Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 62 (2006) 9210–9217

Diastereoselective alkylation of iminomethylenephosphinates possessing an asymmetric center at the phosphorus atom

Takehiro Yamagishi, Terumitsu Haruki and Tsutomu Yokomatsu*

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 1 June 2006; revised 3 July 2006; accepted 11 July 2006
Available online 31 July 2006

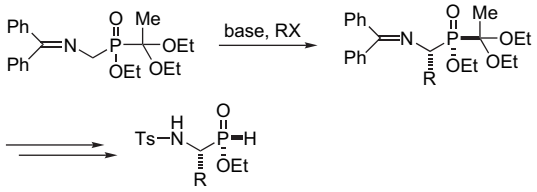
Abstract—Diastereoselective synthesis of α-aminophosphinates was achieved by alkylation of imines with a 1,1-diethoxyethylphosphinyl group. These products were readily converted into α-amino-*H*-phosphinates.

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 were shown to be effective inhibitors against aspartic acid proteases and Zn metalloproteases.[3] For the preparation of various α-aminophosphinic acid derivatives, α-amino-*H*-phosphinates have been utilized as versatile synthetic intermediates.[4] This class of compounds has previously been prepared through the addition of phosphinic acid[5] or silyl phosphonite[6] to imines. An alternative synthesis of α-amino-*H*-phosphinates involves the alkylation of iminomethylenephosphinates having a diethoxymethyl group at the phosphorus atom, followed by conversion of the diethoxymethylphosphinyl moiety to P–H group with 6 M HCl at reflux.[7] In this methodology, the alkylated products were given as a mixture of diastereomers arising from the chirality of the phosphorus atom, and the relative configuration of the major isomer as well as its stereoselectivity remained unclear. The methodology was limited by the harsh conditions necessary for the deprotection of the acetal group.[8]

During our studies on the stereoselctive synthesis of α-amino-*H*-phosphinic acid derivatives, we envisioned iminomethylenephosphinates bearing a 1,1-diethoxyethyl group instead of a diethoxymethyl group, which could be successfully employed as a substrate for the stereoselective alkylation of phosphorus-stabilized carbanions. The 1,1-diethoxyethyl group may give rise to a pronounced steric hindrance around the carbanions and could work as a good directing group for the diastereoselective alkylation of the carbanions.

In this paper, we wish to describe our experimental results on the alkylation of racemic iminomethylenephosphinates possessing a 1,1-diethoxyethyl group at the phosphorus atom. As expected, these reactions proceeded in a highly diastereoselective manner to give α-substituted α-aminophosphinates, which were readily converted to α-substituted α-amino-*H*-phosphinates under mild conditions (Scheme 1).



Scheme 1.

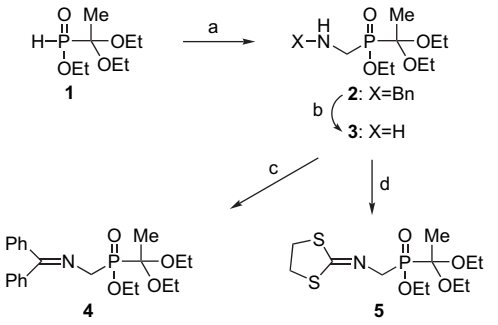
2. Results and discussion

The requisite starting materials **4** and **5** were prepared as shown in Scheme 2. The addition of *H*-phosphinate **1**[8] to 1,3,5-hexahydrotriazine provided benzylamine **2**, which was subjected to hydrogenolytic removal of the benzyl group giving amine **3**. Treatment of **3** with benzophenone in toluene at reflux afforded imine **4**. Following Hoppe's procedure,[9] **3** was converted to imine **5**.

First, alkylation of **4** with benzyl bromide (2 equiv) was examined in THF at −78 °C by using representative strong bases (Scheme 3). When BuLi was used as a basic reagent, the reaction was completed within 1.5 h to give a diastereomeric mixture of (R^*,R_P^*)-**6** and (S^*,R_P^*)-**6** in a 51% yield.

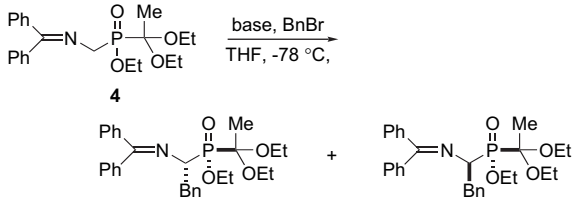
Keywords: α-Amino-*H*-phosphinates; Phosphorus; Alkylations; Diastereoselectivity.
* Corresponding author. Tel./fax: +81 426 76 3239; e-mail: yokomatu@ps.toyaku.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.07.029



Scheme 2. Reagents and conditions: (a) 1,3,5-tribenzylhexahydrotriazine, toluene, reflux, 85%; (b) H_2, $Pd(OH)_2$–C, MeOH, 83%; (c) benzophenone, toluene, reflux, 87%; (d) CS_2, 1,2-dibromoethane, NEt_3, K_2CO_3, $CHCl_3$, reflux, 32%.

The ratio was determined to be 2.2:1 preferring (R^*,R_P^*)-**6** on the basis of ^{31}P (121 MHz) NMR analysis. Upon using LDA, the yield was significantly increased to 70% albeit the diastereoselectivity was similar to that for BuLi. While utilizing lithium 2,2,6,6-tetramethylpiperidide (LTMP) took longer reaction time (20 h) compared to the cases of BuLi and LDA (1.5 h), the diastereoselectivity was improved up to 6.9:1. KHMDS was found to be a good base for inducing a high diastereoselectivity with a modest yield. The best result was observed when the reaction was carried out with LHMDS; (R^*,R_P^*)-**6** and (S^*,R_P^*)-**6** were obtained in a 78% yield with a ratio of 10.1:1 and the individual diastereomers were isolated in a pure state by flash column chromatography on silica gel. Although the exact reason why LHMDS was the most effective among examined basic reagents remained unclear, it seems likely to be associated with steric bulk of the basic reagents.

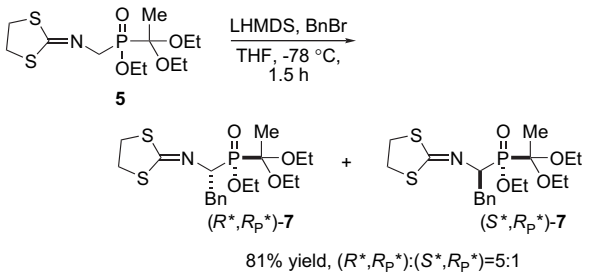


base	time (h)	yield (%)	(R^*,R_P^*):(S^*,R_P^*)
BuLi	1.5	51	2.2:1
LDA	1.5	70	3.0:1
LTMP	20	58	6.9:1
KHMDS	1.5	52	10.1:1
LHMDS	1.5	78	10.1:1

Scheme 3.

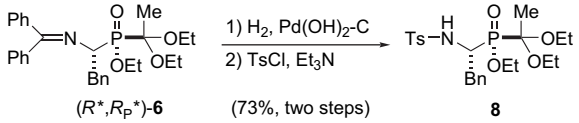
The benzylation of **5** under optimized conditions provided (R^*,R_P^*)-**7** and (S^*,R_P^*)-**7** in a 81% yield, however, (R^*,R_P^*)-selectivity (5:1) was eroded in comparison to the case of **4** (Scheme 4). This result indicated *N*-diphenylmethyleneamine derivative **4** was a relatively good substrate.

The relative stereochemistry of (R^*,R_P^*)-**6** was verified after conversion to the corresponding tosylamide **8** (Scheme 5). Hydrogenolysis of (R^*,R_P^*)-**6** in the presence of $Pd(OH)_2$–C, followed by tosylation of the resulting amine afforded **8**. The stereochemistry of **8** was confirmed by X-ray



Scheme 4.

crystallographic analysis (Fig. 1). The relative configuration of (R^*,R_P^*)-**7** was ascertained by comparison with an authentic sample prepared from (R^*,R_P^*)-**6** through exchanging the protecting group at the nitrogen atom.



Scheme 5.

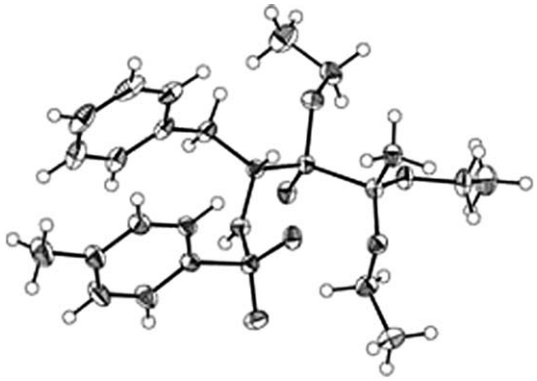
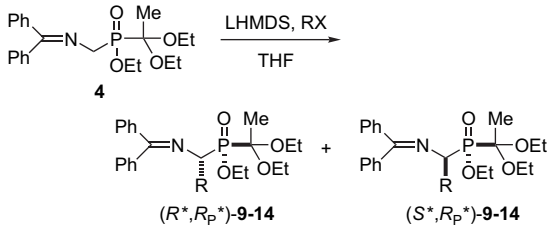


Figure 1. ORTEP drawing of the X-ray crystal structure of **8**.

The diastereoselective alkylation of **4** with several electrophiles was further examined. The results are summarized in Table 1.

Reactions with allyl bromide derivatives and iodomethane proceeded smoothly at −78 °C and were completed within 1.5 h providing (R^*,R_P^*)-**9**–**11** and (S^*,R_P^*)-**9**–**11** in good yields (entries 1–3). On the other hand, when the same conditions were applied to the less reactive alkyl halides (*n*-BuBr, *i*-PrI, *i*-BuBr), reactions were quite sluggish. However, the alkylation products ((R^*,R_P^*)-**12**–**14** and (S^*,R_P^*)-**12**–**14**) were obtained in 47–71% yields, upon warming the reaction mixture from −78 to 0 °C or at room temperature (entries 4–6). In view of diastereoselectivity, the reaction of allyl bromide gave (R^*,R_P^*)-**9** predominantly in a ratio of 7.7:1 (entry 1). The reactions of methallyl bromide and *i*-BuBr also showed good selectivity (entries 2 and 6). Unfortunately, reactions with other electrophiles (MeI, *n*-BuBr, *i*-PrI) resulted in decrease of diastereoselectivity (entries 3–5). The relative configuration of (R^*,R_P^*)-**9**–**14** was estimated analogously to (R^*,R_P^*)-**6**, whose stereochemistry was previously determined. Although a similar reaction of

Table 1. Diastereoselective alkylation of **4** with several electrophiles

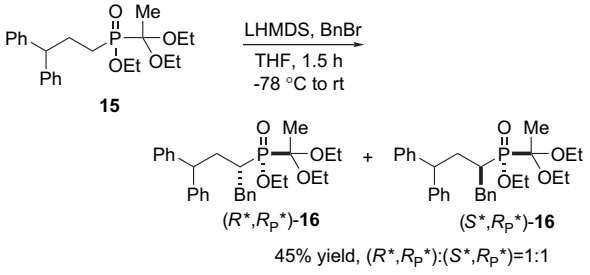


Entry	RX[a]	Temp (°C)	Time (h)	Product	Yield (%)[b]	(*R**,*R*P*): (*S**,*R*P*)[c]
1	Allyl bromide	−78	1.5	**9**	90	7.7:1
2	Methallyl bromide	−78	1	**10**	98	7.8:1
3	MeI	−78	1.5	**11**	77	4.5:1
4	*n*-BuBr	−78 to 0	24	**12**	50	4.8:1
5	*i*-PrI	−78 to 0	24	**13**	47	6.8:1
6	*i*-BuI[d]	−78 to rt	20	**14**	71	10.0:1

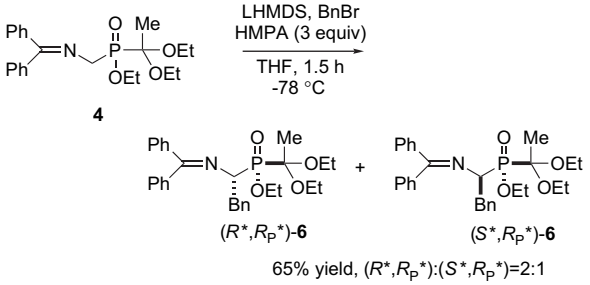
[a] Electrophiles (2 equiv) were utilized unless stated otherwise.
[b] Combined yield of (*R**,*R*P*)- and (*S**,*R*P*)-products.
[c] Determined by ^{31}P NMR (121 MHz, $CDCl_3$) analysis of crude products.
[d] *i*-BuI (5 equiv) was utilized.

4 with *p*-nitrobromobenzene was examined, formation of any S_NAr products was not detected. Thus, suitable electrophiles in this methodology were confirmed to be alkyl halide derivatives.

To probe the origin of the diastereocontrol, we performed the following experiments. The LHMDS-mediated benzylation of phosphinate **15** without a nitrogen atom, prepared from **1** and 3,3-diphenylpropyl bromide, proceeded in a nonstereoselective manner ((*R**,*R*P*)-**16**/(*S**,*R*P*)-**16**=1:1) in contrast to the reaction of **4** (Scheme 6). When the LHMDS-mediated benzylation of **4** was carried out in the presence of additive HMPA (3 equiv), the diastereoselectivity was lowered ((*R**,*R*P*)-**6**/(*S**,*R*P*)-**6**=2:1) compared to that without HMPA (Scheme 7). These results represent that the chelation



Scheme 6.



Scheme 7.

of the lithium atom to the nitrogen atom of the substrates is likely to be a significant factor for the occurrence of good (*R**,*R*P*)-selectivity.

On the basis of the above-mentioned results, the stereoselectivity in the alkylation of **4** is possibly accounted for by invoking the anion intermediate **17** bearing a planar sp^2 carbanionic carbon, wherein the lithium atom is coordinated by phosphinyl oxygen and a nitrogen atom (Fig. 2). An approach of electrophiles from the side of the 1,1-diethoxyethyl group was hindered by this bulky moiety, therefore, the access of the electrophiles occurred preferentially from the opposite side of a 1,1-diethoxyethyl group leading to (*R**,*R*P*)-products. Similar working models were proposed by Denmark and Hannesian for the asymmetric alkylation of anions derived from phosphonamidates[10] and phosphonamide,[11] respectively.

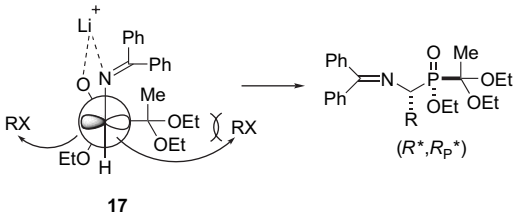
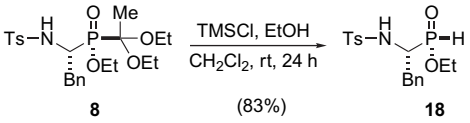


Figure 2.

Finally, the 1,1-diethoxyethyl moiety of **8** was readily removed by treatment with TMSCl and ethanol at room temperature furnishing α-amino-*H*-phosphinate **18** (Scheme 8). It is worthy to note that this deprotection step proceeded in a highly diastereoselective manner (20:1) to give **18** in good yield, while the deprotection step may be prone to epimerization at the phosphorus atom. Compound **18** was isolated in pure form by column chromatography on silica gel.



Scheme 8.

3. Conclusion

In conclusion, we have developed a method for preparing α-aminophosphinates through alkylation of iminomethylenephosphinates with 1,1-diethoxyethyl moiety. The feature of this method is a high diastereoselectivity controlled by the asymmetric center at the phosphorus atom. The protective group of the alkylated product was removed under mild conditions giving α-amino-*H*-phosphinate. Application to chiral variants is ongoing.

4. Experimental

4.1. General

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 a Finnigan TSQ-700 by electrospray ionization. Elemental analysis were recorded on an Elemental Vavio EL. NMR spectra were obtained on Bruker DPX400 NMR spectrometer operating at 400 MHz for ^{1}H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P. ^{31}P NMR spectra were also obtained on Varian Mercury-300BB instrument operating at 121 MHz. The chemical shift data for each signal on ^{1}H NMR are given in units of δ relative to $CHCl_3$ (δ=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 (δ=77.0). The chemical shifts of ^{31}P are recorded relative to external 85% H_3PO_4 (δ=0) with broadband ^{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.). Preparative HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-986; detector, UV-975, measured at 254 nm; column, GL Sciences Inertsil PREP SIL; flow rate, 15.0 mL min^{-1}. Analytical TLC was carried out with precoated silica gel 60 F_{254} plates (Merck).

4.1.1. Ethyl (benzylamino)methyl(1,1-diethoxyethyl)-phosphinate (2). A stirred solution of **1** (22.4 g, 100 mmol) and 1,3,5-tribenzylhexahydro-1,3,5-triazine (11.79 g, 33 mmol) in toluene (165 mL) was heated to 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 **2** (27.9 g, 85%). A pale yellow oil; TLC R_f=0.36 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.22 (5H, m), 4.30–4.19 (2H, m), 3.90 (1H, d, J=13.4 Hz), 3.86 (1H, d, J=13.4 Hz), 3.76–3.67 (4H, m), 3.08 (1H, dd, J=6.4, 14.6 Hz), 2.95 (1H, dd, J=9.8, 14.6 Hz), 1.54 (3H, d, J=11.0 Hz), 1.34 (3H, t, J=7.1 Hz), 1.19 (3H, t, J=7.1 Hz), 1.18 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 128.1, 127.9, 126.1, 101.1 (d, J_{CP}=137.2 Hz), 61.6 (d, J_{CP}=7.2 Hz), 58.0 (d, J_{CP}=4.9 Hz), 57.4 (d, J_{CP}=7.0 Hz), 54.8 (d, J_{CP}=13.1 Hz), 44.5 (d, J_{CP}=92.5 Hz), 20.3 (d, J_{CP}=11.7 Hz), 16.5 (d, J_{CP}=5.1 Hz), 15.2, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.63; IR (neat) 3321, 1155, 1036 cm^{-1}; MS m/z 330 (MH^+). HRMS calcd for $C_{16}H_{29}NO_4P$: 330.1834 (MH^+). Found: 330.1831.

4.1.2. Ethyl aminomethyl(1,1-diethoxyethyl)phosphinate (3). To a solution of **2** (10.01 g, 30.4 mmol) in MeOH (304 mL) was added $Pd(OH)_2$–C (1.83 g) 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 (334 mL) was added Et_3N (6.9 mL, 6.7 mmol) and the mixture was stirred for 30 min at room temperature. To the mixture was added Et_2O (100 mL) and resulting crystal was removed by filtration. The filtrate was concentrated to give **3** (6.03 g, 83%). A pale yellow oil; TLC R_f=0.30 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28–4.19 (2H, m), 3.79–3.62 (4H, m), 3.11 (1H, dd, J=2.1, 15.7 Hz), 2.98 (1H, dd, J=7.3, 15.7 Hz), 1.53 (3H, d, J=10.9 Hz), 1.34 (3H, t, J=7.0 Hz), 1.21 (6H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.3 (d, J_{CP}=29.0 Hz), 61.6 (d, J_{CP}=7.3 Hz), 58.0 (d, J_{CP}=4.9 Hz), 57.4 (d, J_{CP}=6.6 Hz), 38.2 (d, J_{CP}=85.4 Hz), 19.7 (d, J_{CP}=11.6 Hz), 16.4 (d, J_{CP}=4.9 Hz), 15.1, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.29; IR (neat) 3012, 1160, 1036 cm^{-1}; MS m/z 240 (MH^+). HRMS calcd for $C_9H_{23}NO_4P$: 240.1365 (MH^+). Found: 240.1360.

4.1.3. Ethyl 1,1-diethoxyethyl{[(diphenylmethylene)amino]methyl}phosphinate (4). A suspension of **3** (970 mg, 4.0 mmol) and benzophenone (810 mg, 4.0 mmol) in toluene (11 mL) was heated to 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 ($CHCl_3$) to give **4** (1.42 g, 87%). A colorless oil; TLC R_f=0.26 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.24 (10H, m), 4.27–4.23 (2H, m), 4.05 (1H, dd, J=14.0, 26.9 Hz), 3.98 (1H, dd, J=14.0, 26.9 Hz), 3.73–3.61 (4H, m), 1.57 (3H, d, J=11.2 Hz), 1.34 (3H, t, J=7.1 Hz), 1.14 (6H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.5, 130.2, 128.5–127.9 (aromatic), 101.2 (d, J_{PC}=140.4 Hz), 62.0 (d, J_{PC}=7.3 Hz), 57.9 (d, J_{PC}=5.1 Hz), 57.7 (d, J_{PC}=6.9 Hz), 51.8 (d, J_{PC}=96.6 Hz), 20.5 (d, J_{PC}=11.8 Hz), 16.6 (d, J_{PC}=5.1 Hz), 15.3, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.44; IR (neat) 1620, 1158, 1036 cm^{-1}; MS m/z 404 (MH^+). HRMS calcd for $C_{22}H_{31}NO_4P$ (MH^+): 404.1991. Found: 404.1994.

4.1.4. Ethyl 1,1-diethoxyethyl[(1,3-dithiolan-2-ylideneamino)methyl]phosphinate (5). To a solution of **3** (5.00 g, 20.9 mmol) in $CHCl_3$ (42 mL) was added CS_2 (3.1 mL, 52.0 mmol) and Et_3N (11.7 mL, 83.6 mmol) and stirred for 30 min at room temperature. To the mixture was added 1,2-dibromoethane (4.5 mL, 52 mmol) and heated to reflux for 1 h. Concentration of the mixture gave a residue, which was dissolved in EtOH (25 mL). To this solution was added K_2CO_3 (2.89 g, 20.9 mmol) and heated to reflux for 4 h. The mixture 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 **5** (2.30 g, 32%). A pale yellow oil; TLC R_f=0.37 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (1H, dd, J=7.1, 14.3 Hz), 4.25 (1H, dd, J=7.1, 14.3 Hz), 3.95 (1H, dd, J=10.5, 14.5 Hz), 3.91 (1H, dd, J=12.0, 14.5 Hz), 3.83–3.63 (4H, m), 3.59 (2H, t, J=6.1 Hz), 3.43 (2H, t, J=6.5 Hz), 1.57 (3H, t, J=11.2 Hz), 1.34 (3H, t, J=7.1 Hz), 1.21 (3H, t, J=7.0 Hz), 1.20 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4 (d, J_{PC}=16.5 Hz), 100.9 (d, J_{PC}=141.2 Hz), 61.8 (d, J_{PC}=7.2 Hz), 57.8 (d, J_{PC}=5.1 Hz), 57.4 (d, J_{PC}=7.1 Hz), 56.5 (d, J_{PC}=97.2 Hz), 37.5, 34.6, 20.3 (d, J_{PC}=11.8 Hz), 16.3 (d, J_{PC}=5.0 Hz), 15.2, 15.0; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.22; IR (neat) 1595, 1157, 1037 cm^{-1}; MS m/z 342 (MH^+). HRMS calcd for $C_{12}H_{25}NO_4PS_2$ (MH^+): 342.0963. Found: 342.0948.

4.1.5. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-2-phenylethyl}-phosphinate ((*R**,*R*$_P$*)-6 and (*S**,*R*$_P$*)-6).** To a solution of **4** (400 mg, 1.0 mmol) in THF (4.7 mL) was added 1.0 M THF solution of LHMDS (1.5 mL, 1.5 mmol) and stirred for 30 min at the same temperature. To the mixture was added benzyl bromide (0.24 mL, 2.0 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 (*R**,*R*P*)-**6** and (*S**,*R*P*)-**6** (358 mg, 78%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 1:1).

(*R**,*R*P*)-**6**: A pale yellow oil; TLC R_f=0.61 (hexane/EtOAc=1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–6.96 (15H, m), 4.32–4.18 (2H, m), 4.04–4.00 (1H, m), 3.83–3.64 (4H, m), 3.46 (1H, ddd, *J*=1.9, 6.2, 13.3 Hz), 3.36–3.31 (1H, m), 1.66 (3H, d, *J*=11.1 Hz), 1.34 (3H, t, *J*=7.1 Hz), 1.21 (3H, t, *J*=7.0 Hz), 1.18 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.4–126.1 (aromatic), 102.2 (d, J_{PC}=134.7 Hz), 65.8 (d, J_{PC}=95.3 Hz), 62.0 (d, J_{PC}=7.1 Hz), 58.0 (d, J_{PC}=6.5 Hz), 57.8 (d, J_{PC}=4.8 Hz), 36.8, 21.0 (d, J_{PC}=12.1 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.5, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.44; IR (neat) 1620, 1155, 1034 cm^{-1}; MS *m*/*z* 494 (MH^+). HRMS calcd for $C_{29}H_{37}NO_4P$ (MH^+): 494.2460. Found: 494.2451.

(*S**,*R*P*)-**6**: A pale yellow oil; TLC R_f=0.53 (hexane/EtOAc=1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–6.98 (15H, m), 4.30–4.17 (2H, m), 4.08–4.06 (1H, m), 3.86–3.65 (4H, m), 3.51–3.46 (1H, m), 3.38–3.31 (1H, m), 1.43 (3H, d, *J*=10.9 Hz), 1.27 (3H, t, *J*=7.1 Hz), 1.15 (3H, t, *J*=7.0 Hz), 1.11 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 135.7–126.1 (aromatic), 102.1 (d, J_{PC}=136.7 Hz), 64.1 (d, J_{PC}=92.7 Hz), 62.1 (d, J_{PC}=7.5 Hz), 58.4 (d, J_{PC}=4.7 Hz), 57.5 (d, J_{PC}=7.2 Hz), 36.9, 20.6 (d, J_{PC}=11.8 Hz), 16.9 (d, J_{PC}=4.8 Hz), 15.4, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.59; IR (neat) 1618, 1153, 1034 cm^{-1}; MS *m*/*z* 494 (MH^+). HRMS calcd for $C_{29}H_{37}NO_4P$ (MH^+): 494.2460. Found: 494.2442.

4.1.6. (1*R,*R*P*)- and (1*S**,*R*P*)-Ethyl 1,1-diethoxyethyl[1-(1,3-dithiolan-2-ylideneamino)-2-phenylethyl]phosphinate ((*R**,*R*P*)-7 and (*S**,*R*P*)-7).** These compounds were prepared from **5** (341 mg, 1.0 mmol) in an analogous manner to that for (*R**,*R*P*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*P*)-**7** and (*S**,*R*P*)-**7** (350 mg, 81%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 1:1).

(*R**,*R*P*)-**7**: A pale yellow oil; TLC R_f=0.38 (hexane/EtOAc=1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.15 (5H, m), 4.32–4.25 (2H, m), 3.80–3.66 (5H, m), 3.34–3.28 (3H, m), 3.21–3.16 (3H, m), 1.60 (3H, d, *J*=11.1 Hz), 1.35 (3H, t, *J*=7.1 Hz), 1.23 (3H, t, *J*=6.9 Hz), 1.21 (3H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (d, J_{PC}=17.5 Hz), 138.5 (d, J_{PC}=13.6 Hz), 129.9, 127.9, 126.2, 102.1 (d, J_{PC}=135.7 Hz), 71.4 (d, J_{PC}=100.6 Hz), 62.1 (d, J_{PC}=7.4 Hz), 58.2 (d, J_{PC}=4.2 Hz), 57.6 (d, J_{PC}=7.4 Hz), 37.4, 35.8, 34.3, 20.9 (d, J_{PC}=12.0 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.6, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.97; IR (neat) 1591, 1153, 1039 cm^{-1}; MS *m*/*z* 432 (MH^+). HRMS calcd for $C_{19}H_{31}NO_4PS_2$ (MH^+): 432.1432. Found: 432.1408.

(*S**,*R*P*)-**7**: A pale yellow oil; TLC R_f=0.25 (hexane/EtOAc=1:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (5H, m), 4.35–4.26 (2H, m), 3.98–3.90 (1H, m), 3.76–3.60 (4H, m), 3.49 (1H, ddd, *J*=5.4, 11.1, 13.4 Hz), 3.34–3.15 (4H, m), 3.04 (1H, ddd, *J*=2.1, 5.4, 13.4 Hz), 1.56 (3H, d, *J*=10.9 Hz), 1.38 (3H, t, *J*=7.1 Hz), 1.22 (6H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3 (d, J_{PC}=16.0 Hz), 138.5 (d, J_{PC}=14.1 Hz), 129.9, 128.0, 126.2, 101.6 (d, J_{PC}=138.5 Hz), 70.7 (d, J_{PC}=95.7 Hz), 62.3 (d, J_{PC}=7.5 Hz), 58.5 (d, J_{PC}=4.3 Hz), 57.7 (d, J_{PC}=8.0 Hz), 37.4, 35.9, 34.4, 20.9 (d, J_{PC}=11.4 Hz), 16.8 (d, J_{PC}=4.2 Hz), 15.7, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.08; IR (neat) 1591, 1151, 1034 cm^{-1}; MS *m*/*z* 432 (MH^+). HRMS calcd for $C_{19}H_{31}NO_4PS_2$ (MH^+): 432.1432. Found: 432.1409.

4.1.7. (1*R,*R*P*)-Ethyl 1,1-diethoxyethyl(1-{[(4-methylphenyl)sulfonyl]amino}-2-phenylethyl)phosphinate (8).** To a solution of (*R**,*R**P)-**6** (360 mg, 0.72 mmol) in MeOH (7.2 mL) was added $Pd(OH)_2$–C (43.2 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 the residue in CH_2Cl_2 (3.2 mL) was added Et_3N (0.21 mL, 1.51 mmol) and TsCl (288 mg, 1.51 mmol) and the mixture was stirred for 2 h at room temperature. The mixture 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 **8** (306 mg, 88%). Colorless plates; mp 126–132 °C; TLC R_f=0.38 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.09 (5H, m), 5.59 (1H, dd, *J*=7.5, 7.7 Hz), 4.24–4.12 (2H, m), 4.10–4.00 (1H, m), 3.79–3.63 (4H, m), 3.22 (1H, ddd, *J*=6.3, 9.8, 14.5 Hz), 2.89 (1H, ddd, *J*=7.7, 12.0, 14.3 Hz), 2.37 (3H, s), 1.53 (3H, d, *J*=11.6 Hz), 1.25 (3H, t, *J*=7.0 Hz), 1.20 (6H, t, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 138.8, 137.5, 129.5–126.4 (aromatic), 102.9 (d, J_{PC}=141.2 Hz), 62.3 (d, J_{PC}=7.5 Hz), 58.9 (d, J_{PC}=4.5 Hz), 58.2 (d, J_{PC}=7.4 Hz), 53.1 (d, J_{PC}=87.1 Hz), 36.9, 21.4, 19.5 (d, J_{PC}=12.1 Hz), 16.3 (d, J_{PC}=5.8 Hz), 15.4, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.19; IR (KBr) 3117, 1332, 1156, 1034 cm^{-1}; MS *m*/*z* 484 (MH^+). Anal. Calcd for $C_{23}H_{34}NO_6PS$: C, 57.13; H, 7.09. Found: C, 57.12; H, 7.01.

4.2. Crystal data for compound 8

X-ray crystal data of **8** were collected by Mac-Science DIP Image plate diffractometer. The structure was solved by a direct method using SIR97[12] and refined with a full matrix least-squares method.[13] Molecular formula=$C_{23}H_{34}NO_6PS$, M_r=483.55, monoclinic, space group=$P2_1/C$, a=13.0570 (3) Å, b=15.2600 (3) Å, c=16.0060 (3) Å, V=2547.50 (10) Å^3, T=100 (2) K, Z=4, D_x=1.261 mg m^{-3}, (Mo Kα)=0.71073 Å, μ=0.226 mm^{-1}, R=0.0538 over 5574 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 600772. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.3. Preparation of various α-aminophosphinates

4.3.1. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]but-3-enyl}phosphinate ((*R**,*R*$_P$*)-9 and (*S**,*R*$_P$*)-9).** This compound was prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol) and allyl bromide (85 μL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**9** and (*S**,*R*$_P$*)-**9** (200 mg, 90%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 2:1).

(*R**,*R*$_P$*)-**9**: A pale yellow oil; TLC R_f=0.34 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.23 (10H, m), 5.61–5.50 (1H, m), 5.04–4.96 (2H, m), 4.31–4.17 (2H, m), 3.99 (1H, ddd, *J*=3.3, 9.7, 9.7 Hz), 3.76–3.66 (4H, m), 2.90–2.79 (2H, m), 1.59 (3H, d, *J*=11.0 Hz), 1.33 (3H, t, *J*=7.1 Hz), 1.18 (3H, t, *J*=7.1 Hz), 1.15 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 135.9, 135.6–127.9 (aromatic), 117.2, 102.0 (d, J_{PC}=134.6 Hz), 63.3 (d, J_{PC}=96.2 Hz), 61.9 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.6 Hz), 57.7 (d, J_{PC}=4.9 Hz), 35.1, 21.0 (d, J_{PC}=12.2 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.27; IR (neat) 1639, 1618, 1155, 1032 cm^{-1}; MS *m*/*z* 444 (MH^+). HRMS calcd for $C_{25}H_{35}NO_4P$ (MH^+): 444.2304. Found: 444.2281.

(*S**,*R*$_P$*)-**9**: A pale yellow oil; TLC R_f=0.28 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.24 (10H, m), 5.63–5.51 (1H, m), 5.04–4.96 (2H, m), 4.32–4.18 (2H, m), 4.04–4.02 (1H, m), 3.75–3.61 (4H, m), 2.89–2.70 (2H, m), 1.38 (3H, d, *J*=11.1 Hz), 1.27 (3H, t, *J*=7.1 Hz), 1.18 (3H, t, *J*=7.0 Hz), 1.15 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4 (d, J_{PC}=2.5 Hz), 136.0, 117.2, 101.8 (d, J_{PC}=136.6 Hz), 62.0 (d, J_{PC}=6.8 Hz), 61.6 (d, J_{PC}=95.2 Hz), 58.2 (d, J_{PC}=4.5 Hz), 57.3 (d, J_{PC}=7.1 Hz), 35.2 (d, J_{PC}=1.9 Hz), 20.6 (d, J_{PC}=12.0 Hz), 16.8 (d, J_{PC}=4.8 Hz), 15.4, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.72; IR (neat) 1635, 1618, 1155, 1032 cm^{-1}; MS *m*/*z* 444 (MH^+). HRMS calcd for $C_{25}H_{35}NO_4P$ (MH^+): 444.2304. Found: 444.2299.

4.3.2. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-3-methylbut-3-enyl}phosphinate ((*R**,*R*$_P$*)-10 and (*S**,*R*$_P$*)-10).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and methallyl bromide (0.1 mL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**10** and (*S**,*R*$_P$*)-**10** (224 mg, 98%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=10:1 to 2:1).

(*R**,*R*$_P$*)-**10**: A colorless oil; TLC R_f=0.38 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.26 (10H, m), 4.68 (1H, s), 4.66 (1H, s), 4.32–4.19 (2H, m), 4.09–4.02 (1H, m), 3.75–3.62 (4H, m), 2.78 (2H, t, *J*=6.9 Hz), 1.60 (3H, d, *J*=11.1 Hz), 1.39 (3H, s), 1.35 (3H, t, *J*=7.1 Hz), 1.19 (3H, t, *J*=7.1 Hz), 1.16 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (d, J_{PC}=2.4 Hz), 135.6, 132.3–127.8 (aromatic), 114.0, 102.1 (d, J_{PC}=134.8 Hz), 61.9 (d, J_{PC}=96.2 Hz), 61.9 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.2 Hz), 57.7 (d, J_{PC}=4.2 Hz), 38.9, 22.3, 20.9 (d, J_{PC}=12.0 Hz), 16.6 (d, J_{PC}=5.1 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.75; IR (neat) 1649, 1620, 1155, 1034 cm^{-1}; MS *m*/*z* 458 (MH^+). HRMS calcd for $C_{26}H_{37}NO_4P$ (MH^+): 458.2460. Found: 458.2485.

(*S**,*R*$_P$*)-**10**: A colorless oil; TLC R_f=0.30 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.21 (10H, m), 4.71 (1H, s), 4.65 (1H, s), 4.24–4.18 (2H, m), 4.12–4.08 (1H, m), 3.82–3.64 (4H, m), 2.78 (2H, t, *J*=4.0 Hz), 1.44 (3H, d, *J*=10.9 Hz), 1.37 (3H, s), 1.25 (3H, t, *J*=7.1 Hz), 1.13 (3H, t, *J*=7.1 Hz), 1.10 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.9, 130.0–127.9 (aromatic), 114.2, 102.1 (d, J_{PC}=136.8 Hz), 62.0 (d, J_{PC}=7.3 Hz), 60.4 (d, J_{PC}=94.6 Hz), 58.4 (d, J_{PC}=4.6 Hz), 57.5 (d, J_{PC}=7.2 Hz), 38.9, 22.5, 20.6 (d, J_{PC}=11.7 Hz), 16.8 (d, J_{PC}=4.8 Hz), 15.4, 15.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.03; IR (neat) 1653, 1618, 1153, 1036 cm^{-1}; MS *m*/*z* 458 (MH^+). HRMS calcd for $C_{26}H_{37}NO_4P$ (MH^+): 458.2460. Found: 458.2443.

4.3.3. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]ethyl}phosphinate ((*R**,*R*$_P$*)-11 and (*S**,*R*$_P$*)-11).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and methyl iodide (62 μL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**6**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**11** and (*S**,*R*$_P$*)-**11** (161 mg, 77%). Analytical samples of individual isomers were obtained upon re-purification by preparative HPLC (EtOAc/MeOH=50:1).

(*R**,*R*$_P$*)-**11**: A colorless oil; TLC R_f=0.18 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.21 (10H, m), 4.09–4.03 (2H, m), 3.95 (1H, ddd, *J*=6.8, 6.8, 13.1 Hz), 3.75–3.56 (4H, m), 1.59 (3H, d, *J*=11.0 Hz), 1.47 (3H, dd, *J*=7.0, 15.5 Hz), 1.29 (3H, t, *J*=7.0 Hz), 1.16 (3H, t, *J*=7.1 Hz), 1.14 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (d, J_{PC}=2.0 Hz), 135.7–127.7 (aromatic), 101.8 (d, J_{PC}=133.4 Hz), 61.7 (d, J_{PC}=7.2 Hz), 58.1 (d, J_{PC}=97.0 Hz), 57.5 (d, J_{PC}=4.7 Hz), 57.4 (d, J_{PC}=6.9 Hz), 20.9 (d, J_{PC}=12.0 Hz), 16.6 (d, J_{PC}=5.0 Hz), 16.1 (d, J_{PC}=4.1 Hz), 15.5, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.62; IR (neat) 1618, 1155, 1039 cm^{-1}; MS *m*/*z* 418 (MH^+). HRMS calcd for $C_{23}H_{33}NO_4P$ (MH^+): 418.2147. Found: 418.2150.

(*S**,*R*$_P$*)-**11**: A colorless oil; TLC R_f=0.18 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.19 (10H, m), 4.31–4.24 (2H, m), 4.04 (1H, ddd, *J*=6.9, 6.9, 13.8 Hz), 3.79–3.49 (4H, m), 1.48 (3H, dd, *J*=6.9, 15.5 Hz), 1.41 (3H, d, *J*=10.8 Hz), 1.33 (3H, t, *J*=7.1 Hz), 1.12 (3H, t, *J*=7.1 Hz), 1.07 (3H, t, *J*=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2 (d, J_{PC}=2.1 Hz), 136.0–127.7 (aromatic), 101.6 (d, J_{PC}=135.7 Hz), 62.0 (d, J_{PC}=7.5 Hz), 58.1 (d, J_{PC}=4.5 Hz), 57.4 (d, J_{PC}=6.9 Hz), 56.8 (d, J_{PC}=100.0 Hz), 20.8 (d, J_{PC}=11.7 Hz), 16.8 (d, J_{PC}=4.8 Hz), 16.3 (d, J_{PC}=4.7 Hz), 15.4, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.09; IR (neat) 1616, 1153, 1034 cm^{-1}; MS

m/*z* 418 (MH^+). HRMS calcd for $C_{23}H_{33}NO_4P$ (MH^+): 418.2147. Found: 418.2136.

4.3.4. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]pentyl}phosphinate ((*R**,*R*$_P$*)-12 and (*S**,*R*$_P$*)-12).** To a solution of **4** (200 mg, 0.5 mmol) in THF (2.5 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 *n*-butyl bromide (107 μL, 1.0 mmol) and stirred for 24 h at 0 °C. 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 column chromatography (hexane/EtOAc=10:1 to 2:1) to give a mixture of (*R**,*R*$_P$*)-**12** and (*S**,*R*$_P$*)-**12** (115 mg, 50%). Analytical samples of individual isomers were obtained upon re-purification by preparative HPLC ($CHCl_3$/MeOH=50:1).

(*R**,*R*$_P$*)-**12**: A colorless oil; TLC R_f=0.38 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.24 (10H, m), 4.27–4.16 (2H, m), 3.95 (1H, ddd, *J*=2.7, 2.7, 10.2 Hz), 3.79–3.49 (4H, m), 2.17–2.03 (2H, m), 1.37 (3H, d, *J*=10.9 Hz), 1.25 (3H, t, *J*=7.1 Hz), 1.22–1.17 (2H, m), 1.14 (3H, t, *J*=7.1 Hz), 1.12 (3H, t, *J*=7.1 Hz), 1.03–0.95 (2H, m), 0.83 (3H, t, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (d, J_{PC}=2.8 Hz), 136.7–128.4 (aromatic), 102.3 (d, J_{PC}=135.4 Hz), 62.3 (d, J_{PC}=94.4 Hz), 62.3 (d, J_{PC}=7.4 Hz), 58.7 (d, J_{PC}=4.4 Hz), 57.8 (d, J_{PC}=7.1 Hz), 30.6 (d, J_{PC}=2.4 Hz), 29.6 (d, J_{PC}=13.1 Hz), 22.9, 21.0 (d, J_{PC}=12.0 Hz), 17.3 (d, J_{PC}=4.8 Hz), 15.8, 15.6, 14.3; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.77; IR (neat) 1616, 1153, 1034 cm^{-1}; MS *m*/*z* 460 (MH^+). HRMS calcd for $C_{26}H_{38}NO_4P$ (MH^+): 460.2617. Found: 460.2627.

(*S**,*R*$_P$*)-**12**: A colorless oil; TLC R_f=0.32 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.24 (10H, m), 4.25–4.16 (2H, m), 3.95 (1H, ddd, *J*=2.6, 2.6, 10.2 Hz), 3.78–3.49 (4H, m), 2.17–2.00 (2H, m), 1.37 (3H, d, *J*=10.9 Hz), 1.25 (3H, t, *J*=7.1 Hz), 1.23–1.16 (2H, m), 1.14 (3H, t, *J*=7.1 Hz), 1.08 (3H, t, *J*=7.1 Hz), 1.01–0.95 (2H, m), 0.83 (3H, t, *J*=7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (d, J_{PC}=2.8 Hz), 136.1–127.9 (aromatic), 102.1 (d, J_{PC}=133.5 Hz), 63.8 (d, J_{PC}=95.8 Hz), 61.9 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.4 Hz), 57.7 (d, J_{PC}=4.8 Hz), 30.2, 29.4 (d, J_{PC}=12.9 Hz), 22.5, 21.0 (d, J_{PC}=12.1 Hz), 16.7 (d, J_{PC}=4.9 Hz), 15.5, 15.2, 13.9; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.16; IR (neat) 1618, 1155, 1034 cm^{-1}; MS *m*/*z* 460 (MH^+). HRMS calcd for $C_{26}H_{38}NO_4P$ (MH^+): 460.2617. Found: 460.2620.

4.3.5. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-2-methylpropyl}phosphinate ((*R**,*R*$_P$*)-13 and (*S**,*R*$_P$*)-13).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and *iso*-propyl iodide (100 μL, 1.0 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**12**. Purification of the residue by column chromatography (hexane/EtOAc=5:1 to 1:1) gave a mixture of (*R**,*R*$_P$*)-**13** and (*S**,*R*$_P$*)-**13** (104 mg, 47%). Analytical samples of individual isomers were obtained upon re-purification by preparative HPLC ($CHCl_3$/MeOH=50:1).

(*R**,*R*$_P$*)-**13**: A colorless oil; TLC R_f=0.37 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.26 (10H, m), 4.29–4.13 (2H, m), 3.82–3.60 (4H, m), 3.70 (1H, dd, *J*=3.5, 3.5 Hz), 2.64–2.54 (1H, m), 1.52 (3H, d, *J*=11.0 Hz), 1.31 (3H, t, *J*=7.1 Hz), 1.16 (3H, t, *J*=6.9 Hz), 1.14 (3H, t, *J*=7.0 Hz), 1.04 (3H, d, *J*=6.7 Hz), 0.92 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9 (d, J_{PC}=2.9 Hz), 135.8–127.9 (aromatic), 102.0 (d, J_{PC}=134.0 Hz), 68.9 (d, J_{PC}=94.4 Hz), 61.6 (d, J_{PC}=7.4 Hz), 57.8 (d, J_{PC}=4.6 Hz), 57.7 (d, J_{PC}=6.9 Hz), 30.2, 21.7 (d, J_{PC}=8.9 Hz), 20.8 (d, J_{PC}=12.3 Hz), 19.4 (d, J_{PC}=6.4 Hz), 16.7 (d, J_{PC}=5.1 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.63; IR (neat) 1616, 1155, 1034 cm^{-1}; MS *m*/*z* 446 (MH^+). HRMS calcd for $C_{25}H_{37}NO_4P$ (MH^+): 446.2460. Found: 446.2479.

(*S**,*R*$_P$*)-**13**: A colorless oil; TLC R_f=0.37 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.26 (10H, m), 4.25–4.16 (2H, m), 3.87 (1H, dd, *J*=3.1, 3.1 Hz), 3.78–3.50 (4H, m), 2.64–2.54 (1H, m), 1.36 (3H, d, *J*=12.8 Hz), 1.25 (3H, t, *J*=6.9 Hz), 1.24 (3H, d, *J*=6.1 Hz), 1.12 (3H, t, *J*=7.0 Hz), 1.04 (3H, t, *J*=7.1 Hz), 0.82 (3H, d, *J*=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8 (d, J_{PC}=2.8 Hz), 136.0–127.9 (aromatic), 101.9 (d, J_{PC}=134.9 Hz), 66.2 (d, J_{PC}=93.8 Hz), 61.7 (d, J_{PC}=7.3 Hz), 58.4 (d, J_{PC}=3.9 Hz), 57.2 (d, J_{PC}=7.6 Hz), 30.3, 22.2 (d, J_{PC}=12.8 Hz), 20.6 (d, J_{PC}=12.1 Hz), 18.5 (d, J_{PC}=3.1 Hz), 16.8 (d, J_{PC}=4.9 Hz), 15.4, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.14; IR (neat) 1616, 1153, 1034 cm^{-1}; MS *m*/*z* 446 (MH^+). HRMS calcd for $C_{25}H_{37}NO_4P$ (MH^+): 446.2460. Found: 446.2457.

4.3.6. (1*R,*R*$_P$*)- and (1*S**,*R*$_P$*)-Ethyl 1,1-diethoxyethyl{1-[(diphenylmethylene)amino]-3-methylbutyl}phosphinate ((*R**,*R*$_P$*)-14 and (*S**,*R*$_P$*)-14).** These compounds were prepared from **4** (200 mg, 0.5 mmol), 1.0 M THF solution of LHMDS (0.75 mL, 0.75 mmol), and *iso*-butyl iodide (0.29 mL, 2.5 mmol) in an analogous manner to that for (*R**,*R*$_P$*)-**12**. Purification of the residue by flash column chromatography ($CHCl_3$) gave a mixture of (*R**,*R*$_P$*)-**14** and (*S**,*R*$_P$*)-**14** (162 mg, 71%). Analytical samples of individual isomers were obtained upon re-purification by flash column chromatography (hexane/EtOAc=5:1 to 2:1).

(*R**,*R*$_P$*)-**14**: A pale yellow oil; TLC R_f=0.33 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.12 (10H, m), 4.18–4.02 (2H, m), 3.90 (1H, ddd, *J*=2.5, 9.8, 9.8 Hz), 3.60–3.44 (4H, m), 1.92–1.85 (2H, m), 1.80–1.71 (1H, m), 1.44 (3H, d, *J*=11.0 Hz), 1.20 (3H, t, *J*=7.1 Hz), 1.04 (3H, t, *J*=7.0 Hz), 0.99 (3H, t, *J*=7.1 Hz), 0.71 (3H, d, *J*=6.6 Hz), 0.38 (3H, d, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 130.0–127.9 (aromatic), 102.2 (d, J_{PC}=134.2 Hz), 62.2 (d, J_{PC}=94.9 Hz), 62.0 (d, J_{PC}=7.3 Hz), 57.8 (d, J_{PC}=6.4 Hz), 57.7 (d, J_{PC}=4.8 Hz), 39.8, 24.8 (d, J_{PC}=12.6 Hz), 23.7, 21.3, 20.6 (d, J_{PC}=12.1 Hz), 16.7 (d, J_{PC}=5.0 Hz), 15.5, 15.2; ^{31}P NMR (162 MHz, $CDCl_3$) δ 43.15; IR (neat) 1618, 1155, 1034 cm^{-1}; MS *m*/*z* 460 (MH^+). HRMS calcd for $C_{26}H_{39}NO_4P$ (MH^+): 460.2617. Found: 460.2641.

4.3.7. Ethyl 3,3-diphenylpropyl(1,1-diethoxyethyl)phosphinate (15). To a stirred suspension of 60% NaH (420 mg,

10.5 mmol) in DMF (25 mL) was added a solution of **1** (2.19 g, 10.0 mmol) in THF (10 mL). After stirring for 1 h at 0 °C, stirring was continued for 3 h at room temperature. To the mixture was added a solution of 3,3-diphenylpropyl bromide (4.19 g, 15 mmol) in THF (15 mL) at 0 °C and stirred for 12 h at room temperature. The mixture 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 **15** (2.32 g, 57%). A colorless oil; TLC R_f=0.33 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.16 (10H, m), 4.29–4.10 (2H, m), 3.93 (1H, t, J=7.9 Hz), 3.80–3.56 (4H, m), 2.52–2.34 (2H, m), 1.80–1.55 (2H, m), 1.42 (3H, d, J=11.1 Hz), 1.30 (3H, t, J=7.1 Hz), 1.17 (3H, t, J=6.8 Hz), 1.15 (3H, t, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9 (d, J_{PC}= 17.3 Hz), 128.4–126.2 (aromatic), 101.1 (d, J_{PC}=138.1 Hz), 61.3 (d, J_{PC}=6.7 Hz), 57.9 (d, J_{PC}=4.7 Hz), 57.4 (d, J_{PC}=7.0 Hz), 52.0 (d, J_{PC}=14.4 Hz), 26.9 (d, J_{PC}=3.9 Hz), 24.2 (d, J_{PC}=86.3 Hz), 20.4 (d, J_{PC}=12.4 Hz), 16.6 (d, J_{PC}=5.3 Hz), 15.4, 15.1; ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.09; IR (neat) 1158, 1038 cm^{-1}; MS *m/z* 405 (MH^+). HRMS calcd for $C_{23}H_{34}O_4P$ (MH^+): 405.2195. Found: 405.2181.

4.3.8. (1*R,R_P*)- and (1*S**,R_P*)-Ethyl 1-benzyl-3,3-diphenylpropyl(1,1-diethoxyethyl)phosphinate ((*R**,R_P*)-16 and (*S**,R_P*)-16).** These compounds were prepared from **15** (210 mg, 0.49 mmol), 1.0 M THF solution of LHMDS (0.74 mL, 0.74 mmol), and benzyl bromide (0.12 mL, 0.98 mmol) in an analogous manner to that for (*R**,R_P*)-**12**. Purification of the residue by flash column chromatography (hexane/EtOAc=4:1 to 1:1) gave a mixture of (*R**,R_P*)-**16** and (*S**,R_P*)-**16** (108 mg, 45%) in a ratio of 1:1. A colorless oil; TLC R_f=0.30 (hexane/EtOAc=1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–6.77 (15H, m), 4.36–4.06 (2H, m), 4.03–3.95 (0.5H, m), 3.92–3.88 (0.5H, m), 3.79–3.57 (4H, m), 3.49–3.43 (0.5H, m), 3.40–3.34 (0.5H, m), 2.83–2.57 (2H, m), 2.18–2.03 (2H, m), 1.45 (1.5H, d, J=10.9 Hz), 1.38 (1.5H, t, J=7.1 Hz), 1.37 (3H, d, J=11.3 Hz), 1.28–1.13 (7.5H, m); ^{31}P NMR (162 MHz, $CDCl_3$) δ 49.89, 48.88; IR (neat) 1153, 1035 cm^{-1}; MS *m/z* 495 (MH^+). HRMS calcd for $C_{30}H_{40}O_4P$ (MH^+): 495.2640. Found: 495.2645.

4.3.9. (1*R,R_P*)-Ethyl 1-{[(4-methylphenyl)sulfonyl]-amino}-2-phenylethylphosphinate (18).** To a solution of (*R**,R_P*)-**8** (60 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL) was added EtOH (50 μL) and TMSCl (32 μL, 0.24 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 **18** (37 mg, 83%). Colorless crystals; mp 121–124 °C; TLC R_f=0.28 ($CHCl_3$/MeOH=20:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.02 (9H, m), 7.12 (1H, d, J=570.7 Hz), 4.12–4.06 (2H, m), 3.74 (1H, ddd, J=5.7, 9.0, 16.5 Hz), 3.04 (1H, ddd, J=5.6, 9.5, 14.6 Hz), 2.89 (1H, ddd, J=9.3, 12.0, 14.1 Hz), 2.37 (3H, s), 1.30 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 137.2, 135.5, 129.6–126.4 (aromatic), 63.3 (d, J_{PC}=7.4 Hz), 53.5 (d, J_{PC}=109.3 Hz), 33.1, 21.5, 16.1 (d, J_{PC}=5.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.83; IR (KBr) 3087, 1331, 1161, 1043 cm^{-1}; MS *m/z* 368 (MH^+). HRMS calcd for $C_{17}H_{23}NO_4PS$ (MH^+): 368.1085. Found: 368.1080.

Acknowledgements

This work was partially supported by a grant for private universities from The Promotion and Mutual Aid Corporation for Private Schools of Japan and the Ministry of Education, Culture, Sports, Science, and Technology. The authors wish to thank Mr. Haruhiko Fukaya (the analytical center of this university) for the X-ray crystallographic analysis.

References and notes

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.; Wiley: Chichester, UK, 2000.
3. For a review, see: Collinsová, M.; Jirácek, J. *Curr. Med. Chem.* **2000**, *7*, 629.
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.
5. Baylis, E. K.; Campbell, C. D.; Dingwall, J. G. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2845.
6. (a) Jiao, X.-Y.; Verbruggen, C.; Borloo, M.; Bollaert, W.; Groot, A. D.; Dommisse, R.; Haemers, A. *Synthesis* **1994**, 23; (b) Boyd, E. A.; Chan, W. C.; Loh, V. M., Jr. *Tetrahedron Lett.* **1996**, *37*, 1647.
7. McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319.
8. (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.
9. Hoppe, D.; Beckmann, L. *Liebigs Ann. Chem.* **1979**, 2066.
10. (a) Denmark, S. E.; Chen, C.-T. *J. Org. Chem.* **1994**, *59*, 2922; (b) Denmark, S. E.; Chen, C.-T. *J. Am. Chem. Soc.* **1995**, *117*, 11879.
11. (a) Hanessian, S.; Bennani, Y. L.; Delome, D. *Tetrahedron Lett.* **1990**, *31*, 6461; (b) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465; (c) Hanessian, S.; Bennani, Y. L.; Hervé, Y. *Synlett* **1993**, 35.
12. 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.
13. Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.