Sulfinimine-Mediated Asymmetric Synthesis of Acyclic and Cyclic α-Aminophosphonates

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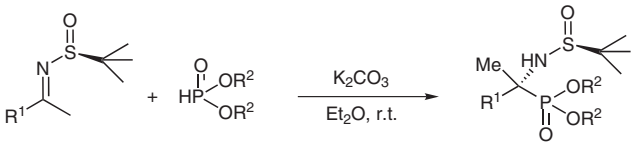
Abstract: Nucleophilic addition of dialkylphosphites to *N-tert*-butanesufinimines proceeds smoothly at room temperature in the presence of potassium carbonate or potassium fluoride, affording acyclic α-alkyl-α-aminophosphonates and a series of cyclic α-aminophosphonates in good chemical yields and modest to high diastereoselectivities.

Key words: asymmetric synthesis, cyclic α-aminophosphonates, ω-chloro-α-aminophosphonate, ω-phosphoryl-α-aminophosphonate

α-Aminoalkylphosphonic acids are of considerable value due to their potential biological activities.[1] Since the bioactivity of these compounds depends on the absolute configuration of the molecules, studies on the asymmetric synthesis of aminophosphonic acids has aroused great interest from organic chemists.[2–6] While many methods are so far available for the preparation of acyclic α-aminoalkylphosphonates, few routes leading to chiral cyclic α-aminoalkylphosphonates and ω-phosphoryl-α-aminophosphonates have been developed.[7–9] The most remarkable of the latter approaches was initiated by Shibasaki, and was based on chiral heterobimetallic lanthanoid catalytic enantioselective hydrophosphonylation, which led to cyclic α-aminophosphonates.[10]

Recently, we have reported a convenient *N-tert*-butylsulfinimine-mediated asymmetric synthesis of chiral α-aminophosphonates at room temperature using potassium carbonate as a base,[11] which gave reasonable chemical and enantiomeric yields. Herein we wish to describe further results obtained using *N-tert*-butylsulfinimines[12] as chiral auxiliaries under similar reaction conditions, but leading to different chiral acyclic and cyclic quaternary α-aminophosphonates. Our strategy involved, firstly, the synthesis of chiral acyclic quaternary α-aminophosphonates using different dialkyl phosphites. Particularly importantly, a one-pot synthesis of chiral cyclic α-aminophosphonates or chiral functionalized α-aminophosphonates starting from ω-chloro-substituted sulfinimine was then developed.

Optically active acyclic quaternary α-aminophosphonates were obtained through the nucleophilic addition of ketosulfinimine **1**, containing either electron-withdrawing or electron-donating groups on the phenyl ring, to dialkyl phosphite **2** (Scheme 1). The results are shown in Table 1.



(S_S)-**1** **2** (S_S,R_C)-**3**

R^1 = Ph, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$, *t*-Bu; R^2 = Me, Et, Pr, *i*-Pr

Scheme 1

Table 1 Synthesis of Chiral Acyclic Quaternary α-Aminophosphonates **3**

Entry	R^1	R^2	Time (h)	Yield (%)[a]	de (%)[b]
3a[c]	Ph	Me	24	85	>95
3b	Ph	Et	48	84	>95
3c	*p*-$MeOC_6H_4$	Et	72	82	>95
3d	*p*-$NO_2C_6H_4$	Et	40	88	85
3e	Ph	*n*-Pr	72	81	>95
3f	*p*-$MeOC_6H_4$	*n*-Pr	72	70	91
3g	*p*-$NO_2C_6H_4$	*n*-Pr	48	85	85
3h	Ph	*i*-Pr	72	<20	–
3i	*p*-$MeOC_6H_4$	*i*-Pr	72	<10	–
3j	*p*-$NO_2C_6H_4$	*i*-Pr	48	74	18
3k	*t*-Bu	*i*-Pr	48	N.R.	–

[a] Isolated yield of two isomers.
[b] From the ^{31}P NMR of the crude product.
[c] Detailed spectral data for **3a** have been previously reported.[11]

As shown in Table 1, the R^2 group of dialkyl phosphite **2** has a crucial influence on both the reaction rate and the diastereoselectivity; these also depend to a lesser extent on the electronic effect of the substituents on phenyl ring. Electron-withdrawing groups accelerate the reaction, but have a deleterious effect on the diastereoselectivity.

Optically active cyclic quaternary α-aminophosphonates and chiral functionalized α-aminophosphonates were obtained through the reaction of ω-chloro-substituted ketosulfinimine **4** with dimethyl phosphite under similar reaction conditions.

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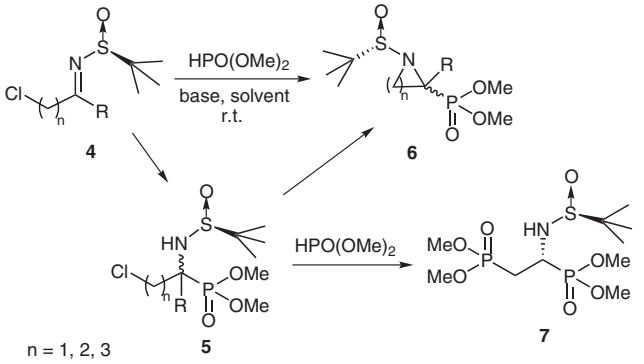
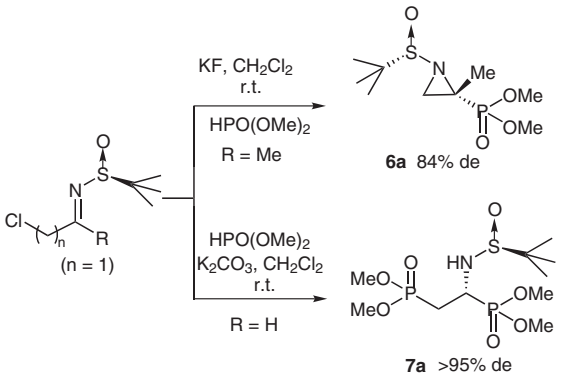


Scheme 2

ω-Chloro-substituted sulfinimines were prepared by condensing commercially available (*S*)-*tert*-butylsulfinimine with chloro-substituted aldehydes and ketones in the presence of $Ti(OEt)_4$ (2–3 equiv).[13] With the ω-chloro-substituted sulfinimines in hand, treatment of these compounds with two equivalents of dimethyl phosphonate in the presence of potassium fluoride, potassium carbonate or cesium carbonate, afforded the corresponding quaternary α-aminophosphonates in good to excellent yields and diastereoselectivities (Scheme 2). The product obtained depended on the sulfinimine and base used. When n = 1 and R = Me, aziridinyl 2-phosphonate **6a** was obtained using K_2CO_3 as a base at room temperature. The diastereoselectivity improved dramatically through the use of KF instead of K_2CO_3 (Scheme 3, Table 2). When n = 1 and R = H, 2-phosphoryl-1-aminophosphonate **7a** was obtained in high diastereoselectivity and good yield in the presence of K_2CO_3 (Scheme 3).

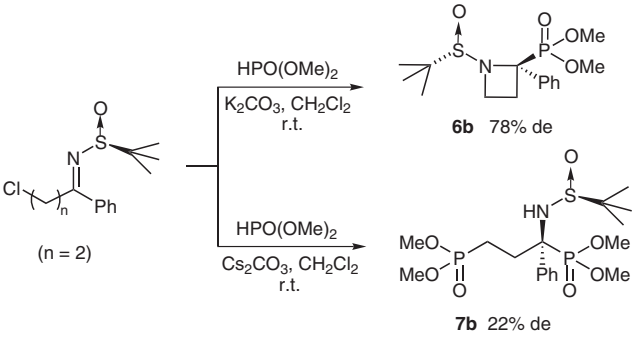


Scheme 3

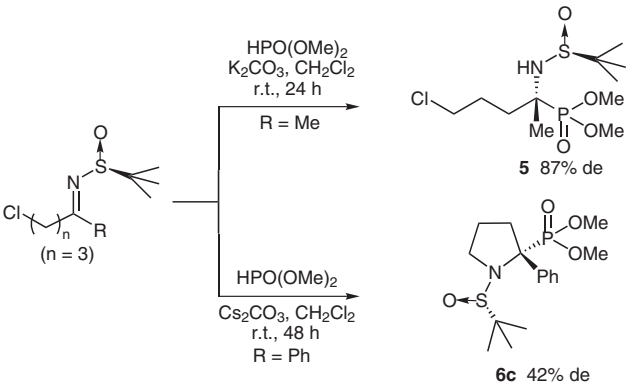
When n = 2 and R = Ph, azetidinyl 2-phosphonate **6b** was obtained in good yield and medium diastereoselectivity in the presence of K_2CO_3. However, 1,3-bis(*O*,*O*-dimethylphosphoryl)-1-butylsulfinylamino-1-phenylpropane (**7b**) was obtained in a poor diastereoselective excess when using Cs_2CO_3 as a base (Scheme 4).

When n = 3 and R = Me, 4-chloro-1-methyl-1-aminophosphonate **5** was obtained in good yield and diastereoselectivity using K_2CO_3 as a base; the reaction in the presence of Cs_2CO_3, gave only 2-phenyl-2-dimethylphosphorylpyrrolidine **6c** (Scheme 5).

As indicated in Table 2, chiral cyclic three-, four- and five-membered α-aminophosphonates, chiral ω-chloro-α-aminophosphonates or chiral ω-phosphoryl-α-aminophosphonates were prepared in good yields and medium to high diastereoselectivities. It is interesting that all the compounds can be prepared selectively simply by chang-



Scheme 4



Scheme 5

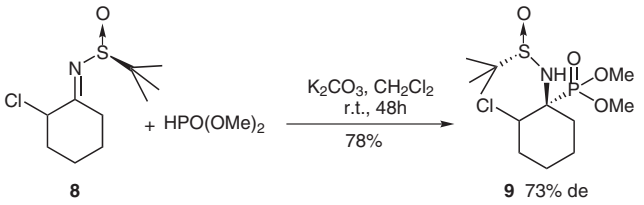
Table 2 Distribution of Reaction Products from Nucleophilic Addition of Dimethyl Phosphonate to Sulfinimine in Dichloromethane

Entry	n	R	Base	Time (h)	Yield (%)[a] **5**	**6**	**7**	de (%)[b]
1	1	Me	K_2CO_3	10	84	0	0	59
2	1	Me	CsF	24	80	0	0	67
3	1	Me	KF	30	75	0	0	84
4	1	H	K_2CO_3	10	0	0	86	>95
5	2	Ph	K_2CO_3	48	82	0	0	78
6	2	Ph	Cs_2CO_3	24	0	87	0	22
7	3	Me	K_2CO_3	24	0	0	85	87
8	3	Ph	Cs_2CO_3	72	83	0	0	42

[a] Isolated yield.
[b] Determined by ^{31}P NMR of the crude product.

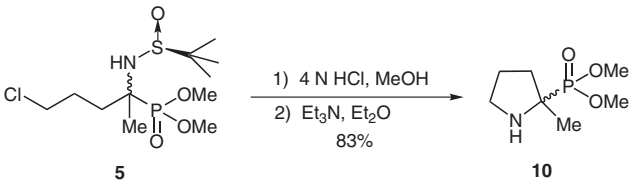
ing the base used in the reaction. Unfortunately, the diastereoisomers **5**, **6** and **7** are inseparable by ordinary chromatography. The absolute configuration of the products are predicted on the basis of our earlier report.[10]

Addition of dimethylphosphonate **2** to cyclic sulfinimine **8** also proceeds smoothly under these reaction conditions, providing the corresponding β-chloro-substituted cyclic product **9** in medium chemical yield and diastereoselectivity (Scheme 6).



Scheme 6

In the presence of methanolic hydrochloric acid (4N), the *N*-sulfinyl group of the ω-chloro-substituted α-aminophosphonate compounds can easily be eliminated to give the corresponding cyclic product in excellent yield. (Scheme 7).



Scheme 7

Mild reaction conditions (weak base) were essential for the transformation described here, since the substituted product resulted when stronger bases (NaOR, LiHMDS) were applied.

In conclusion, a simple and efficient methodology involving nucleophilic addition of dialkylphosphites to *N*-*tert*-butanesulfinimines leading to chiral acyclic α-aminophosphonates and chiral cyclic α-aminophosphonates has been developed in good chemical yields and modest to high diastereoselectivities under mild conditions using K_2CO_3 or KF as base at room temperature.

All chemicals were obtained from commercial suppliers and used without further purification unless otherwise noted. All solvents were dried by standard procedures. Petroleum ether (PE), where used, had a boiling range of 60–90 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent (unless otherwise indicated) on a Bruker Avance 300 or a Varian Mercury 300 spectrometer, and ^{31}P NMR spectra were taken at 120 MHz with $CDCl_3$ as solvent on a Varian EM 390 or a Bruker AM 300 spectrometer (external 85% H_3PO_4). IR spectra were taken on a Shimadzu IR 440 spectrometer, EI-MS measurements were performed on an HP 5989A apparatus. HRMS data were recorded on a Finnigan MAT 8430 spectrometer. Elemental analyses were conducted on a Heraeus Rapid CHNO apparatus.

Dialkyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]ethylphosphonates (3); General Procedure

To a 15 mL round-bottom flask fitted with a magnetic stir bar, was placed a solution of dialkyl phosphite **2** (4 mmol) in Et_2O (10 mL) and K_2CO_3 (0.690 g, 5 mmol). The reaction mixture was stirred for 15 min at r.t., then sulfinimine (*S*)-(+)-**1** (1.0 mmol) was added. After stirring for 24–72 h at this temperature, the reaction mixture was quenched with sat. aq NH_4Cl (5 mL), then extracted into CH_2Cl_2 (2 × 5 mL). The organic layer was successively washed with H_2O (5 mL) and brine (5 mL), then dried (Na_2SO_4). The solvent was removed and the residue was subjected to column chromatography on silica gel (acetone–EtOAc, 1:2).

Data for compound **3a** have been previously reported.[11]

Diethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-phenylethylphosphonate (3b)

Yield: 84%; colorless oil; de >95%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (s, 9 H), 1.25 (m, 6 H), 2.12 (d, *J* = 15.9 Hz, 3 H), 4.04 (m, 4 H), 4.10 (m, 1 H), 7.48 (m, 3 H), 7.81 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 23.40.

IR (KBr): 3500, 2983, 1448, 1240, 1047, 968, 803, 570 cm^{-1}.

MS (ESI): *m*/*z* = 384.2 $[M + Na]^+$.

HRMS: *m*/*z* $[M+Na]^+$ calcd for $C_{16}H_{28}NO_4PSNa$: 384.1379; found: 384.1369.

Anal. Calcd for $C_{16}H_{28}NO_4PS$: C, 53.17; H, 7.81; N, 3.88. Found: C, 53.06; H, 8.32; N, 3.31.

Diethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-(4-methoxyphenyl)ethylphosphonate (3c)

Yield: 82%; colorless oil; de >95%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 1.26 (m, 6 H), 2.13 (d, *J* = 15.9 Hz, 3 H), 3.77 (s, 3 H), 4.02 (m, 4 H), 4.08 (m, 1 H), 7.68 (m, 2 H), 7.88 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 23.58.

IR (KBr): 3486, 2983, 1611, 1513, 1255, 1048, 838, 567 cm^{-1}.

MS (ESI): *m*/*z* = 414.2 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{30}NO_5PS$: C, 52.16; H, 7.72; N, 3.58. Found: C, 51.94; H, 7.94; N, 3.82.

Diethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-(4-nitrophenyl)ethylphosphonate (3d)

Yield: 88%; colorless oil; de 85%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (s, 9 H), 1.25 (m, 6 H), 2.15 (d, *J* = 15.9 Hz, 3 H), 4.03 (m, 4 H), 4.15 (m, 1 H), 7.80 (m, 2 H), 8.23 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 21.86.

IR (KBr): 3483, 2984, 1737, 1523, 1349, 1018, 856, 562 cm^{-1}.

MS (ESI): *m*/*z* = 429.2 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{27}N_2O_6PS$: C, 47.28; H, 6.70; N, 6.89. Found: C, 47.01; H, 6.84; N, 6.92.

Dipropyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-phenylethylphosphonate (3e)

Yield: 81%; colorless oil; de >95%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (m, 6 H), 1.27 (s, 9 H), 1.63 (m, 4 H), 2.13 (d, *J* = 15.9 Hz, 3 H), 3.91 (m, 4 H), 4.15 (s, 1 H), 7.35 (m, 3 H), 7.73 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 23.14.

IR (KBr): 3493, 2970, 1464, 1239, 1065, 792, 571 cm^{-1}.

MS (ESI): m/z = 412.2 $[M + Na]^+$.

HRMS: m/z $[M + Na]^+$ calcd for $C_{18}H_{32}NO_4PSNa$: 412.1695; found: 412.1682.

Dipropyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-(4-methoxyphenyl)ethylphosphonate (3f)
Yield: 70%; colorless oil; de 91%.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 6 H), 1.26 (s, 9 H), 1.63 (m, 4 H), 2.12 (d, J = 15.6 Hz, 3 H), 3.75 (s, 3 H), 3.90 (m, 4 H), 4.13 (s, 1 H), 7.55 (m, 2 H), 7.93 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 23.31.

IR (KBr): 3472, 2970, 1611, 1513, 1255, 1002, 838, 567 cm^{-1}.

MS (ESI): m/z = 442.3 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{34}NO_5PS$: C, 54.40; H, 8.17; N, 3.34. Found: C, 54.47; H, 8.35; N, 3.69.

Dipropyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-(4-nitrophenyl)ethylphosphonate (3g)
Yield: 85%; colorless oil; de 85%.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (m, 6 H), 1.27 (s, 9 H), 1.64 (m, 4 H), 2.15 (d, J = 15.6 Hz, 3 H), 3.93 (m, 4 H), 4.15 (s, 1 H), 7.79 (m, 2 H), 8.24 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 21.60.

IR (KBr): 3500, 2971, 1523, 1349, 1002, 856, 561 cm^{-1}.

MS (ESI): m/z = 457.2 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{31}N_2O_6PS$: C, 49.76; H, 7.19; N, 6.45. Found: C, 49.58; H, 7.36; N, 6.42.

Diisopropyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-(4-nitrophenyl)ethylphosphonate (3j)
Yield: 74%; colorless oil; de 18%.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.3 Hz, 3 H), 1.27 (m, 18 H), 2.13 (d, J = 15.9 Hz, 3 H), 4.10 (d, J = 5.7 Hz, 1 H), 4.58 (m, 2 H), 7.81 (m, 2 H), 8.23 (m, 2 H).

^{31}P NMR (120 MHz, $CDCl_3$): δ = 19.81.

IR (KBr): 3484, 2983, 1523, 1349, 1237, 987, 855, 564 cm^{-1}.

MS (ESI): m/z = 457.2 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{31}N_2O_6PS$: C, 49.76; H, 7.19; N, 6.45. Found: C, 49.50; H, 7.35; N, 6.35.

Synthesis of 5, 6, 7 and 9; General Procedure
In a N_2-flushed 15 mL round-bottom flask fitted with a magnetic stir bar was placed a solution of dimethyl phosphite (4 mmol) in Et_2O (10 mL) and base (5 mmol) was added. The reaction mixture was stirred for 15 min at r.t., then the corresponding sulfinimine (1.0 mmol) was added. After stirring for 10–72 h at this temperature, the reaction mixture was quenched with H_2O (5 mL), and extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was successively washed with H_2O (5 mL) and brine (5 mL), then dried (Na_2SO_4). The solvent was removed and the residue was subjected to column chromatography on silica gel (PE–EtOAc, 1:2).

Dimethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinyl]-2-methylaziridin-2-ylphosphonate (6a)
Yield: 75%; colorless oil; de 84%.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.30 (s, 9 H), 1.71 (d, J = 12.3 Hz, 3 H), 2.21 (d, J = 7.5 Hz, 1 H), 2.67 (d, J = 8.7 Hz, 1 H), 3.81 (d, J = 8.7 Hz, 3 H), 3.86 (d, J = 10.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.7, 54.1, 53.3, 39.9, 34.7, 22.5, 22.2.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 23.04.

IR (KBr): 3480, 2961, 1655, 1458, 1253, 1031, 840 cm^{-1}.

MS (ESI): m/z = 270.2 $[M + H]^+$.

HRMS: m/z $[M^+]$ calcd for $C_9H_{20}NO_4PS$: 269.0851; found: 269.0862.

Dimethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinyl]-2-phenylazetidin-2-ylphosphonate (6b)
Yield: 82%; colorless oil; de 78%.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (s, 9 H), 1.95–2.24 (m, 2 H), 3.40 (m, 2 H), 3.69 (d, J = 3.0 Hz, 3 H), 3.73 (d, J = 3.0 Hz, 3 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.39 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.2, 133.4, 128.7, 128.1, 55.4, 52.5, 31.6, 31.5, 22.1, 19.6.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 31.74.

IR (KBr): 3467, 2958, 1688, 1597, 1245, 1031, 693 cm^{-1}.

MS (ESI): m/z = 346.2 $[M + H]^+$.

HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{25}NO_4PS$: 346.1225; found: 346.1236.

Dimethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinyl]-2-phenylpyrrolidin-2-ylphosphonate (6c)
Yield: 83%; colorless oil; de 42%.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 2.02 (m, 2 H), 2.10 (m, 2 H), 2.45 (m, 1 H), 2.72 (m, 1 H), 3.75 (m, 6 H), 7.35 (m, 3 H), 7.58 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4, 133.5, 128.6, 128.1, 55.5, 52.7, 32.5, 30.8, 22.5, 20.1, 16.8.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 24.71.

IR (KBr): 3420, 2975, 1702, 1223, 1060, 700 cm^{-1}.

MS (ESI): m/z = 382.2 $[M + Na]^+$.

HRMS: m/z $[M + H]^+$ calcd for $C_{16}H_{27}NO_4PS$: 360.1385; found: 360.1393.

Tetramethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]ethane-1,2-diyldiphosphonate (7a)
Yield: 86%; colorless oil; de >95%.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9 H), 1.81 (m, 2 H), 3.88 (m, 12 H), 3.94 (m, 1 H), 5.32 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.0, 55.1, 54.8, 54.4, 31.1, 22.5, 16.5.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 22.25.

IR (KBr): 3484, 2962, 1672, 1495, 1250, 1038, 845 cm^{-1}.

MS (ESI): m/z = 366.2 $[M + H]^+$.

HRMS: m/z $[M + Na]^+$ calcd for $C_{10}H_{25}NO_7P_2SNa$: 388.07107; found: 388.07192.

Anal. Calcd for $C_{10}H_{25}NO_7P_2S$: C, 32.88; H, 6.90; N, 3.83. Found: C, 32.62; H, 7.11; N, 3.48.

Tetramethyl (*R*)-1-[(*S*)-*tert*-Butylsulfinylamino]-1-phenylpropane-1,3-diyldiphosphonate (7b)
Yield: 87%; colorless oil; de 22%.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.33 (s, 9 H), 2.18 (m, 2 H), 2.70 (m, 2 H), 3.47–3.80 (m, 12 H), 5.61 (s, 1 H), 7.28 (m, 3 H), 7.93 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.4, 133.5, 130.1, 128.4, 57.6, 55.7, 55.3, 54.8, 52.7, 22.3, 18.9, 15.5.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 24.54 (dd, J_{P-P} = 15.6 Hz, J_{P-H} = 129.6 Hz), 34.22 (dd, J_{P-P} = 9.2 Hz, J_{P-H} = 75.1 Hz).

IR (KBr): 3424, 2960, 1640, 1459, 1227, 1034, 836 cm^{-1}.

MS (ESI): *m*/*z* = 456.2 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{31}NO_7PSNa$: 478.1178; found: 478.1188.

Dimethyl (*R*)-5-Chloro-2-[(*S*)-*tert*-Butylsulfinylamino]pentan-2-ylphosphonate (5)

Yield: 85%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (s, 9 H), 1.51 (d, *J* = 12.3 Hz, 3 H), 1.96 (m, 4 H), 3.54 (m, 2 H), 3.67 (d, *J* = 5.4 Hz, 1 H), 3.82 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.6, 54.4, 53.5, 45.1, 44.7, 31.1, 25.2, 22.6, 19.5.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 29.15.

IR (KBr): 3420, 2961, 1650, 1459, 1229, 1059, 830 cm^{-1}.

MS (ESI): *m*/*z* = 356.2 $[M + Na]^+$.

Anal. Calcd for $C_{11}H_{25}ClNO_4PS$: C, 39.58; H, 7.55; N, 4.20. Found: C, 39.50; H, 7.31; N, 4.15.

Dimethyl (1*R*)-2-Chloro-1-[(*S*)-*tert*-butylsulfinylamino]cyclohexylphosphonate (9)

Yield: 78%; colorless oil; de 73%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 1.71–2.20 (m, 8 H), 2.67 (m, 1 H), 3.83 (m, 6 H), 4.22 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 63.9, 57.6, 54.3, 53.5, 31.7, 29.0, 25.6, 23.1, 21.9, 18.7.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 26.10.

IR (KBr): 3487, 2954, 1458, 1248, 1029, 831, 592 cm^{-1}.

MS (ESI): *m*/*z* = 368.0 $[M + Na]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{12}H_{25}ClNO_4PSNa$: 368.0816; found: 368.0823.

(*R*)-Dimethyl 2-Methylpyrrolidin-2-ylphosphonate (10)

In a 20 mL, single-neck, round-bottom flask equipped with a magnetic stirring bar, was placed **5** (0.36 g, 1.0 mmol) in MeOH (5 mL), then 4 N HCl (5 mL) was added into the solution. The reaction mixture was stirred at r.t. for 6 h then concentrated under vacuum for 30 min. CH_2Cl_2 (10 mL) was added and the solution was cooled to 0 °C in an ice bath. Et_3N was added until pH >7 then the aqueous phase was extracted successively with Et_2O (5 mL) and EtOAc (2 × 5 mL). The combined organic layers were washed with brine (20 mL) and dried (Na_2SO_4). The solvent was removed and the residue was subjected to column chromatography on silica gel (PE–EtOAc, 1:1).

Yield: 83%; colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 15.9 Hz, 3 H), 1.55–1.95 (m, 4 H), 2.23 (m, 1 H), 3.05 (m, 2 H), 3.79 (d, *J* = 2.7 Hz, 3 H), 3.82 (d, *J* = 2.4 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.0, 52.6, 36.8, 36.0, 22.8, 20.3, 17.2.

^{31}P NMR (120 MHz, $CDCl_3$): δ = 33.04.

IR (KBr): 3403, 2955, 1636, 1456, 1218, 1058, 766, 570 cm^{-1}.

MS (ESI): *m*/*z* = 194.1 $[M + H]^+$.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_7H_{16}NO_3PNa$: 216.0753; found: 216.0760.

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