A Versatile and Highly Stereoselective Synthesis of Diethyl (1-Aminoalkyl)thiophosphonates

Zhilong Chen, Jinfeng Li, Chengye Yuan*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-lin Rd, Shanghai, 200032, P. R. of China
Fax +86(21)54925379; E-mail: yuancy@mail.sioc.ac.cn

Received 8 June 2009; revised 21 July 2009

Abstract: A series of chiral diethyl (1-aminoalkyl)thiophosphonates was synthesized in high yield and excellent enantioselectivity by nucleophilic addition of diethyl thiophosphonate to *N*-(*tert*-butylsulfinyl)imines under mild conditions. There is no evidence indicating that the reaction is influenced by electronic or steric effects of the substrates.

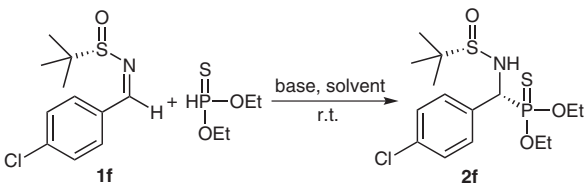
Key words: nucleophilic additions, thiophosphonates, imines, sulfinamides, sulfonamides

As phosphorus analogues of natural α-aminocarboxylic acids, (1-aminoalkyl)phosphonates have demonstrated significant biological activities.[1] These bioactivities are, however, closely related to the stereoconfiguration of the chiral atom of the molecule. Consequently, the asymmetric synthesis of such compounds is attracting much attention amongst organic chemists.[2–4]

As reported by our laboratory, induced asymmetric addition of dialkyl phosphonates to chiral aldimines is one of the convenient methods for the synthesis of optically active (1-aminoalkyl)phosphonates. It is important to note that, initiated by Davis,[5] and then modified and significantly improved by Ellman, *N*-(*tert*-butylsulfinyl)imines[6] have become extremely useful chiral auxiliaries for the preparation of optically active amines and their derivatives. As found by our group very recently,[3a] diethyl phosphonates smoothly undergo nucleophilic addition with Ellman's sulfinylimine, affording chiral (1-aminoalkyl)phosphonates in excellent chemical yield and high enantioselectivity.[5] In this protocol, the reaction conditions were remarkably simplified: potassium carbonate could be used instead of lithium hexamethyldisilazide as required in the standard procedure, and, consequently, the reaction temperature could be changed from –78 °C to ambient temperature. It should be emphasized that this is the first time that the reaction involving nucleophilic addition to Ellman's sulfinylimine could be carried out at room temperature. This special report greatly aroused our interest, and we presumed that the weak P–H bond may be stable at room temperature and suited to a sulfinylimine. On the basis of this postulation, Zhang[7] used ethyl (diethoxymethyl)methylphosphinate as another kind of nucleophile containing a P–H bond. As expected, the reaction took place with the slightly stronger base rubidium carbonate, providing optically pure (1-aminoalkyl)-*H*-phosphinates with two stereogenic atoms. These experimental data support Hu's report that the stability and nucleophilicity of the nucleophiles are critical for the reaction involving sulfinylimines.[8]

Replacement of the phosphoryl oxygen of the (1-aminoalkyl)phosphonates by a sulfur atom would result in another group of potent biologically active molecules, namely dialkyl (1-aminoalkyl)thiophosphonates. Thompson's group[9] described a method for the synthesis of dialkyl (1-aminoalkyl)thiophosphonates on the basis of a diastereoselective addition of dimethyl thiophosphonates to benzaldimines bearing chiral auxiliary groups. Unfortunately, both the chemical yield and the diastereoselectivity of that method are not high enough for the procedure to be used synthetically. To the best of our knowledge, this is the only paper that describes the asymmetric synthesis of (1-aminoalkyl)thiophosphonates. Herein we report a convenient and highly stereoselective synthetic protocol for the preparation of chiral diethyl (1-aminoalkyl)thiophosphonates by nucleophilic addition of diethyl thiophosphonate to Ellman's sulfinylimine. In comparison with Thompson's report, our method provides much better chemical yields and remarkably higher stereoselectivity.

In the initial experiments, (*S*)-*N*-(*tert*-butylsulfinyl)-*p*-chlorobenzylideneamine (**1f**) was chosen as the model substrate to study the reaction (Scheme 1, Table 1). With diethyl thiophosphonate as the nucleophile, potassium carbonate as the base, and dichloromethane as the solvent, the reaction proceeded smoothly, and was completed at room temperature within 24 hours. To our delight, the reaction afforded the desired product **2f** in extremely high chemical yield (99%) and excellent enantioselectivity (92%) (entry 1). From Table 1 it can be seen that other bases were ineffective in promoting the reaction (entries 2–4), usually requiring longer reaction times. In compari-



Scheme 1

SYNTHESIS 2009, No. 23, pp 3930–3940
Advanced online publication: 19.10.2009
DOI: 10.1055/s-0029-1217054; Art ID: F11709SS

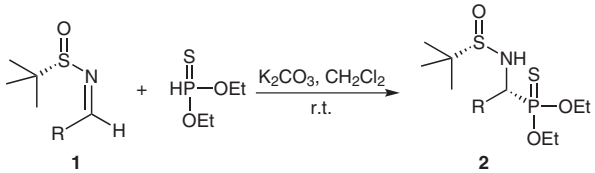
son with our previous research involving dimethylphosphinates and/or ethyl diethoxymethylphosphinates,[3a,7] it seems that a weaker base should increase the enantioselectivity of the reaction. However, this was not observed when weaker bases were used. Other solvents, such as diethyl ether (entry 5), toluene (entry 6), tetrahydrofuran (entry 7), and *n*-hexane (entry 8), did promote the reaction, but they afforded no better results than dichloromethane. According to these optimization results, we decided to select the reaction conditions of entry 1 as standard for studying the scope and applications with different sulfinylimines.

Table 1 Optimization of the Reaction Conditions[a]

Entry	Base	Solvent	Time (h)	Yield[b] (%)	de[c] (%)
1	K_2CO_3	CH_2Cl_2	24	99	92
2	Na_2CO_3	CH_2Cl_2	120	99	71
3	Li_2CO_3	CH_2Cl_2	120	–[d]	–[d]
4	KF	CH_2Cl_2	120	83	71
5	K_2CO_3	Et_2O	12	99	65
6	K_2CO_3	toluene	12	70	78
7	K_2CO_3	THF	12	99	44
8	K_2CO_3	*n*-hexane	12	99	72

[a] Reagents and conditions: imine (0.5 mmol), diethyl thiophosphonate (2.0 equiv), base (2.0 equiv), in air.
[b] Isolated yield.
[c] The de was determined by ^{31}P NMR spectroscopy of the crude products.
[d] No reaction was observed.

Further investigation into the reaction was carried out under the standard conditions (Scheme 2, Table 2). A variety of structurally diverse (*S*)-*N*-(*tert*-butylsulfinyl) aldimines **1** were tested, including aromatic and aliphatic ones. All reactions gave (1-aminoalkyl)thiophosphonates **2** in high yields and excellent enantioselectivities. It is noteworthy that there were few influences on the yield and enantioselectivity concerning the electronic or steric properties of the substrates. Slightly better enantioselectivities could be observed in the electron-rich aromatic systems compared to the electron-poor ones; alkyl substrates gave better results (entries 12 and 13, >95% de). Note that products **2l** and **2m** are the analogues of valine and phenylalanine, respectively. In the case of an unsaturated system (entry 14), only 1,2-addition products were afforded.



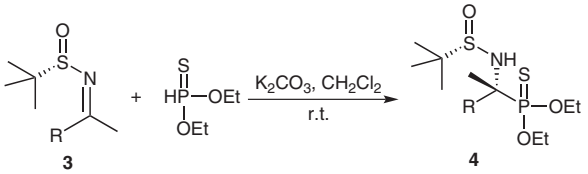
Scheme 2

Table 2 Addition of Diethyl Thiophosphonate to (*S*)-*N*-(*tert*-Butylsulfinyl) Aldimines **1**[a]

Entry	Product	R	Time (h)	Yield[b] (%)	de[c] (%)	^{31}P NMR (δ)
1	**2a**	Ph	24	99	94	92.1
2	**2b**	4-MeC_6H_4	36	80	>95	92.2
3	**2c**	4-PhC_6H_4	24	99	92	91.9
4	**2d**	2-naphthyl	48	88	94	91.8
5	**2e**	4-FC_6H_4	24	98	94	91.6
6	**2f**	4-ClC_6H_4	24	99	94	91.2
7	**2g**	4-BrC_6H_4	24	99	92	91.0
8	**2h**	4-MeOC_6H_4	36	99	94	92.2
9	**2i**	4-$Me_2N$$C_6H_4$	24	99	>95	92.6
10	**2j**	4-MeSC_6H_4	36	99	90	90.5
11	**2k**	2-HSC_6H_4	24	99	>95	89.8
12	**2l**	Bn	12	87	>95	96.5
13	**2m**	*i*-Pr	12	98	>95	96.4
14	**2n**	*E*-CH=CHPh	24	84	>95	91.7

[a] Reagents and conditions: imine (0.5 mmol), diethyl thiophosphonate (2.0 equiv), K_2CO_3 (2.0 equiv).
[b] Isolated yield.
[c] The de was determined by ^{31}P NMR spectroscopy of the crude products.

On the basis of our previous work, we supposed that under the same conditions, (*S*)-*N*-(*tert*-butylsulfinyl) methyl ketimines might also react with diethyl thiophosphonate (Scheme 3, Table 3). A similar study was carried out with **3a** as our model substrate (Table 3, entry 1). To our delight, we found that the desired product **4a** was obtained in both good yield (99%) and excellent enantioselectivity (>95%, by ^{31}P NMR of the crude product). Further studies on this reaction were carried out, with the results summarized in Table 3. As expected, good yields and enantioselectivities were observed with either electron-donating or electron-withdrawing groups of the aromatic system. Other substrates also gave excellent results.



Scheme 3

To confirm the absolute configuration of the products, a single-crystal X-ray analysis of **4g** was carried out.[10] As shown in Figure 1, the configuration of the chiral carbon atom of the product is proved to be *R*.

Table 3 Addition of Diethyl Thiophosphonate to (*S*)-*N*-(*tert*-Butylsulfinyl) Ketimines **3**[a]

Entry	Product	R	Time (h)	Yield[b] (%)	de[c] (%)	^{31}P NMR (δ)
1	**4a**	Ph	24	99	>95	95.7
2	**4b**	4-MeC_6H_4	24	80	>95	95.9
3	**4c**	4-PhC_6H_4	36	95	>95	95.5
4	**4d**	2-naphthyl	24	88	>95	95.7
5	**4e**	4-FC_6H_4	18	99	>95	95.2
6	**4f**	4-ClC_6H_4	24	90	>95	94.9
7	**4g**	4-BrC_6H_4	12	99	>95	94.7
8	**4h**	4-morpholinophenyl	36	99	>95	96.0
9	**4i**	4-O_2NC_6H_4	12	99	>95	93.7
10	**4j**	4-NCC_6H_4	12	99	>95	94.0
11	**4k**	2-HSC_6H_4	24	99	>95	93.8
12	**4l**	2-pyridyl	18	98	>95	100.3
13	**4m**	*E*-CH=CHPh	24	94	>95	95.1
14	**4n**	*n*-Bu	18	87	>95	94.2

[a] Reagents and conditions: imine (0.5 mmol), diethyl thiophosphonate (1.0 mmol), K_2CO_3 (1.0 mmol).
[b] Isolated yield.
[c] The de was determined by ^{31}P NMR spectroscopy of the crude products.

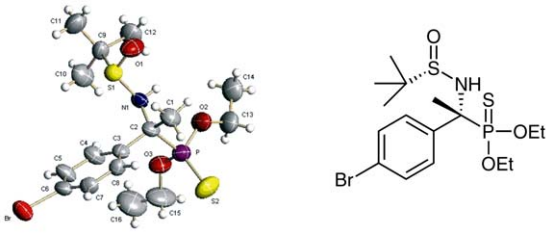
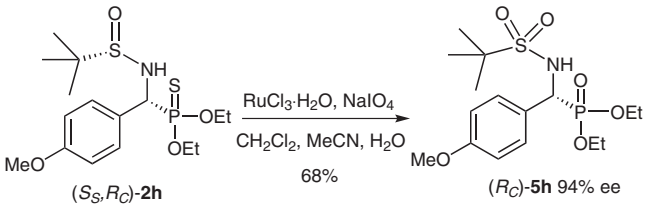


Figure 1 X-ray crystal structure and absolute configuration of (S_S,R_C)-**4g**

To determine the accurate de values of the products, we oxidized (S_S,R_C)-**2h** with ruthenium(III) chloride hydrate and sodium periodate (Scheme 4).[11] Surprisingly, in addition to the *tert*-butylsulfinyl group, the thiophosphoryl (P=S) group was also oxidized to phosphoryl (P=O)! This reaction is therefore a convenient approach to converting (1-aminoalkyl)thiophosphonates into the corresponding (1-aminoalkyl)phosphonates. Thompson reported their attempts to oxidize thiophosphoryl (P=S) to phosphoryl (P=O) with various oxidation agents: *m*-chloroperoxybenzoic acid, *tert*-butyl hydroperoxide, monoperoxyphthalic acid, magnesium salt (MMPP), and hydrogen peroxide. Unfortunately, **5h** only formed in low yield (29%) (Scheme 4), and the enantiomeric excess of the oxidation product (R_C)-**5h** was determined by chiral HPLC. The high ee value indicates that this synthetic method is a general and convenient route to optically pure [1-(sulfonylamino)alkyl]phosphonates.



Scheme 4 Conversion of a [1-(*tert*-butylsulfinylamino)alkyl]thiophosphonate into the corresponding [1-(*tert*-butylsulfonylamino)alkyl]phosphonate

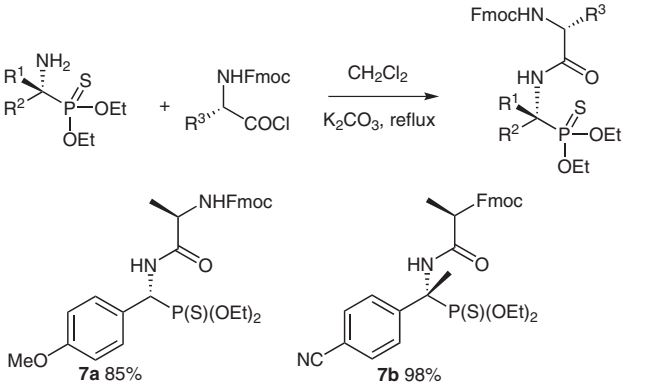
Compounds **2** and **4** can easily be converted into the corresponding (1-aminoalkyl)thiophosphonates (Scheme 5, Table 4). Initially, the reaction was carried out under reflux with 6 N hydrochloric acid, but this failed to provide the product, and we found that the reactant had decomposed. After careful examination and analysis, we concluded that the conditions might have been too harsh. The high acid concentration and reflux very probably led to the decomposition of the reactant. Therefore, we de-

Scheme 5

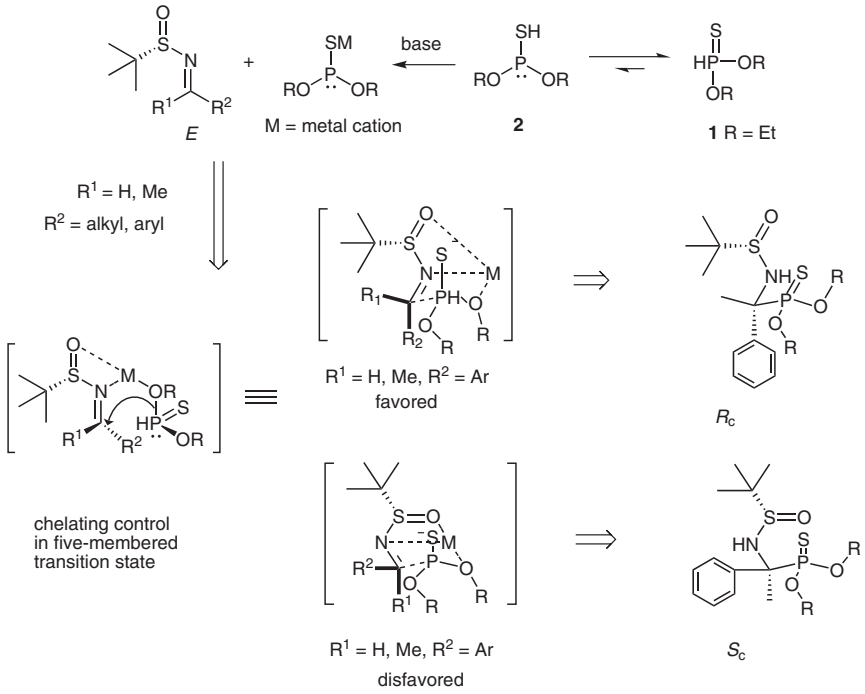
Table 4 Synthesis of Diethyl (1-Aminoalkyl)thiophosphonates **6**

Entry	Product	R^1	R^2	Yield[a] (%)	ee[b] (%)
1	**6a**	H	Ph	95	94
2	**6b**	H	4-MeOC_6H_4	97	>95
3	**6c**	Me	4-BrC_6H_4	97	>95
4	**6d**	Me	4-NCC_6H_4	98	>95

[a] Isolated yield.
[b] The ee value depends on the ee value obtained in the formation of compound **2** or **4**.



Scheme 6 Synthesis of peptide or amide linkages with (1-aminoalkyl)thiophosphonates



Scheme 7 Postulated mechanism

creased the concentration of the hydrochloric acid, and the reaction was carried out at room temperature, and, finally, positive results were obtained.

Furthermore, peptide or amide linkage could be established with (1-aminoalkyl)thiophosphonates in excellent yields, as demonstrated in Scheme 6.

It was assumed that the mechanism of the reaction might be associated with a chelating effect. The nucleophilic addition occurred in favor of the bigger function group R^2 occupying the equatorial position and therefore resulted in the R_C products, as indicated in Scheme 7.

In summary, we have reported for the first time a facile and convenient synthetic method for the preparation of chiral (1-aminoalkyl)thiophosphonates in excellent yields and high enantioselectivities on the basis of nucleophilic addition of dialkyl thiophosphonates to Ellman's imine.

All reactions were performed under a N_2 or argon atmosphere, unless indicated otherwise. All reagents were purchased from commercial sources and used as received. THF was freshly distilled over Na. Column chromatography was performed over silica gel (300–400 mesh). All yields given refer to isolated yields. IR spectra were obtained on a Shimadzu IR-440 spectrometer. ^{1}H NMR spectra (300 MHz) were recorded on a Bruker AM-300 spectrometer with $CDCl_3$ as solvent and TMS as internal standard, unless indicated otherwise. ^{13}C NMR spectra (100 MHz) were recorded on a Bruker AM-400 spectrometer with $CDCl_3$ as solvent, unless indicated otherwise. ^{19}F NMR spectra (282 MHz) were recorded on a Bruker AM-300 spectrometer with $CDCl_3$ as solvent and TFA as internal standard, downfield shifts being designated as negative, unless indicated otherwise. ^{31}P NMR (100 MHz) spectra were recorded on a Bruker AM-400 spectrometer with $CDCl_3$ as solvent and 85% H_3PO_4 as internal standard, unless indicated otherwise. Mass spectra were recorded at 2010 eV on a Hewlett-Packard and HP 5989A apparatus. HRMS data were recorded on a MAT 8430 spectrometer. Elemental analysis was conducted on a Heraeus Rapid-CHNO apparatus. Optical rotation values were measured on a Perkin-Elmer 241 M instrument. All reactions were monitored with the aid of TLC. Diethyl thiophosphonate,[9] (*S*)-*N*-(*tert*-butylsulfinyl) aldimine **1**,[3] and (*S*)-*N*-(*tert*-butylsulfinyl) ketimine **3**[7,12] were prepared according to literature procedures, and the spectroscopic data of **1**[3] and **3**[7,12] were identical to those provided in the literature.

Stereoselective Synthesis of Diethyl (S_S,R_C)-(+)-1-(*tert*-Butylsulfinylamino)alkylthiophosphonates (S_S,R_C)-2; General Procedure

The appropriate imine **1** (0.5 mmol) was added to a 20-mL Schlenk flask containing diethyl thiophosphonate (158 mg, 1 mmol) and K_2CO_3 (138 mg, 1 mmol) in CH_2Cl_2 (2.5 mL) at r.t. The mixture was then stirred for 24 h while carefully monitored by TLC. After the reaction had gone to completion, H_2O (5 mL) was added to quench it. Then the organic layer was separated and the aqueous layer was washed with Et_2O (3 × 10 mL). The organic layer was again washed with brine (3 × 10 mL) and dried overnight (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel); this afforded the corresponding pure (S_S,R_C)-**2**.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(phenyl)methyl]thiophosphonate (2a)

Colorless oil; yield: 182 mg (99%); $[\alpha]_D^{25}$ +128.3 (*c* 0.99, $CHCl_3$).

IR (KBr): 3231, 2981, 1494, 1475, 1455, 1052 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 5 H), 4.77 (dd, *J* = 15.7, 3 Hz, 1 H), 4.16 (dd, *J* = 9.3, 3.0 Hz, 1 H), 4.10–4.19 (m, 2 H), 3.90–3.96 (m, 1 H), 3.80–3.85 (m, 1 H), 1.32 (t, *J* = 3.6 Hz, 3 H), 1.28 (s, 9 H), 1.13 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.0 (d, *J* = 4.5 Hz, 1 C), 129.2 (d, *J* = 6.0 Hz, 2 C), 128.3 (d, *J* = 3.7 Hz, 1 C), 128.0 d, *J* = 2.9 Hz, 2 C), 64.1 (d, *J* = 6.7 Hz, 1 C), 63.9 (d, *J* = 7.5 Hz, 1 C), 60.5 (d, J_{PC} = 118.3 Hz, 1 C), 56.1 (s, 1 C), 22.5 (s, 3 C), 16.1 (d, *J* = 6.7 Hz, 1 C), 15.8 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 92.1 (s, 1 P).

MS (EI): *m*/*z* = 364.1 $[M + H]^+$, 386.2 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{26}NO_3PS$: C, 49.57; H, 7.21; N, 3.85. Found: C, 49.77; H, 7.21; N, 3.69.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(4-tolyl)methyl]thiophosphonate (2b)

Colorless oil; yield: 151 mg (80%); $[\alpha]_D^{25}$ +113.5 (*c* 1.00, $CHCl_3$).

IR (KBr): 3228, 2980, 1514, 1022, 832 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 7.5 Hz, 2 H), 7.25 (d, *J* = 7.5 Hz, 2 H), 4.74 (dd, *J* = 15.3, 3.0 Hz, 1 H), 4.42 (dd, *J* = 8.1, 3.0 Hz, 1 H), 4.09–4.19 (m, 2 H), 3.92–4.01 (m, 1 H), 3.79–3.88 (m, 1 H), 2.35 (s, 3 H), 1.27–1.32 (m, 3 H), 1.22 (s, 9 H), 1.15 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (s, 1 C), 130.0 (d, *J* = 5.2 Hz, 1 C), 129.2 (d, *J* = 5.2 Hz, 2 C), 128.8 (d, *J* = 2.2 Hz, 2 C), 64.1 (d, *J* = 7.4 Hz, 1 C), 63.9 (d, *J* = 7.4 Hz, 1 C), 60.5 (d, J_{PC} = 119.9 Hz, 1 C), 56.0 (s, 1 C), 22.6 (s, 3 C), 22.1 (s, 1 C), 16.1 (d, *J* = 6.7 Hz, 1 C), 16.0 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 92.2 (s, 1 P).

ESI-MS: *m*/*z* = 378.1 $[M + H]^+$, 400.1 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{28}NO_3PS_2$: C, 50.91; H, 7.48; N, 3.71. Found: C, 50.66; H, 7.49; N, 3.58.

Diethyl (S_S,R_C)-(+)-[(Biphenyl-4-yl)(*tert*-butylsulfinylamino)methyl]thiophosphonate (2c)

Colorless solid; yield: 215 mg (99%); mp 115–117 °C; $[\alpha]_D^{25}$ +102.2 (*c* 1.00, $CHCl_3$).

IR (KBr): 3230, 2987, 1488, 1390, 1071, 1013, 972, 774 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.62 (m, 4 H), 7.41–7.48 (m, 4 H), 4.82 (dd, *J* = 15.7, 3 Hz, 1 H), 4.49 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.12–4.22 (m, 2 H), 3.86–4.01 (m, 1 H), 3.80–3.85 (m, 1 H), 1.32 (t, *J* = 3.0 Hz, 3 H), 1.30 (s, 9 H), 1.16 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.2 (d, *J* = 3.7 Hz, 1 C), 140.5 (s, 1 C), 133.0 (d, *J* = 5.2 Hz, 1 C), 129.7 (d, *J* = 5.9 Hz, 2 C), 127.8 (s, 2 C), 127.4 (s, 2 C), 127.0 (s, 2 C), 126.8 (d, *J* = 2.2 Hz, 2 C), 64.3 (d, *J* = 7.4 Hz, 1 C), 64.0 (d, *J* = 7.5 Hz, 1 C), 60.53 (d, J_{PC} = 119.1 Hz, 1 C), 56.1 (s, 1 C), 22.5 (s, 3 C), 16.2 (d, *J* = 6.7 Hz, 1 C), 16.0 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 91.9 (s, 1 P).

ESI-MS: *m*/*z* = 462.3 $[M + Na]^+$.

Anal. Calcd for $C_{21}H_{30}NO_3PS_2$: C, 57.38; H, 6.88; N, 3.19. Found: C, 57.58; H, 6.99; N, 3.04.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(2-naphthyl)methyl]thiophosphonate (2d)

Colorless solid; yield: 184 mg (88%); mp 109–114 °C; $[\alpha]_D^{25}$ +80.3 (*c* 1.04, $CHCl_3$).

IR (KBr): 3302, 2977, 1600, 1508, 1473, 1398, 1365, 1075, 962, 747 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.81–7.86 (m, 4 H), 7.47–7.56 (m, 4 H), 4.95 (dd, *J* = 15.7, 3 Hz, 1 H), 4.54 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.11–4.121 (m, 1 H), 3.90–3.96 (m, 1 H), 3.91–3.97 (m, 1 H), 3.81–3.87 (m, 1 H), 1.22–1.33 (m, 12 H), 1.11 (t, 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.3 (s, 1 C), 132.9 (d, *J* = 2.9, 1 C), 131.5 (d, *J* = 6.0 Hz, 1 C), 129.0 (d, *J* = 7.4 Hz, 1 C), 128.0 (s, 1 C), 127.7 (d, *J* = 1.4 Hz, 2 C), 126.5 (d, *J* = 3.7 Hz, 1 C), 126.3 (s, 1 C), 126.2 (s, 1 C), 64.3 (d, *J* = 7.4 Hz, 1 C), 64.0 (d, *J* = 7.5 Hz, 1 C), 60.8 (J_{PC} = 119.1 Hz, 1 C), 56.1 (s, 1 C), 22.6 (s, 3 C), 16.2 (d, *J* = 6.9 Hz, 1 C), 15.9 (d, *J* = 6.9 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 91.8 (s, 1 P).

ESI-MS: *m*/*z* = 414.1 $[M + H]^+$, 436.1 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{28}NO_3PS_2$: C, 55.18; H, 6.64; N, 3.39. Found: C, 55.28; H, 6.74; N, 3.38.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(4-fluorophenyl)methyl]thiophosphonate (2e)

Colorless oil; yield: 212 mg (98%); $[\alpha]_D^{25}$ +118.8 (*c* 1.05, $CHCl_3$).

IR (KBr): 3228, 2981, 1604, 1510, 1389, 1021, 964, 846, 785 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.41 (m, 2 H), 7.04 (d, *J* = 8.1 Hz, 2 H), 4.775 (dd, *J* = 15.3, 3.0 Hz, 1 H), 4.43 (dd, *J* = 9.0 Hz, 3.0 Hz, 1 H), 4.10–4.20 (m, 2 H), 3.86–3.99 (m, 2 H), 1.32 (t, *J* = 3.6 Hz, 3 H), 1.25 (s, 9 H), 1.15 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7 (s, 0.5 C), 161.2 (s, 0.5 C), 131.0 (m, 2 C), 129.7 (m, 1 C), 115.2 (m 2 C), 64.2 (d, *J* = 7.5 Hz, 1 C), 64.0 (d, *J* = 7.5 Hz, 1 C), 59.8 (d, J_{PC} = 119.8 Hz, 1 C), 56.1 (s, 1 C), 22.5 (s, 3 C), 16.1 (d, *J* = 6.7 Hz, 1 C), 16.0 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 91.6 (d, *J* = 14.4 Hz, 1 P).

^{19}F NMR (282 MHz, $CDCl_3$): δ = 114.1 (s, 1 F).

ESI-MS: *m*/*z* = 382.0 $[M + H]^+$, 404.0 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{25}FNO_3PS_2$: C, 47.23; H, 6.61; N, 3.67. Found: C, 47.28; H, 6.83; N, 3.55.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(4-chlorophenyl)methyl]thiophosphonate (2f)

Colorless oil; yield: 201 mg (99%); $[\alpha]_D^{25}$ –1.85 (*c* 0.98, $CHCl_3$).

IR (KBr): 3231, 2981, 1492, 1389, 1017, 963, 792 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (m, 4 H), 4.76 (dd, *J* = 16.5, 3.0 Hz, 1 H), 4.44 (dd, *J* = 9.6, 3.0 Hz, 1 H), 4.11–4.21 (m, 2 H), 3.89–4.02 (m, 2 H), 1.32 (t, *J* = 2.1 Hz, 3 H), 1.28 (s, 9 H), 1.18 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.4 (s, 1 C), 132.7 (d, *J* = 5.2 Hz, 1 C), 1130.6 (d, *J* = 5.2 Hz, 2 C), 128.3 (d, *J* = 2.9 Hz, 2 C), 64.2 (d, *J* = 6.7 Hz, 1 C), 64.1 (d, *J* = 7.4 Hz, 1 C), 59.9 (d, J_{PC} = 119.0 Hz, 1 C), 56.2 (s, 1 C), 22.5 (s, 3 C), 16.1 (d, *J* = 6.7 Hz, 1 C), 15.9 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 91.2 (s, 1 P).

MS (EI): *m*/*z* = 398.1 $[M + H]^+$, 420.1 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{25}ClNO_3PS_2$: C, 45.28; H, 6.33; N, 3.52. Found: C, 45.03; H, 6.39; N, 3.38.

Diethyl (S_S,R_C)-(+)-[(4-Bromophenyl)(*tert*-butylsulfinylamino)methyl]thiophosphonate (2g)

Colorless oil; yield: 216 mg (99%); $[\alpha]_D^{25}$ +117.3 (*c* 0.99, $CHCl_3$).

IR (KBr): 3228, 2980, 1448, 1405, 1389, 1074, 1050, 1020, 964, 840, 792 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 5.4 Hz, 2 H), 7.27 (dd, *J* = 5.4, 2.4 Hz, 2 H), 4.73 (dd, *J* = 15.9, 3.0 Hz, 1 H), 4.43 (dd, *J* = 9.0, 3.0 Hz, 1 H), 4.10–4.20 (m, 2 H), 3.87–4.00 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.25 (s, 9 H), 1.16 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.2 (d, *J* = 5.2 Hz, 1 C), 131.3 (d, *J* = 3.0 Hz, 2 C), 130.9 (d, *J* = 5.2 Hz, 2 C), 122.5 (s, 1 C), 64.2 (d, *J* = 7.4 Hz, 1 C), 64.1 (d, *J* = 8.2 Hz, 1 C), 60.0 (d, J_{PC} = 119.1 Hz, 1 C), 56.2 (s, 1 C), 22.5 (s, 3 C), 16.1 (d, *J* = 6.7 Hz, 1 C), 16.0 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$, H_3PO_4), δ = 91.0 (s, 1 P).

ESI-MS: *m*/*z* = 444.0 $[M + H]^+$, 466.0 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{25}BrNO_3PS_2$: C, 40.73; H, 5.90; N, 3.17. Found: C, 41.04; H, 5.95; N, 3.03.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(4-methoxyphenyl)methyl]thiophosphonate (2h)

Colorless oil; yield: 197 mg (99%); $[\alpha]_D^{25}$ +116.3 (*c* 1.00, $CHCl_3$).

IR (KBr): 3231, 2980, 1612, 1513, 1467, 1251, 1023, 962, 840, 744 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 9.0 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 4.74 (dd, *J* = 14.7, 3.0 Hz, 1 H), 4.41 (dd, *J* = 8.1, 3.0 Hz, 1 H), 4.10–4.20 (m, 2 H), 3.84–4.00 (m, 2 H), 1.32 (t, *J* = 7.2 Hz, 3 H), 1.28 (s, 9 H), 1.17 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0 (s, 1 C), 130.7 (d, *J* = 6.0 Hz, 2 C), 125.8 (s, 1 C), 113.8 (d, *J* = 5.2 Hz, 2 C), 64.4 (d, *J* = 7.4 Hz, 1 C), 64.1 (d, *J* = 7.5 Hz, 1 C), 60.2 (d, J_{PC} = 121.3 Hz, 1 C), 56.2 (s, 1 C), 55.4 (s, 1 C), 22.8 (s, 3 C), 16.4 (d, *J* = 6.7 Hz, 1 C), 16.2 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 92.2 (s, 1 P).

ESI-MS: *m*/*z* = 394.1 $[M + H]^+$, 416.1 $[M + Na]^+$.

ESI-HRMS: *m*/*z* [M + 23] calcd for $C_{16}H_{28}NO_4PS_2Na^+$: 416.10934; found: 416.10896.

Diethyl (S_S,R_C)-(+)-{(*tert*-Butylsulfinylamino)[4-(dimethylamino)phenyl]methyl}thiophosphonate (2i)

Colorless oil; yield: 209 mg (99%); $[\alpha]_D^{25}$ +156.0 (*c* 1.05, $CHCl_3$).

IR (KBr): 3305, 2979, 2896, 1615, 1525, 1450, 1361, 1074, 1044, 1018, 950, 824, 759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.24 (dd, *J* = 9.0, 3.6 Hz, 2 H), 6.68 (d, *J* = 9.0 Hz, 2 H), 4.68 (dd, *J* = 13.8, 3.0 Hz, 1 H), 4.36 (dd, *J* = 7.5, 3.0 Hz, 1 H), 4.07–4.17 (m, 2 H), 3.96–3.98 (m, 1 H), 3.83–3.86 (m, 1 H), 2.96 (s, 6 H), 1.29 (td, *J* = 6.6, 3.9 Hz, 3 H), 1.24 (s, 9 H), 1.17 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4 (s, 1 C), 130.2 (d, *J* = 6.0 Hz, 2 C), 120.3 (s, 1 C), 111.8 (2 C, s), 64.1 (d, *J* = 7.4 Hz, 1 C), 63.7 (d, *J* = 7.4 Hz, 1 C), 60.2 (d, J_{PC} = 121.4 Hz, 1 C), 55.8 (s, 1 C), 40.3 (s, 2 C), 22.6 (s, 3 C), 16.2 (d, *J* = 6.4 Hz, 1 C), 16.0 (d, *J* = 5.9 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): 92.6 (s, 1 P).

ESI-MS: *m*/*z* = 398.0 $[M + H]^+$, 420.0 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{31}N_2O_3PS_2$: C, 50.22; H, 7.69; N, 6.89. Found: C, 50.44; H, 7.78; N, 6.68.

Diethyl (S_S,R_C)-(+)-{(*tert*-Butylsulfinylamino)[4-(methylsulfanyl)phenyl]methyl}thiophosphonate (2j)

Colorless oil; yield: 203 mg (99%); $[\alpha]_D^{25}$ +112.8 (*c* 0.99, $CHCl_3$).

IR (KBr): 3228, 2980, 1598, 1494, 1389, 1080, 1019, 964, 835, 792 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 6.0 Hz, 2 H), 7.21 (d, *J* = 6.0 Hz, 2 H), 4.73 (dd, *J* = 12.0, 3.0 Hz, 1 H), 4.41 (dd, *J* = 6.0, 3.0 Hz, 1 H), 4.10–4.19 (m, 2 H), 3.85–4.00 (m, 2 H), 2.94 (s, 3 H), 1.32 (t, *J* = 2.1 Hz, 3 H), 1.27 (s, 9 H), 1.16 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.0 (s, 1 C), 130.4 (s, 1 C), 129.7 (d, *J* = 6.0 Hz, 2 C), 125.8 (d, *J* = 2.8 Hz, 2 C), 64.2 (d, *J* = 7.6 Hz, 1 C), 64.0 (d, *J* = 7.6 Hz, 1 C), 60.2 (d, J_{PC} = 120.0 Hz, 1 C), 56.1 (s, 1 C), 22.6 (s, 3 C), 16.1 (d, *J* = 7.6 Hz, 1 C), 16.0 (d, *J* = 7.6 Hz, 1 C), 15.4 (s, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 90.5 (1 P, s).

ESI-MS: *m*/*z* = 410.0 $[M + H]^+$, 432.0 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{28}NO_3PS_3$: C, 46.92; H, 6.89; N, 3.42. Found: C, 46.65; H, 6.96; N, 3.28.

Diethyl (S_S,R_C)-(+)-[(*tert*-Butylsulfinylamino)(2-sulfanylphenyl)methyl]thiophosphonate (2k)

Pale yellow oil; yield: 181 mg (99%); $[\alpha]_D^{25}$ +57.0 (*c* 1.00, $CHCl_3$).

IR (KBr): 3231, 2981, 1494, 1475, 1455, 1052 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.35 (m, 1 H), 7.14 (t, *J* = 3.6 Hz, 1 H), 7.01 (t, *J* = 3.6 Hz, 1 H), 5.08 (dd, *J* = 15.0, 3.0 Hz, 1 H), 4.51 (dd, *J* = 8.1, 3.6 Hz, 1 H), 3.98–4.22 (m, 1 H), 1.31–1.35 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2 (d, *J* = 6.0 Hz, 1 C), 128.4 (d, *J* = 16.4 Hz, 1 C), 126.8 (d, *J* = 2.8 Hz, 1 C), 126.7 (d, *J* = 3.6 Hz, 1 C), 64.7 (d, *J* = 7.6 Hz, 1 C), 64.4 (d, *J* = 7.6 Hz, 1 C), 57.4 (d, J_{PC} = 124.4 Hz, 1 C), 56.5 (s, 1 C), 22.8 (s, 3 C), 16.4 (d, *J* = 6.8 Hz, 1 C), 16.3 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 89.8 (s, 1 P).

ESI-MS: *m*/*z* = 370.0 $[M + H]^+$, 392.0 $[M + Na]^+$.

Anal. Calcd for $C_{13}H_{24}NO_3PS_3$: C, 42.26; H, 6.65; N, 3.79. Found: C, 42.52; H, 6.62; N, 3.66.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-2-phenylethyl]thiophosphonate (2l)

Colorless oil; yield: 164 mg (87%); $[\alpha]_D^{25}$ –8.5 (*c* 1.00, $CHCl_3$).

IR (KBr): 3030, 2980, 2929, 1604, 1474, 1456, 1389, 1365, 1083, 1050, 1026, 962, 740 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.41 (m, 5 H), 4.77 (dd, *J* = 15.7, 3 Hz, 1 H), 4.16 (dd, *J* = 9.3, 3.0 Hz, 1 H), 4.10–4.19 (m, 2 H), 3.90–3.96 (m, 1 H), 3.80–3.85 (m, 1 H), 1.32 (t, *J* = 3.6 Hz, 3 H), 1.28 (s, 9 H), 1.13 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.2 (d, *J* = 14.0 Hz, 1 C), 129.6 (s, 2 C), 128.4 (s, 2 C), 126.2 (s, 1 C), 64.7 (d, *J* = 7.6 Hz, 1 C), 63.0 (d, *J* = 7.6 Hz, 1 C), 59.6 (d, J_{PC} = 117.6 Hz, 1 C), 56.4 (s, 1 C), 37.5 (d, *J* = 7.6 Hz, 1 C), 22.5 (s, 3 C), 16.2 (d, *J* = 6.8 Hz, 1 C), 16.1 (d, *J* = 4.4 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 96.5 (s, 1 P).

ESI-MS: *m*/*z* = 378.1 $[M + H]^+$, 400.1 $[M + Na]^+$.

HRMS (ESI): *m*/*z* [M + 23] calcd for $C_{16}H_{28}NO_3PS_2Na^+$: 400.1144; found: 400.1140.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-2-methylpropyl]thiophosphonate (2m)

Colorless oil; yield: 157 mg (98%); $[\alpha]_D^{25}$ +89.3 (*c* 1.00, $CHCl_3$).

IR (KBr): 3246, 2978, 2933, 1474, 1388, 1203, 1087, 793 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): 4.16–4.25 (m, 5 H), 3.48 (dd, *J* = 18.6, 8.4 Hz, 1 H), 2.31–2.37 (m, 1 H), 1.24–1.38 (m, 15 H), 0.96–1.00 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.1 (d, *J* = 8.2 Hz, 1 C), 63.0 (d, *J* = 8.2 Hz, 1 C), 62.0 (d, J_{PC} = 112.4 Hz, 1 C), 57.1 (s, 1 C), 29.8 (d, *J* = 5.9 Hz, 1 C), 23.0 (s, 3 C), 21.2 (d, *J* = 12.4 Hz, 2 C), 16.3 (d, *J* = 32.0 Hz, 1 C), 16.1 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 96.4 (s, 1 P).

ESI-MS: *m*/*z* = 330.1 $[M + H]^+$, 352.1 $[M + Na]^+$.

Anal. Calcd for $C_{12}H_{28}NO_3PS_2$: C, 43.75; H, 8.57; N, 4.25. Found: C, 43.81; H, 8.90; N, 4.04.

Diethyl (*R*,*E*)-1-[(*S*)-1,1-dimethylethylsufinamido]-3-phenylallylphosphonate (2n)

Colorless oil; yield: 164 mg (84%); $[\alpha]_D^{25}$ +129.4 (*c* 1.01, $CHCl_3$).

IR (KBr): 3228, 2981, 1475, 1449, 1389, 1077, 1022, 794, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 7.8 Hz, 2 H), 7.30–7.38 (m, 3 H), 6.75 (dd, *J* = 15.9, 5.4 Hz, 1 H), 6.00–6.10 (m, 1 H),

4.34–4.39 (m, 1 H), 4.10–4.26 (m, 5 H), 1.34 (t, *J* = 8.4 Hz, 3 H), 1.25–1.30 (m, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1 (d, *J* = 3.4 Hz, 1 C), 128.6 (s, 2 C), 128.3 (d, *J* = 0.9 Hz, 1 C), 128.2 (s, 1 C), 126.8 (s, 2 C), 126.8 (s, 1 C), 121.7 (d, *J* = 2.2 Hz, 1 C), 64.0 (d, *J* = 1.7 Hz, 1 C), 63.8 (d, *J* = 0.4 Hz, 1 C), 60.0 (d, *J* = 7.6 Hz, 1 C), 56.0 (s, 1 C), 22.6 (s, 3 C), 16.2 (d, *J* = 0.2 Hz, 2 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 91.7 (s, 1 P).

MS (EI): *m*/*z* = 390.1 $[M + H]^+$, 412.1 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{28}NO_3PS_2$: C, 52.42; H, 7.25; N, 3.60. Found: C, 52.47; H, 7.45; N, 3.44.

Stereoselective Synthesis of Diethyl (S_S,R_C)-(+)-1-(*tert*-Butylsulfinylamino)alkylthiophosphonates (S_S,R_C)-4; General Procedure

The appropriate imine **3** (0.5 mmol) was added to a 20-mL Schlenk flask containing diethyl thiophosphonate (158 mg, 1 mmol) and K_2CO_3 (138 mg, 1 mmol) in CH_2Cl_2 (2.5 mL) at r.t. The mixture was then stirred for 24 h while carefully monitored by TLC. After the reaction had gone to completion, H_2O (5 mL) was added to quench it. Then the organic layer was separated and the aqueous layer was washed with Et_2O (3 × 10 mL). The organic layer was again washed with brine (3 × 10 mL) and dried overnight (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by chromatography (silica gel); this afforded the corresponding pure (S_S,R_C)-**4**.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(phenyl)ethyl]thiophosphonate (4a)

Colorless oil; yield: 189 mg (99%); $[\alpha]_D^{25}$ +94.3 (*c* 0.99, $CHCl_3$).

IR (KBr): 2982, 1495, 1474, 1448, 1386, 1079, 1020, 962, 794 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.57 (m, 2 H), 7.33–7.36 (m, 3 H), 4.50 (d, *J* = 6.6 Hz, 1 H), 3.97–4.15 (m, 4 H), 2.13 (d, *J* = 18.0 Hz, 3 H), 1.31 (s, 9 H), 1.25 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0 (d, *J* = 5.2 Hz, 1 C), 129.2 (d, *J* = 4.4 Hz, 2 C), 127.9 (d, *J* = 3.7 Hz, 1 C), 127.5 (d, *J* = 3.0 Hz, 2 C), 64.4 (d, *J* = 7.4 Hz, 1 C), 64.2 (d, *J* = 8.2 Hz, 1 C), 64.0 (d, J_{PC} = 118.3 Hz, 1 C), 57.0 (s, 1 C), 24.1 (s, 1 C), 22.8 (s, 3 C), 16.1 (d, *J* = 4.5 Hz, 1 C), 16.0 (d, *J* = 5.9 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 95.7 (s, 1 P).

ESI-MS: *m*/*z* = 378.1 $[M + H]^+$, 400.2 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{28}NO_3PS_2$: C, 50.91; H, 7.48; N, 3.71. Found: C, 50.52; H, 7.73; N, 3.56.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(4-tolyl)ethyl]thiophosphonate (4b)

Colorless oil; yield: 175 mg (90%); $[\alpha]_D^{25}$ +100.2 (*c* 1.01, $CHCl_3$).

IR (KBr): 3247, 2981, 2960, 1513, 1446, 1386, 1079, 1020, 961, 786 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 6.3, 2.4 Hz, 2 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 4.45 (d, *J* = 6.0 Hz, 1 H), 3.98–4.13 (m, 4 H), 2.37 (d, *J* = 2.1 Hz, 3 H), 2.10 (d, *J* = 17.7 Hz, 3 H), 1.30 (s, 9 H), 1.22–1.28 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0 (d, *J* = 3.7 Hz, 1 C), 134.1 (d, *J* = 4.4 Hz, 1 C), 129.3 (d, *J* = 4.5 Hz, 2 C), 128.6 (d, *J* = 3.0 Hz, 2 C), 64.6 (d, *J* = 7.5 Hz, 1 C), 64.4 (d, *J* = 8.2 Hz, 1 C), 64.2 (d, J_{PC} = 122.1 Hz, 1 C), 57.2 (s, 1 C), 24.4 (s, 1 C), 23.1 (s, 3 C), 21.3 (s, 1 C), 16.3 (d, *J* = 4.5 Hz, 1 C), 16.2 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 95.9 (s, 1 P).

ESI-MS: *m*/*z* = 238.1, 392.2 $[M + H]^+$, 414.1 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{30}NO_3PS_2$: C, 52.15; H, 7.72; N, 3.58. Found: C, 52.01; H, 8.21; N, 3.42.

Diethyl (S_S,R_C)-(+)-[1-(Biphenyl-4-yl)-1-(*tert*-butylsulfinylamino)ethyl]thiophosphonate (4c)

Colorless oil; yield: 203 mg (95%); $[\alpha]_D^{25}$ +84.9 (*c* 0.99, $CHCl_3$).

IR (KBr): 3248, 3050, 2981, 1599, 1474, 1376, 1077, 1020, 960, 790 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.99–8.01 (m, 1 H), 7.80–7.87 (m, 3 H), 7.69–7.73 (m, 1 H), 7.50–7.53 (m, 2 H), 4.57 (d, *J* = 6.3 Hz, 1 H), 4.00–4.10 (m, 4 H), 2.25 (d, *J* = 18.0 Hz, 3 H), 1.33 (s, 9 H), 1.21–1.28 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.6 (s, 1 C), 132.7 (s, 1 C), 129.0 (s, 1 C), 128.3 (s, 1 C), 127.4 (s, 1 C), 126.9 (s, 1 C), 126.7 (s, 1 C), 126.1 (s, 1 C), 64.4 (d, *J* = 8.1 Hz, 1 C), 64.2 (d, *J* = 8.2 Hz, 1 C), 64.3 (d, J_{PC} = 119.1 Hz, 1 C), 57.0 (s, 1 C), 24.5 (s, 1 C), 22.9 (s, 3 C), 16.1 (d, *J* = 6.0 Hz, 1 C), 16.0 (d, *J* = 5.2 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 95.5 (s, 1 P).

ESI-MS: *m*/*z* = 274.1, 428.2 $[M + H]^+$, 450.2 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{30}NO_3PS_2$: C, 56.18; H, 7.07; N, 3.28. Found: C, 56.01; H, 7.40; N, 3.16.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(2-naphthyl)ethyl]thiophosphonate (4d)

Colorless oil; yield: 127 mg (88%); $[\alpha]_D^{25}$ +85.0 (*c* 0.96, $CHCl_3$).

IR (KBr): 3242, 2982, 1601, 1488, 1388, 1077, 1019, 961, 845, 786 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.66 (m, 6 H), 7.37–7.49 (m, 3 H), 4.53 (d, *J* = 6.6 Hz, 1 H), 4.02–4.13 (m, 4 H), 2.16 (d, *J* = 18.0 Hz, 3 H), 1.33 (s, 9 H), 1.23–1.30 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8 (s, 1 C), 140.6 (s, 1 C), 136.3 (s, 2 C), 129.9 (s, 2 C), 127.7 (s, 2 C), 126.4 (s, 1 C), 64.7 (d, *J* = 8.2 Hz, 1 C), 64.6 (d, *J* = 8.2 Hz, 1 C), 64.2 (d, J_{PC} = 110.9 Hz, 1 C), 57.3 (s, 1 C), 24.5 (s, 1 C), 23.1 (s, 3 C), 16.4 (d, *J* = 5.2 Hz, 1 C), 16.3 (d, *J* = 5.9 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 95.7 (s, 1 P).

MS (EI): *m*/*z* = 300.1, 454.1 $[M + H]^+$, 476.2 $[M + Na]^+$.

ESI-HRMS: *m*/*z* calcd for $C_{22}H_{32}NO_3PS_2Na^+$: 476.1464; found: 476.1453.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(4-fluorophenyl)ethyl]thiophosphonate (4e)

Colorless oil; yield: 197 mg (99%); $[\alpha]_D^{25}$ +97.9 (*c* 1.04, $CHCl_3$).

IR (KBr): 3247, 2982, 1603, 1501, 1475, 1387, 1230, 1165, 1079, 1020, 961, 842, 788 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.54 (m, 2 H), 7.04 (t, *J* = 8.4 Hz, 2 H), 4.46 (d, *J* = 6.3 Hz, 1 H), 4.00–4.10 (m, 4 H), 2.11 (d, *J* = 18.0 Hz, 3 H), 1.31 (s, 9 H), 1.25 (t, *J* = 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.7 (d, *J* = 243.9 Hz, 0.5 C), 161.2 (d, *J* = 243.9 Hz, 0.5 C), 132.7 (s, 1 C), 131.0 (m, 2 C), 114.5 (m, 2 C), 64.4 (d, *J* = 8.2 Hz, 1 C), 64.2 (d, *J* = 8.28 Hz, 1 C), 63.6 (d, J_{PC} = 112.4 Hz, 1 C), 57.0 (s, 1 C), 24.2 (s, 1 C), 22.5 (s, 3 C), 16.1 (d, *J* = 5.2 Hz, 1 C), 16.0 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 95.2 (d, *J* = 3.7 Hz, 1 P).

^{19}F NMR (282 MHz, $CDCl_3$): δ = 114.8 (s, 1 F).

ESI-MS: *m*/*z* = 242.1, 396.1 $[M + H]^+$, 418.1 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{27}FNO_3PS_2$: C, 48.59; H, 6.88; N, 3.54. Found: C, 48.29; H, 7.06; N, 3.40.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(4-chlorophenyl)ethyl]thiophosphonate (4f)
Colorless oil; yield: 184 mg (90%); $[\alpha]_D^{25}$ +94.7 (*c* 0.98, $CHCl_3$).

IR (KBr): 2982, 1495, 1474, 1448, 1386, 1079, 1020, 962, 794 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (dd, *J* = 9.0, 3.0 Hz, 2 H), 7.33 (d, *J* = 9.0 Hz, 2 H), 4.47 (d, *J* = 6.3 Hz, 1 H), 4.00–4.11 (m, 4 H), 2.10 (d, *J* = 17.7 Hz, 3 H), 1.30 (s, 9 H), 1.22–1.28 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0 (d, *J* = 6.0 Hz, 1 C), 134.3 (s, 1 C), 130.8 (d, *J* = 4.5 Hz, 2 C), 128.0 (d, *J* = 3.0 Hz, 2 C), 64.7 (d, *J* = 7.5 Hz, 1 C), 64.5 (d, *J* = 8.1 Hz, 1 C), 63.9 (d, J_{PC} = 111.7 Hz, 1 C), 57.3 (s, 1 C), 24.4 (s, 1 C), 23.0 (s, 3 C), 16.3 (d, *J* = 6.0 Hz, 1 C), 16.2 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 94.9 (s, 1 P).

ESI-MS: *m*/*z* = 412.1 $[M + H]^+$, 434.1 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{27}ClNO_3PS_2$: C, 46.65; H, 6.61; N, 3.40. Found: C, 46.43; H, 6.62; N, 3.26.

Diethyl (S_S,R_C)-(+)-[1-(4-Bromophenyl)-1-(*tert*-butylsulfinylamino)ethyl]thiophosphonate (4g)
Colorless solid; yield: 233 mg (99%); mp 102–104 °C; $[\alpha]_D^{25}$ +75.4 (*c* 0.99, $CHCl_3$).

IR (KBr): 3080, 2982, 1598, 1487, 1455, 1389, 1068, 1020, 968, 857, 792 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 7.2 Hz, 2 H), 7.42 (d, *J* = 7.2 Hz, 2 H), 4.46 (d, *J* = 6.6 Hz, 1 H), 4.00–4.11 (m, 4 H), 2.09 (d, *J* = 18.0 Hz, 3 H), 1.29 (s, 9 H), 1.22–1.28 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.3 (d, *J* = 5.2 Hz, 1 C), 130.9 (d, *J* = 4.5 Hz, 2 C), 130.7 (d, *J* = 2.2 Hz, 2 C), 122.3 (s, 1 C), 64.5 (d, *J* = 7.5 Hz, 1 C), 64.3 (d, *J* = 8.2 Hz, 1 C), 63.8 (d, J_{PC} = 114.5 Hz, 1 C), 57.0 (s, 1 C), 24.1 (s, 1 C), 22.8 (s, 3 C), 16.1 (d, *J* = 6.1 Hz, 1 C), 16.0 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 94.7 (s, 1 P).

MS (EI): *m*/*z* = 378.0, 480.2 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{27}BrNO_3PS_2$: C, 42.11; H, 5.96; N, 3.07. Found: C, 42.38; H, 5.92; N, 2.89.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(4-morpholinophenyl)ethyl]thiophosphonate (4h)
Colorless oil; yield: 231 mg (99%); $[\alpha]_D^{25}$ +79.6 (*c* 1.03, $CHCl_3$).

IR (KBr): 3245, 3051, 2980, 1611, 1517, 1451, 1382, 1123, 1020, 960, 933, 829, 784 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (dd, *J* = 9.0, 2.7 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 4.41 (d, *J* = 6.3 Hz, 1 H), 4.00–4.10 (m, 4 H), 3.87 (t, *J* = 4.8 Hz, 4 H), 3.22 (t, *J* = 4.8 Hz, 4 H), 2.10 (d, *J* = 17.4 Hz, 3 H), 1.29 (s, 9 H), 1.22–1.28 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.7 (s, 1 C), 130.4 (d, *J* = 5.2 Hz, 2 C), 127.4 (d, *J* = 5.9 Hz, 1 C), 114.2 (s, 2 C), 67.1 (s, 2 C), 64.5 (d, *J* = 7.4 Hz, 1 C), 64.3 (d, *J* = 8.2 Hz, 1 C), 64.0 (d, J_{PC} = 123.5 Hz, 1 C), 57.1 (s, 1 C), 48.8 (s, 2 C), 24.5 (s, 1 C), 23.1 (3 C, s), 16.4 (d, *J* = 6.7 Hz, 1 C), 16.3 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 96.0 (1 P, s).

ESI-MS: *m*/*z* = 342.1, 485.2 $[M + Na]^+$.

Anal. Calcd for $C_{20}H_{35}N2O_4PS_2$: C, 51.93; H, 7.63; N, 6.06. Found: C, 51.93; H, 8.05; N, 5.82.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(4-nitrophenyl)ethyl]thiophosphonate (4i)
Colorless solid; yield: 211 mg (99%); mp 65–67 °C; $[\alpha]_D^{25}$ +90.1 (*c* 0.99, $CHCl_3$).

IR (KBr): 3297, 2879, 1512, 1344, 1082, 1018, 967, 854, 792 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, *J* = 6.3 Hz, 2 H), 7.72 (d, *J* = 6.3 Hz, 2 H), 4.55 (d, *J* = 7.5 Hz, 1 H), 4.02–4.14 (m, 4 H), 2.16 (d, *J* = 18.0 Hz, 3 H), 1.31 (s, 9 H), 1.22–1.29 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3 (s, 1 C), 145.1 (d, *J* = 5.2 Hz, 1 C), 130.1 (d, *J* = 4.5 Hz, 2 C), 122.5 (d, *J* = 2.2 Hz, 2 C), 64.7 (d, *J* = 8.2 Hz, 1 C), 64.5 (d, *J* = 8.2 Hz, 1 C), 64.2 (1 C, d, J_{PC} = 118.6 Hz), 57.3 (s, 1 C), 24.2 (s, 1 C), 22.8 (s, 3 C), 16.1 (d, *J* = 6.0 Hz, 1 C), 16.0 (d, *J* = 7.4 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 93.7 (s, 1 P).

ESI-MS: *m*/*z* = 393.8, 445.1 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{27}N_2O_5PS_2$: C, 45.48; H, 6.44; N, 6.63. Found: C, 45.70; H, 6.47; N, 6.45.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(4-cyanophenyl)ethyl]thiophosphonate (4j)
Colorless solid; yield: 202 mg (99%); mp 81–83 °C; $[\alpha]_D^{25}$ +94.3 (*c* 0.99, $CHCl_3$).

IR (KBr): 3308, 2980, 2223, 1608, 1505, 1475, 1456, 1388, 1077, 1023, 972, 851, 798 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (s, 5 H), 4.31 (d, *J* = 7.5 Hz, 1 H), 4.02–4.12 (m, 4 H), 2.13 (d, *J* = 18.3 Hz, 3 H), 1.30 (s, 9 H), 1.23 (t, *J* = 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0 (d, *J* = 5.2 Hz, 1 C), 131.2 (d, *J* = 4.5 Hz, 2 C), 129.9 (d, *J* = 4.4 Hz, 2 C), 118.6 (s, 1 C), 111.7 (d, *J* = 14.8 Hz, 1 C), 64.6 (d, *J* = 7.5 Hz, 1 C), 64.5 (d, *J* = 8.2 Hz, 1 C), 64.0 (d, J_{PC} = 114.1 Hz, 1 C), 57.2 (s, 1 C), 24.0 (s, 1 C), 22.7 (s, 3 C), 16.1 (d, *J* = 5.9 Hz, 1 C), 16.0 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 94.0 (s, 1 P).

MS (ESI): 270.9, 425.1 $[M + Na]^+$, 537.0.

Anal. Calcd for $C_{17}H_{27}N_2O_3PS_2$: C, 50.73; H, 6.76; N, 6.96. Found: C, 50.97; H, 6.68; N, 6.81.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(2-sulfanylphenyl)ethyl]thiophosphonate (4k)
Pale yellow oil; yield: 192 mg (99%); $[\alpha]_D^{25}$ +80.3 (*c* 1.03, $CHCl_3$).

IR (KBr): 3238, 3075, 2982, 2904, 1474, 1386, 1079, 1024, 964, 790 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.35 (m, 1 H), 7.03–7.15 (m, 1 H), 7.00–7.03 (m, 1 H), 4.57 (d, *J* = 6.3 Hz, 1 H), 4.06–4.15 (m, 4 H), 2.13 (d, *J* = 17.7 Hz, 3 H), 1.25–1.31 (m, 15 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.0 (s, 1 C), 128.0 (d, *J* = 6.7 Hz, 1 C), 126.5 (d, *J* = 3.7 Hz, 1 C), 126.4 (d, *J* = 3.7 Hz, 1 C), 64.7 (d, *J* = 8.2 Hz, 1 C), 64.4 (d, *J* = 8.2 Hz, 1 C), 63.1 (d, J_{PC} = 125.1 Hz, 1 C), 57.0 (s, 1 C), 25.0 (s, 1 C), 22.8 (s, 3 C), 16.1 (d, *J* = 6.7 Hz, 1 C), 16.0 (d, *J* = 6.7 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 93.8 (s, 1 P).

ESI-MS: *m*/*z* = 262.9, 384.1 $[M + H]^+$, 406.1 $[M + Na]^+$.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{26}NO_3PS_3Na^+$: 406.0706; found: 406.0704.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-(2-pyridyl)ethyl]thiophosphonate (4l)
Colorless oil; yield: 185 mg (98%); $[\alpha]_D^{25}$ +89.8 (*c* 1.00, $CHCl_3$).

IR (KBr): 3464, 3245, 2982, 1575, 1476, 1419, 1380, 1076, 1021, 964, 788 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.77–8.78 (m, 1 H), 8.54–8.56 (m, 1 H), 7.81–7.85 (m, 1 H), 7.30–7.32 (m, 1 H), 4.50 (d, *J* = 6.6 Hz, 1 H), 4.01–4.15 (m, 4 H), 2.13 (d, *J* = 17.7 Hz, 3 H), 1.30 (s, 9 H), 1.22–1.27 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4 (d, *J* = 4.5 Hz, 1 C), 148.6 (d, *J* = 3.7 Hz, 1 C), 136.6 (d, *J* = 4.5 Hz, 1 C), 133.1 (s, 1 C), 122.4 (d, *J* = 2.9 Hz, 1 C), 64.6 (d, *J* = 8.2 Hz, 1 C), 64.3 (d, *J* = 8.2 Hz, 1 C), 62.8 (d, J_{PC} = 124.8 Hz, 1 C), 57.1 (s, 1 C), 23.8 (s, 1 C), 22.7 (s, 3 C), 16.1 (d, *J* = 7.5 Hz, 1 C), 15.9 (d, *J* = 7.4 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 100.3 (s, 1 P).

ESI-MS: *m*/*z* = 379.1 $[M + H]^+$, 400.1 $[M + Na]^+$.

ESI-HRMS: *m*/*z* calcd for $C_{15}H_{27}N_2O_3PS_2Na^+$: 401.1080; found: 400.1093.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-methyl-3-phenylallyl]thiophosphonate (4m)

Colorless oil; yield: 191 mg (94%); $[\alpha]_D^{25}$ +46.9 (*c* 0.99, $CHCl_3$).

IR (KBr): 2981, 2958, 1470, 1388, 1079, 1051, 960, 785 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.11–4.25 (m, 4 H), 3.97–4.15 (m, 4 H), 3.92 (d, *J* = 4.8 Hz, 1 H), 1.82–1.86 (m, 2 H), 1.54 (d, *J* = 22.4 Hz, 3 H), 1.32–1.45 (m, 10 H), 1.30 (s, 9 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5 (d, *J* = 3.7 Hz, 1 C), 133.6 (d, *J* = 11.9 Hz, 1 C), 128.6 (s, 2 C), 128.1 (s, 1 C), 126.8 (s, 2 C), 126.7 (s, 1 C), 64.4 (d, *J* = 7.4 Hz, 1 C), 63.8 (d, *J* = 8.2 Hz, 1 C), 62.7 (d, J_{PC} = 124.3 Hz, 1 C), 56.5 (s, 1 C), 22.6 (s, 1 C), 22.3 (s, 3 C), 16.3 (d, *J* = 6.7 Hz, 1 C), 16.2 (d, *J* = 6.0 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 94.2 (s, 1 P).

ESI-MS: *m*/*z* = 358.1 $[M + H]^+$, 380.1 $[M + Na]^+$.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{33}NO_3PS_2^+$: 358.1636; found: 358.1634.

Diethyl (S_S,R_C)-(+)-[1-(*tert*-Butylsulfinylamino)-1-methylpentyl]thiophosphonate (4n)

Colorless oil; yield: 155 mg (87%); $[\alpha]_D^{25}$ +46.9 (*c* 0.99, $CDCl_3$).

IR (KBr): 2981, 2958, 1470, 1388, 1079, 1051, 960, 785 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.11–4.25 (m, 4 H), 3.97–4.15 (m, 4 H), 3.92 (d, *J* = 4.8 Hz, 1 H), 1.82–1.86 (m, 2 H), 1.54 (d, *J* = 22.4 Hz, 3 H), 1.32–1.45 (m, 10 H), 1.30 (s, 9 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.3 (d, *J* = 2.0 Hz, 1 C), 63.1 (d, *J* = 2.0 Hz, 1 C), 60.4 (d, *J* = 30.1 Hz, 1 C), 56.5 (s, 1 C), 36.3 (d, *J* = 1.1 Hz, 1 C), 25.1 (d, *J* = 2.0 Hz, 1 C), 23.0 (s, 1 C), 22.8 (s, 3 C), 19.8 (s, 1 C), 16.1 (d, *J* = 1.5 Hz, 2 C), 14.0 (d, *J* = 1.5 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 94.2 (s, 1 P).

ESI-MS: *m*/*z* = 358.1 $[M + H]^+$, 380.1 $[M + Na]^+$.

ESI-HRMS: *m*/*z* calcd for $C_{14}H_{33}NO_3PS_2^+$: 358.1636; found: 358.1634.

Diethyl (R_C)-(+)-[(*tert*-Butylsulfonylamino)(4-methoxyphenyl)methyl]phosphonate (5h)

$RuCl_3·H_2O$ (3 mg, 1.0 mmol%) and $NaIO_4$ (3.65 g, 15 equiv) were added to a CH_2Cl_2–MeCN–H_2O mixture (1.0:0.04:0.7, 38 mL), and the resulting mixture was stirred for 1 h. A soln of (S_S,R_C)-**2h** (0.45 g, 1 mmol) in CH_2Cl_2 (2 mL) was added rapidly to the mixture. The final concentration of (S_S,R_C)-**2h** was 0.03 M. When the reaction was completed, as indicated by TLC (approximately 3.5 h), excess anhyd $MgSO_4$ was added to remove the H_2O, and the mixture was filtered through a plug of Celite and the solid was washed with CH_2Cl_2 before the filtrate was again treated overnight with anhyd $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (silica gel, EtOAc–PE, 1:1); this afforded pure (R_C)-**5h**.

Colorless solid; yield: 142 mg (68%); mp 90–95 °C; $[\alpha]_D^{25}$ +24.2 (*c* 1.02, $CDCl_3$).

IR (KBr): 3215, 2985, 1742, 1613, 1469, 1313, 1233, 1132, 1022, 900, 843 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.39 (m 2 H), 6.90–6.92 (m, 2 H), 5.87 (m, 1 H), 4.80 (dd, *J* = 24.0, 9.9 Hz, 1 H), 4.23–4.29 (m, 2 H), 3.91–3.95 (m, 1 H), 3.83 (s, 3 H), 3.69–3.72 (m, 1 H), 1.36–1.42 (m, 3 H), 1.28 (s, 9 H), 1.11–1.16 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (s, 1 C), 129.5 (d, *J* = 1.5 Hz, 2 C), 128.0 (s, 1 C), 114.3 (d, *J* = 0.6 Hz, 2 C), 63.8 (d, *J* = 1.9 Hz, 1 C), 60.3 (d, *J* = 0.4 Hz, 1 C), 55.5 (d, *J* = 1.7 Hz, 1 C), 54.0 (s, 1 C), 24.3 (s, 3 C), 16.6 (d, *J* = 1.5 Hz, 1 C), 16.2 (d, *J* = 1.5 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 21.9 (s, 1 P).

ESI-MS: *m*/*z* = 394.1 $[M + H]^+$, 416.1 $[M + Na]^+$.

ESI-HRMS: *m*/*z* [M + 23] calcd for $C_{16}H_{28}NO_6PSNa^+$: 416.1265; found: 416.11267.

HPLC (CHIRALPAK AD-H, 4.6 cm × 250 cm, *n*-hexane–*i*-PrOH, 80:20, 0.7 mL/min): t_R = 16.5 min (major), 23.2 min (minor), 94% ee.

Diethyl (1-Aminoalkyl)thiophosphonates 6; General Procedure

The appropriate **2** or **4** (ca. 0.3 mmol) was placed in a round-bottomed glass bottle, and then 4 N aq HCl (3 mL) was added. The soln was stirred for about 3–6 h, until **2** or **4** had disappeared (by TLC). After completion of the reaction, the solvent was first removed, and then excess Et_3N was added; again the solvent was removed, and the residue was subjected to flash chromatography (silica gel, EtOAc–PE, 1:3 to 1:5); this afforded the corresponding pure **6**.

Diethyl (*R*)-[(Amino)(phenyl)methyl]thiophosphonate (6a)

Colorless oil; yield: 75 mg (from 0.30 mmol **2a**, 95%); $[\alpha]_D^{25}$ +15.9 (*c* 1.00, $CHCl_3$).

IR (KBr): 3375, 2982, 1602, 1493, 1389, 1160, 1050, 1025, 958, 812 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.42 (m, 5 H), 4.30 (d, *J* = 14.4 Hz, 1 H), 4.02–4.17 (m, 2 H), 3.90–3.93 (m, 1 H), 3.72–3.74 (m, 1 H), 2.01 (s, 2 H), 1.17–1.32 (m, 3 H), 1.30 (t, *J* = 8.1 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8 (s, 1 C), 127.9 (s, 4 C), 127.4 (s, 1 C), 63.7 (d, *J* = 7.8 Hz, 1 C), 62.9 (d, *J* = 7.5 Hz, 1 C), 59.1 (d, J_{PC} = 112.6 Hz, 1 C), 16.1 (d, *J* = 6.5 Hz, 1 C), 15.8 (d, *J* = 6.4 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$, TMS), δ = 97.7 (s, 1 P).

ESI-MS: *m*/*z* = 259.9 $[M + H]^+$, 105.9 $[MH – HPS(OEt)_2]^+$.

ESI-HRMS: *m*/*z* calcd for $C_{11}H_{19}NO_2PS^+$: 260.0874; found: 260.0869.

Diethyl (*R*)-[(Amino)(4-methoxyphenyl)methyl]thiophosphonate (6b)

Colorless oil; yield: 111 mg (from 0.40 mmol **2h**, 97%); $[\alpha]_D^{25}$ +13.1 (*c* 1.01, $CHCl_3$).

IR (KBr): 3374, 2982, 2837, 1612, 1513, 1465, 1389, 1304, 1251, 1180, 1027, 956, 836 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 5.6 Hz, 2 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 4.17 (d, *J* = 13.5 Hz, 1 H), 3.99–4.09 (m, 1 H), 3.74–3.81 (m, 1 H), 3.83 (s, 3 H), 3.61–3.72 (m, 1 H), 1.23 (t, *J* = 7.2 Hz, 3 H), 1.05 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1 (s, 1 C), 130.7 (s, 2 C), 129.8 (s, 1 C), 114.3 (s, 2 C), 64.7 (d, *J* = 7.9 Hz, 1 C), 63.8 (d, *J* = 7.8 Hz, 1 C), 57.4 (d, J_{PC} = 113.5 Hz, 1 C), 56.0 (s, 1 C), 17.0 (d, *J* = 6.3 Hz, 1 C), 16.9 (d, *J* = 6.4 Hz, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$, H_3PO_4): δ = 97.9 (s, 1 P).

ESI-MS: *m/z* = 273.0 [M – CH_2]$^+$, 311.9 [M + Na]$^+$.

ESI-HRMS: *m/z* calcd for $C_{12}H_{20}NO_3PSNa^+$: 312.0800; found: 312.0794.

Diethyl (*R*)-[1-Amino-1-(4-bromophenyl)ethyl]thiophosphonate (6c)

Colorless oil; yield: 126 mg (from 0.37 mmol **4g**, 97%); $[\alpha]_D^{25}$ +37.4 (*c* 1.00, $CHCl_3$).

IR (KBr): 2982, 1718, 1457, 1367, 1253, 1023, 956, 777 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (s, 4 H), 3.99–4.06 (m, 4 H), 1.99 (s, 2 H), 1.71 (d, *J* = 17.1 Hz, 3 H), 1.21–1.26 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.5 (s, 1 C), 131.6 (s, 2 C), 129.7 (s, 2 C), 122.3 (s, 1 C), 64.8 (d, *J* = 6.0 Hz, 1 C), 64.7 (d, *J* = 5.9 Hz, 1 C), 60.1 (d, J_{PC} = 108.7 Hz, 1 C), 25.9 (d, *J* = 3.8 Hz, 1 C), 17.0 (s, 1 C), 16.9 (s, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$, H_3PO_4): δ = 100.0 (s, 1 P).

ESI-MS: *m/z* = 373.9 [M + Na]$^+$, 304.1 [M – EtOH]$^+$.

Anal. Calcd for $C_{12}H_{19}BrNO_2PS$: C, 40.97; H, 5.44; N, 3.98. Found: C, 41.23; H, 5.43; N, 3.75.

Diethyl (*R*)-[1-Amino-1-(4-cyanophenyl)ethyl]thiophosphonate (6d)

Colorless oil; yield: 203 mg (from 0.69 mmol **4j**, 98%); $[\alpha]_D^{25}$ +49.6 (*c* 1.03, $CHCl_3$).

IR (KBr): 2983, 2229, 1608, 1506, 1388, 1159, 1097, 1045, 1021, 957, 842, 778 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 12.0 Hz, 2 H), 7.63 (d, *J* = 11.7 Hz, 2 H), 4.02–4.07 (m, 4 H), 2.07 (s, 2 H), 1.74 (d, *J* = 16.8 Hz, 2 H), 1.21–1.27 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5 (s, 1 C), 131.6 (s, 2 C), 128.1 (s, 2 C), 119.1 (s, 1 C), 111.2 (s, 1 C), 64.3 (s, 1 C), 64.2 (s, 1 C), 60.0 (d, *J* = 108.7 Hz, 1 C), 25.2 (d, *J* = 2.2 Hz, 1 C), 16.4 (s, 1 C), 16.3 (s, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$, TMS): δ = 99.1 (s, 1 P).

ESI-MS: *m/z* = 145.0 [MH$^+$ – HPS(OEt)$_2$], 321.0 [M + Na]$^+$.

ESI-HRMS: *m/z* calcd for $C_{13}H_{20}N_2O_2PS^+$: 299.0974; found: 299.0978.

Dipeptide-Containing Thiophosphonates 7a and 7b

The appropriate thiophosphonate (1.0 equiv) was put into a 25-mL round-bottomed bottle under argon, and then K_2CO_3 (1.2 equiv) and the appropriate acetyl chloride (1.5 equiv) were added, as well as CH_2Cl_2 (5 mL). The soln was heated to reflux for about 3 h until the thiophosphonate had disappeared (by TLC). After completion of the reaction, the soln was filtered to remove the K_2CO_3, and then the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (silica gel, EtOAc–PE, 1:3); this gave **7a** and **7b**.

Compound 7a

White solid; yield: 108 mg (from 0.22 mmol **6b**, 85%); mp 69–71 °C; $[\alpha]_D^{25}$ –0.1 (*c* 1.00, $CHCl_3$).

IR (KBr): 3310, 2981, 1667, 1612, 1513, 1251, 1023, 960, 740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 4.5 Hz, 2 H), 7.53–7.57 (m, 2 H), 7.24–7.39 (m, 7 H), 6.76 (d, *J* = 8.7 Hz, 2 H), 5.67 (d, *J* = 8.9 Hz, 1 H (NH)), 4.28–4.43 (m, 3 H), 4.06–4.19 (m, 2 H), 3.85–3.90 (m, 1 H), 3.69 (s, 3 H), 3.60–3.62 (m, 1 H), 1.43 (d, *J* = 6.9 Hz, 3 H), 1.22–1.30 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4 (s, 1 C), 159.5 (s, 1 C), 155.9 (s, 1 C), 143.8 (s, 1 C), 143.6 (s, 1 C), 141.2 (s, 2 C), 129.3 (s, 2 C), 127.7 (s, 2 C), 127. 1 (s, 2 C), 126.5 (s, 2 C), 125.1 (s, 1 C), 125.0 (s, 2 C), 119.9 (s, 2 C), 113.7 (s, 2 C), 67.2 (s, 1 C), 64.0 (d, J_{PC} = 110.0 Hz, 1 C), 60.4 (s, 1 C), 55.0 (s, 1 C), 53.8 (s, 1 C), 50.5 (s, 1 C), 47.0 (s, 1 C), 18.6 (s, 1 C), 16.2 (d, *J* = 6.5 Hz, 1 C), 15.9 (d, *J* = 6.9 Hz, 1 C), 14.2 (s, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 92.5 (s, 1 P).

ESI-MS: *m/z* = 429.1 [MH – $C_{15}H_{11}NO_2$(Fmoc)$^+$], 583.1 [M + H]$^+$, 605.0 [M + Na]$^+$.

Anal. Calcd for $C_{30}H_{35}NO_6PS$: C, 61.84; H, 6.05; N, 4.81. Found: C, 61.77; H, 6.38; N, 4.54.

Compound 7b

White solid; yield: 175 mg (from 0.30 mmol **6d**, 98%); mp 74–76 °C; $[\alpha]_D^{25}$ –27.5 (*c* 1.00, $CHCl_3$).

IR (KBr): 3327, 2983, 2229, 1700, 1506, 1451, 1242, 1042, 1020, 963, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 7.8 Hz, 2 H) 7.59 (d, *J* = 7.5 Hz, 2 H), 7.47–7.54 (m, 4 H), 7.24–7.37 (m, 5 H), 5.55 (d, *J* = 7.2 Hz, 1 H), 4.41 (d, *J* = 3.9 Hz, 2 H), 4.21–4.32 (m, 2 H), 3.80–4.03 (m, 4 H), 2.06 (d, *J* = 16.8 Hz, 3 H), 1.39 (d, *J* = 7.2 Hz, 3 H), 1.09–1.26 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.6 (s, 1 C), 171.5 (s, 1 C), 156.2 (s, 2 C), 143.7 (s, 2 C,), 141.3 (s, 2 C), 131.4 (s, 2 C), 128.2 (s, 2 C), 127.5 (s, 2 C), 125.0 (s, 2 C), 120.1 (s, 2 C), 118.8 (s, 1 C), 111.1 (s, 1 C), 64.7 (s, 1 C), 64.7 (d, *J* = 7.7 Hz, 1 C), 64.5 (d, *J* = 7.7 Hz, 1 C), 61.9 (d, J_{PC} = 115.6 Hz, 1 C), 51.0 (s, 1 C), 47.0 (s, 1 C), 22.5 (s, 1 C), 16.0 (s, 1 C), 16.0 (s, 1 C).

^{31}P NMR (100 MHz, $CDCl_3$): δ = 94.5 (s, 1 P).

ESI-MS: *m/z* = 392.1 [M + H]$^+$, 614.1 [M + Na]$^+$.

ESI-HRMS: *m/z* calcd for $C_{31}H_{34}N_3O_5PSNa^+$: 614.1832; found: 614.1849.

Acknowledgement

The project was supported by the National Nature Science Foundation of China (grant nos. 20672132 and 20872165).

References

(1) (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, **1989**. (b) Kukuhar, V. P.; Hudson, H. R. *Aminophosphorus Acids and Aminophosphinic Acids*; Wiley: Chichester, **2000**. (c) Bird, J.; De Mello, R. C.; Harper, G. P.; Hunter, D. J.; Karran, E. H.; Markwell, R. E.; Miles-Williams, A. J.; Rahman, S. S.; Ward, R. W. *J. Med. Chem.* **1994**, *37*, 158. (d) Atherton, F. R.; Hassall, C. H.; Lambert, R. W. *J. Med. Chem.* **1986**, *29*, 29. (e) Mao, M. K.; Franz, J. E. *Synthesis* **1991**, 920.

(2) On resolution with enzymes or chemical methods for obtaining optical pure amino phosphonates, see: (a) Lin, G. Q.; Li, Y. M.; Chen, A. S. *Principles and Applications of Asymmetric Synthesis*; Wiley: New York, **2001**. (b) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **1998**, *9*, 1279. (c) Kirst, H. A.; Kirst, W. K.; Yeh, M. J. *Enzyme Technologies for Pharmaceutical and Biotechnological Applications*; Marcel Dekker: New York, **2001**.

(3) For auxiliary-induced synthesis of optical pure amino phosphonates, see: (a) Chen, Q. Y.; Yuan, C. Y. *Synthesis* **2007**, 3779; and references cited therein. (b) Davis, F. A.; Fanelli, D. L. *J. Org. Chem.* **1998**, *63*, 1981. (c) Smith, A. B. *J. Am. Chem. Soc.* **1994**, *116*, 9377. (d) Smith, A. B.; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*,

10879. (e) Yuan, C. Y.; Cui, S. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *55*, 159.
(4) For catalyzed asymmetrical synthesis of α-aminophosphonates, see: (a) Merino, P.; Marqués, L. E.; Herrera, R. P. *Adv. Synth. Catal.* **2008**, *350*, 1195 . For recent developments, see: (b) Xu, C.; Goddard, R.; Buth, G.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 1. (c) Nakamura, S.; Nakashima, H.; Yamamura, A.; Schibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1209.
(5) For recent reviews, see: (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Syntheses and Reactions of Sulfinimines,* In *Advances in Sulfur Chemistry*, Vol. 2; Raynor, C. M., Ed.; JAI Press: Stamford / CT, **2000**, 249–282. (b) Davis, F. A.; Reddy, R. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *120-121*, 291.
(6) (a) For reviews relating to Ellman's *N*-(*tert*-butylsulfinyl) ketimines, see: Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (b) Mortona, D.; Stockman, R. A. *Tetrahedron* **2006**, *62*, 8869. (c) Zhou, P.; Chen, B. C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003. (d) Davis, F. A.; Chen, B. C. *Chem. Soc. Rev.* **1998**, *27*, 13. (e) Davis, F. A.; Chen, B. C. *Aldrichimica Acta* **2005**, *38*, 93.
(7) Zhang, D. H.; Yuan, C. Y. *Chem. Eur. J.* **2008**, *14*, 6049.
(8) Li, Y.; Hu, J. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 5882.
(9) Tongcharoensirikul, P.; Suarez, A. I.; Voelker, T.; Thompson, C. M. *J. Org. Chem.* **2004**, *69*, 2322.
(10) CCDC 727150 contains the supplementary crystallographic data of compound **6g**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(11) Delphine, S.; Guita, E.; Dominque, A.; Ousmane, D.; Max, K. *J. Org. Chem.* **1997**, *62*, 2414.
(12) (a) Huang, Z. Y.; Zhang, M.; Wang, Y.; Qin, Y. *Synlett* **2005**, 1334. (b) Zhong, Y. W.; Dong, Y. Z.; Fang, K.; Izumi, K. J.; Xu, M. J.; Lin, G. Q. *J. Am. Chem. Soc.* **2005**, *127*, 11956. (c) Wu, Y.; Zhong, K.; Izumi, J.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2004**, *25*, 4747. (d) Bolshan, Y. R.; Batey, B. A. *Org. Lett.* **2005**, *8*, 1481. (e) Wang, Y.; Fei, Q.; Wang Zhou, X.; Huang, Z. Y.; Qin, Y. *J. Org. Chem.* **2006**, *4*, 1588. (f) Allison, B. D.; Hack, M. D.; Phuong, V. K.; Rabinowitz, M. H.; Rosen, M. D. Patent Application US 7304051, **2005**.