), 3.33–3.20 (1H, m), 3.17–3.11 (1H, m), 1.37 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 136.7–127.4 (aromatic), 63.7, 50.0 (d, $J_{CP} = 107.6$ Hz), 32.7, 16.6 (d, $J_{CP} = 5.7$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.82; IR (KBr) 3284, 2372, 1657, 1205, 1041 cm^{-1}; MS m/z 318 (MH^+); HRMS: (MH^+) calcd for $C_{17}H_{21}NO_3P$, 318.1259; found, 318.1257.

4.3. Crystal data for compound (R^*,S_P^*)-4

X-ray crystal data of (R^*,S_P^*)-**4** were collected by a Mac-Science DIP Image plate diffractometer. The structure was solved by a direct method using SIR97[14] and refined with a full matrix least-squares method.[15] Molecular formula = $C_{17}H_{20}NO_3P$, $M_r = 317.31$, monoclinic, space group = $P2_1/C$, $a = 10.4630(18)$ Å, $b = 9.5200(7)$ Å, $c = 16.795(3)$ Å, $V = 1586.4(4)$ Å^3, $T = 100(2)$ K, $Z = 4$, $D_x = 1.329$ mg m^{-3}, (Mo Kα) = 0.71073 Å, $\mu = 0.185$ mm^{-1}, $R = 0.0933$ over 3240 independent reflections. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication Numbers CCDC 649212. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4. 1,3,5-Tris[(1*S*)-1-phenylethyl]-1,3,5-triazinane 9

To a solution of paraformaldehyde (6.0 g, 200 mmol) in MeOH (200 mL) were added (*S*)-phenylethylamine **8** (25.6 mL, 200 mmol) and $TsOH \cdot H_2O$ (7.6 g, 40 mmol) and stirred for 20 h at 60 °C. After the mixture was concentrated, the residue was poured into satd $NaHCO_3$ solution and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave **9** (27.0 g). This compound was utilized for the next reaction without further purification. Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.15 (15H, m), 3.70 (3H, q, $J = 6.6$ Hz), 2.33 (3H, s), 1.41 (9H, d, $J = 6.6$ Hz). The ^{13}C NMR spectrum was identical to that of a sample reported in the literature.[10]

4.5. Ethyl 1,1-diethoxyethyl-({[(1*S*)-1-phenylethyl]amino}methyl)phosphinate 10

A stirred solution of **6** (21.0 g, 100 mmol) and **9** (33.9 g, 100 mmol) in toluene (165 mL) was heated at reflux for 12 h followed by cooling to room temperature and concentration under reduced pressure. The resulting residue was purified by flash column chromatography ($CHCl_3$/MeOH = 1:0 to 20:1) to give **10** (20.8 g, 61%). This compound was obtained as a mixture of diastereomers in a ratio of 1:1. Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (5H, m), 4.27–4.11 (2H, m), 3.81 (0.5H, q, $J = 6.6$ Hz), 3.80 (0.5H, q, $J = 6.9$ Hz), 3.73–3.57 (4H, m), 2.94–2.87 (1H, m), 2.83–2.74 (1H, m), 1.53 (1.5H, t, $J = 9.6$ Hz), 1.51 (1.5H, t, $J = 9.6$ Hz), 1.35 (1.5H, t, $J = 6.6$ Hz), 1.35 (1.5H, t, $J = 6.6$ Hz), 1.33 (1.5H, t, $J = 7.1$ Hz), 1.31 (1.5H, t, $J = 7.1$ Hz), 1.19 (1.5H, t, $J = 7.0$ Hz), 1.17 (1.5H, t, $J = 7.1$ Hz), 1.16 (1.5H, t, $J = 7.1$ Hz), 1.15 (1.5H, t, $J = 7.1$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.98, 44.64; IR (neat) 3452, 1155, 1038 cm^{-1}; MS *m*/*z* 344 (MH^+); HRMS: (MH^+) calcd for $C_{17}H_{31}NO_4P$, 344.1991; found, 344.2004.

4.6. Ethyl 1,1-diethoxyethyl-{(2-naphthylmethyl) [(1*S*)-1-phenylethyl]amino}methylphosphinates (*S*,*R*$_P$)-11 and (*S*,*S*$_P$)-11

To a stirred solution of **10** (343 mg, 1.0 mmol) and 2-naphthaldehyde (172 mg, 1.1 mmol) in MeOH/AcOH (10:1, 3.3 mL) were added α-pic-BH_3 (160 mg, 1.5 mmol) and stirred for 20 h at room temperature. The mixture was added with 1 M HCl and stirred for 15 min. The mixture was poured into satd Na_2CO_3 solution and extracted with AcOEt. The combined extracts were washed with brine and dried over K_2CO_3. Removal of the solvent gave a residue, which was purified by column chromatography (hexane/EtOAc = 5:1 to 2:1) to give a mixture of (*S*,*R*$_P$)-**11** and (*S*,*S*$_P$)-**11** (323 mg, 67%). Each isomer was isolated upon re-purification by flash column chromatography (hexane/EtOAc = 5:1 to 2:1).

(*S*,*R*$_P$)-**11**: Colorless oil; $[\alpha]_D^{25} = -54.6$ (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.23 (12H, m), 4.35–4.16 (3H, m), 4.00 (1H, d, $J = 13.6$ Hz), 3.88 (1H, d, $J = 13.8$ Hz), 3.64–3.46 (4H, m), 3.01 (1H, dd, $J = 8.3$, 15.4 Hz), 2.91 (1H, dd, $J = 3.0$, 15.4 Hz), 1.45 (3H, d, $J = 6.9$ Hz), 1.35 (3H, d, $J = 10.8$ Hz), 1.33 (3H, t, $J = 7.0$ Hz) 1.07 (3H, t, $J = 7.0$ Hz), 1.02 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.8–125.4 (aromatic), 101.1 (d, $J_{PC} = 132.6$ Hz), 61.5 (d, $J_{PC} = 7.2$ Hz), 58.3, (d, $J_{PC} = 6.8$ Hz), 58.0 (d, $J_{PC} = 4.4$ Hz), 57.3 (d, $J_{PC} = 7.1$ Hz), 55.6 (d, $J_{PC} = 5.5$ Hz), 45.1 (d, $J_{PC} = 98.6$ Hz), 20.3 (d, $J_{PC} = 11.6$ Hz), 16.7 (d, $J_{PC} = 5.1$ Hz), 15.6, 15.3, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.35; IR (neat) 1155, 1038 cm^{-1}; MS *m*/*z* 484 (MH^+); HRMS: (MH^+) calcd for $C_{28}H_{39}NO_4P$, 484.2617; found, 484.2593.

(*S*,*S*$_P$)-**11**: Colorless oil; $[\alpha]_D^{25} = -39.5$ (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.24 (12H, m), 4.31 (1H, q, $J = 6.8$ Hz), 4.13–3.98 (2H, m), 3.98 (1H, d, $J = 13.5$ Hz), 3.93 (1H, d, $J = 13.7$ Hz), 3.64–3.44 (4H, m), 3.16 (1H, dd, $J = 15.3$, 15.3 Hz), 2.80 (1H, dd, $J = 9.2$, 15.4 Hz), 1.45 (3H, d, $J = 6.9$ Hz), 1.42 (3H, d, $J = 10.8$ Hz), 1.29 (3H, t, $J = 7.1$ Hz) 1.10 (3H, t, $J = 7.0$ Hz), 1.03 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9–125.8 (aromatic), 101.5 (d, $J_{PC} = 132.2$ Hz), 62.0 (d, $J_{PC} = 7.3$ Hz), 58.5 (d, $J_{PC} = 4.3$ Hz), 58.3 (d, $J_{PC} = 6.9$ Hz), 57.7 (d, $J_{PC} = 7.2$ Hz), 56.3 (d, $J_{PC} = 5.0$ Hz), 45.2 (d, $J_{PC} = 98.7$ Hz), 20.9 (d, $J_{PC} = 11.4$ Hz), 17.2 (d, $J_{PC} = 5.4$ Hz) 15.8, 15.6, 14.5; ^{31}P NMR (162 MHz, $CDCl_3$) δ 46.04; IR (neat) 1155, 1038 cm^{-1}; MS *m*/*z* 484 (MH^+); HRMS: (MH^+) calcd for $C_{28}H_{39}NO_4P$, 484.2617; found, 484.2589.

4.7. (*R*$_P$)-Ethyl 1,1-diethoxyethyl{[(diphenylmethylene)-amino]methyl}phosphinate (*R*$_P$)-12

To a solution of (*S*,*R*$_P$)-**11** (1.7 g, 3.5 mmol) in MeOH (35 mL) was added 20% $Pd(OH)_2$–C (700 mg) and stirred for 5 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue. To a solution of the residue in CH_2Cl_2 (40 mL) was added Et_3N (0.49 mL, 3.5 mmol) and the mixture was stirred for 30 min at room temperature. To the mixture was added Et_2O (10 mL) and the resulting crystal was removed by filtration. The filtrate was concentrated to give a residue. A suspension of the residue and benzophenone (700 mg, 3.9 mmol) in toluene (10 mL) was heated at reflux for 12 h with azeotropic removal of water in a Dean-Stark trap. The mixture was cooled to room temperature and concentrated to give a residue, which was purified by flash column chromatography (hexane/EtOAc = 5:1 to 1:1) to give (*R*$_P$)-**12** (720 mg, 51%). Colorless plates; mp 47–48 °C; $[\alpha]_D^{24} = -17.8$ (*c* 0.4, $CHCl_3$). The ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.8. (*S*$_P$)-Ethyl 1,1-diethoxyethyl{[(diphenylmethylene)-amino]methyl}phosphinate (*S*$_P$)-12

This compound was prepared from (*S*,*S*$_P$)-**11** (285 mg, 1.2 mmol) in an analogous manner to that for (*R*$_P$)-**12**. Purification of the residue by flash column chromatography (hexane/EtOAc = 5:1 to 1:1) gave (*S*$_P$)-**12** (218 mg, 45%). Colorless oil; $[\alpha]_D^{24} = +16.6$ (*c* 0.6, $CHCl_3$). The ^{1}H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.9. (1*S*,*S*$_P$)-Ethyl-1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-2-phenylethyl}phosphinate (*S*,*S*$_P$)-2

To a solution of (*S*$_P$)-**12** (200 mg, 0.5 mmol) in THF (2.4 mL) was added 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol) at −78 °C and stirred for 30 min at the same temperature. To the mixture was added BnBr (0.12 mL, 1.0 mmol) and stirred for 1.5 h at the same temperature. The mixture was diluted with satd NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give a mixture of (*S*,*S*$_P$)-**2** and (*R*,*S*$_P$)-**2** (183 mg, 74%). (*S*,*S*$_P$)-**2** was isolated upon re-purification by flash column chromatography

(hexane/EtOAc = 5:1 to 1:1). Pale yellow oil; $[\alpha]_D^{24} = +83.5$ (c 0.1, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.10. (1*S*,*S*$_P$)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-3-methylbutyl}phosphinate (*S*,*S*$_P$)-13

To a solution of (S_P)-**12** (146 mg, 0.36 mmol) in THF (1.8 mL) was added 1.0 M THF solution of LHMDS (0.54 mL, 0.54 mmol) at −78 °C and stirred for 30 min at the same temperature. To the mixture was added *i*-BuI (0.21 mL, 1.8 mmol) and stirred for 1.5 h at room temperature. The mixture was diluted with satd NH_4Cl solution and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give a mixture of (S,S_P)-**13** and (R,S_P)-**13** (112 mg, 68%). (S,S_P)-**13** was isolated upon re-purification by flash column chromatography (hexane/EtOAc = 5:1 to 1:1). Pale yellow oil; $[\alpha]_D^{24} = -13.8$ (c 0.2, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.11. (1*S*,*S*$_P$)-1,1-Diethoxyethyl(1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (*S*,*S*$_P$)-14

To a solution of (S,S_P)-**2** (146 mg, 0.3 mmol) in MeOH (3 mL) was added 20% $Pd(OH)_2$–C (18 mg) and stirred for 40 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite and the filtrate was concentrated to give a residue. To a solution of this residue in CH_2Cl_2 (3.3 mL) were added Et_3N (89 μL, 0.64 mmol) and TsCl (121 mg, 0.64 mmol) and stirred for 2 h at room temperature. After the mixture was concentrated, the residue was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give (S,S_P)-**14** (68 mg, 47%). A colorless oil; $[\alpha]_D^{24} = +80.0$ (c 0.07, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.12. (1*S*,*S*$_P$)-1,1-Diethoxyethyl(1-{[(4-methylphenyl)sulfonyl]amino}-3-methylbutyl)phosphinate (*S*,*S*$_P$)-15

This compound was prepared from (S,S_P)-**13** (90 mg, 0.2 mmol), 20% $Pd(OH)_2$–C (12 mg), Et_3N (60 μL, 0.43 mmol), and TsCl (82 mg, 0.43 mmol) in an analogous manner to that for (S,S_P)-**14**. Purification of the residue by flash column chromatography (hexane/EtOAc = 3:1 to 1:1) gave (S,S_P)-**15** (52 mg, 58%). Colorless oil; $[\alpha]_D^{24} = +16.5$ (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.28 (4H, m), 5.39 (1H, dd, $J = 6.2$, 8.7 Hz), 4.17–4.08 (2H, m), 3.87–3.81 (1H, m), 3.79–3.60 (4H, m), 2.42 (3H, s), 1.75–1.41 (2H, m), 1.51 (3H, d, $J = 11.4$ Hz), 1.26 (3H, t, $J = 7.0$ Hz), 1.23 (6H, t, $J = 7.1$ Hz), 0.82 (3H, d, $J = 6.5$ Hz), 0.80 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.9–127.0 (aromatic), 102.7 (d, $J_{PC} = 139.9$ Hz), 62.1 (d, $J_{PC} = 7.2$ Hz), 58.7, 57.9 (d, $J_{PC} = 7.0$ Hz), 49.5 (d, $J_{PC} = 90.2$ Hz), 40.0, 24.5 (d, $J_{PC} = 7.5$ Hz), 22.7, 21.7, 21.4, 19.6 (d, $J_{PC} = 11.9$ Hz), 16.4 (d, $J_{PC} = 5.1$ Hz), 15.3, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.96; IR (neat) 3125, 1336, 1162, 1038 cm^{-1}; MS m/z 450 (MH^+); HRMS: (MH^+) calcd for $C_{20}H_{36}NO_6PS$, 450.2079; found, 450.2074.

4.13. (1*S*,*R*$_P$)-Ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethylphosphinate (*S*,*R*$_P$)-16

To a solution of (S,S_P)-**14** (42 mg, 0.08 mmol) in CH_2Cl_2 (0.3 mL) was added EtOH (34 μL) and TMSCl (20 μL, 0.16 mmol) at room temperature. After stirring for 2.5 h at the same temperature, the mixture was concentrated to give a residue, which was purified by flash column chromatography ($CHCl_3$/MeOH = 40:1 to 20:1) to give (S,R_P)-**16** (22 mg, 74%). A colorless oil; $[\alpha]_D^{24} = +69.2$ (c 0.08, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.14. (1*S*,*R*$_P$)-Ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-3-methylbutylphosphinate (*S*,*R*$_P$)-17

This compound was prepared from (S,S_P)-**15** (46 mg, 0.1 mmol), EtOH (40 μL), and TMSCl (22 μL, 0.2 mmol) in an analogous manner to that for (S,R_P)-**16**. Purification of the residue by flash column chromatography (hexane/EtOAc = 3:1 to 1:1) gave (S,R_P)-**17** (31 mg, 93%). Colorless oil; $[\alpha]_D^{24} = +50.5$ (c 0.16, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.79–7.30 (4H, m), 6.87 (1H, d, $J = 559.7$ Hz), 5.16 (1H, br s), 4.16–4.04 (2H, m), 3.56–3.53 (1H, m), 2.43 (3H, s), 1.61–1.46 (2H, m), 1.33 (3H, t, $J = 7.1$ Hz), 0.84 (3H, d, $J = 6.6$ Hz), 0.69 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6–127.1 (aromatic), 63.2 (d, $J_{PC} = 7.5$ Hz), 50.3 (d, $J_{PC} = 109.9$ Hz), 35.9, 23.8 (d, $J_{PC} = 9.6$ Hz), 22.9, 21.5, 21.0, 16.2 (d, $J_{PC} = 5.5$ Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.37; IR (neat) 3082, 1330, 1165, 1050 cm^{-1}; MS m/z 368 (MH^+); HRMS: (MH^+) calcd for $C_{14}H_{25}NO_4PS$, 334.1242; found, 334.1237.

4.15. (1*R*,*R*$_P$)-Ethyl-1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-2-phenylethyl}phosphinate (*R*,*R*$_P$)-2

This compound was prepared from (R_P)-**12** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and BnBr (0.12 mL, 1.0 mmol) in an analogous manner to that for (S,S_P)-**2**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (R,R_P)-**2** and (S,R_P)-**2** (181 mg, 73%). (R,R_P)-**2** was isolated upon re-purification by flash column chromatography (hexane/EtOAc = 5:1 to 1:1). A pale yellow oil; $[\alpha]_D^{24} = -84.0$ (c 0.1, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.16. (1*R*,*R*$_P$)-Ethyl 1-amino-2-phenylethyl(1,1-diethoxyethyl)phosphinate (*R*,*R*$_P$)-18

To a solution of (R,R_P)-**2** (327 mg, 0.66 mmol) in MeOH (6.6 mL) was added 20% $Pd(OH)_2$–C (60 mg) and stirred for 40 h at room temperature under a hydrogen atmosphere. The catalyst was removed by filtration through a

pad of Celite and the filtrate was concentrated to give a residue, which was purified by flash column chromatography ($CHCl_3$/MeOH = 1:0 to 20:1) to give (R,R_P)-**18** (108 mg, 50%). Pale yellow oil; $[\alpha]_D^{24} = -22.6$ (c 0.3, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.21 (5H, m), 4.30–4.23 (2H, m), 3.84–3.68 (4H, m), 3.35 (1H, ddd, $J = 3.2$, 3.2, 11.3 Hz), 3.21 (1H, ddd, $J = 3.2$, 5.2, 13.8 Hz), 2.74 (1H, ddd, $J = 7.4$, 11.3, 13.8 Hz), 1.63 (3H, d, $J = 10.7$ Hz), 1.35 (3H, t, $J = 7.1$ Hz), 1.22 (6H, t, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (d, $J_{CP} = 12.9$ Hz), 129.1, 128.3, 126.4, 101.3 (d, $J_{CP} = 131.6$ Hz), 62.0 (d, $J_{CP} = 7.6$ Hz), 58.3 (d, $J_{CP} = 4.4$ Hz), 57.5 (d, $J_{CP} = 6.8$ Hz), 50.5 (d, $J_{CP} = 90.7$ Hz), 36.1, 20.6 (d, $J_{CP} = 11.5$ Hz), 16.5 (d, $J_{CP} = 4.9$ Hz), 15.3, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 45.32; IR (neat) 3100, 1155, 1034 cm^{-1}; MS m/z 330 (MH^+); HRMS: (MH^+) calcd for $C_{16}H_{28}NO_4P$, 330.1834; found, 330.1821.

4.17. The procedure for the preparation of the (*R*)-MTPA and (*S*)-MTPA-amides of (*R*,*R*$_P$)-18

To a stirred suspension of (*R*)-MTPA (20 mg, 0.06 mmol), DCC (31 mg, 0.12 mmol), and DMAP (1.5 mg, 0.012 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of (R,R_P)-**18** (20 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) at 0 °C. After stirring at room temperature until the starting material disappeared, as evidenced by TLC, the mixture was diluted with H_2O and extracted with $CHCl_3$. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of solvent gave a residue which was diluted with Et_2O and passed through silica gel. The filtrate was evaporated to leave (*R*)-MTPA-amide of (R,R_P)-**18**. (*S*)-MTPA-amide of (R,R_p)-**18** was also prepared from (*S*)-MTPA by the same procedure. In the ^{31}P NMR spectra of both amides, signals due to the corresponding diastereoisomer were not detected.

4.18. (1*R*,*R*$_P$)-Ethyl 1,1-diethoxyethyl(1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (*R*,*R*$_P$)-14

To a solution of (R,R_P)-**18** (46 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL) were added Et_3N (21 μL, 0.29 mmol) and TsCl (57 mg, 0.29 mmol) and stirred for 2 h at room temperature. After the mixture was concentrated, the residue was poured into H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography ($CHCl_3$) to give (R,R_P)-**14** (63 mg, 93%). Colorless plates; mp 120–123 °C; $[\alpha]_D^{24} = -79.85$ (c 0.03, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.19. (1*R*,*S*$_P$)-Ethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethylphosphinate (*R*,*S*$_P$)-16

This compound was prepared from (R,R_P)-**14** (60 mg, 0.12 mmol), EtOH (50 μL), and TMSCl (32 μL, 0.24 mmol) in an analogous manner to that for (S,R_P)-**16**. Purification of the residue by flash column chromatography ($CHCl_3$/MeOH = 40:1 to 20:1) gave (R,S_P)-**16** (33 mg, 73%). Colorless plates; mp 112–114 °C; $[\alpha]_D^{24} = -70.1$ (c 0.2, $CHCl_3$). The ^1H and ^{31}P NMR spectra were identical to those of a racemic sample reported in the literature.[8]

4.20. (1*R*)-Diethyl 1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethylphosphonate (*R*)-19

A solution of (R,S_P)-**16** (19 mg, 0.05 mmol), DMSO (3.6 μL, 0.05 mmol), and iodine (0.2 mg, 0.01 mmol) in THF (3.5 mL) was stirred for 1 h at room temperature. The mixture was evaporated to give a residue. To a stirred solution of CH_3CHN_2, prepared from 58% *N*-nitroso-*N*-ethylurea (23 mg, 0.2 mmol), was added a solution of the residue in Et_2O/EtOH = 10:1 (1.1 mL) at 0 °C and the solution was stirred for 30 min at the same temperature. After decomposition of excess CH_3CHN_2 with AcOH, the mixture was diluted with H_2O and extracted with Et_2O. The combined extracts were washed with brine and dried over $MgSO_4$. Removal of the solvent gave a residue which was purified by preparative TLC (hexane/EtOAc = 2:1) to give (*R*)-**19** (7.6 mg, 37%). Pale yellow oil; $[\alpha]_D^{24} = -27.5$ (c 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.06 (9H, m), 5.37 (1H, dd, $J = 3.5$, 9.5 Hz), 4.14–4.06 (5H, m), 3.08 (1H, ddd, $J = 5.9$, 14.3, 14.3 Hz), 2.86 (1H, ddd, $J = 7.5$, 12.5, 14.3 Hz), 2.38 (3H, s), 1.21 (3H, t, $J = 7.1$ Hz), 1.20 (3H, t, $J = 7.1$ Hz). The ^{13}C and ^{31}P NMR spectra were identical to those of a sample reported in the literature.[13]

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References

1. (a) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508; (b) Li, T.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2001.
2. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: Chichester, 2000.
3. For reviews, see: (a) Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629; (b) Yiotakis, A.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135.
4. For selected examples: (a) Matziari, M.; Georgiadis, D.; Dive, V.; Yiotakis, A. *Org. Lett.* **2001**, *3*, 659; (b) Cristau, H.-J.; Coulombeeau, A.; Genevois-Borella, A.; Sanchez, F.; Pirat, J.-L. *J. Organomet. Chem.* **2002**, *643–644*, 381; (c) Liu, X.; Hu, X. E.; Tian, X.; Mazur, A.; Ebetino, F. H. *J. Organomet. Chem.* **2002**, *646*, 212; (d) Li, S.; Whitehead, J. K.; Hammer, R. P. *J. Org. Chem.* **2007**, *72*, 3116.
5. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845.
6. Solodenko, V. A.; Belik, M. Y.; Galushko, S. V.; Kukhar, V. P.; Kozlova, E. V.; Mironenko, D. A.; Svedas, V. S. *Tetrahedron: Asymmetry* **1993**, *4*, 1965.

7. McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319.
8. (a) Yamagishi, T.; Haruki, T.; Yokomatsu, T. *Tetrahedron* **2006**, *62*, 9210; For recent applications of our methodology to the synthesis of α,α′-diaminophosphinates and α-amino-α′-hydroxyphosphinates: (b) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Tetrahedron* **2007**, *63*, 8199; (c) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Synthesis* **2007**, 3226.
9. (a) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385; (b) Froestl, W.; Mickel, S. J.; Hall, R. G.; Sprecher, G.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297.
10. Amoroso, R.; Cardillo, G.; Tomasini, C.; Tortoreto, P. *J. Org. Chem.* **1992**, *57*, 1082.
11. Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron* **2004**, *60*, 7899.
12. Albouy, D.; Brun, A.; Munoz, A.; Etemad-Moghadam, G. *J. Org. Chem.* **1995**, *60*, 6656.
13. Palacios, F.; Aparicio, D.; Ochoa de Rerana, A. M.; de los Santos, J. M.; Gill, J. I.; López de Munain, R. *Tetrahedron: Asymmetry* **2003**, *14*, 689.
14. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115.
15. Sheldrick, G. M. SHELXL*97, Program for the Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.