A New and Convenient Asymmetric Synthesis of \( \alpha \)-Amino- and \( \alpha \)-Alkyl-\( \alpha \)-aminophosphonic Acids Using \( N \)-\textit{tert}-Butylsulfinyl Imines as Chiral Auxiliaries

Qianyi Chen, Chengye Yuan*

State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Lingling Lu, Shanghai 200032, P. R. of China

Fax +86(21)54925379; E-mail: yuancy@mail.sioc.ac.cn

Received 16 August 2007; revised 11 September 2007

Abstract: Nucleophilic addition of dialkyl phosphites to \( \textit{N} \)-\textit{tert}-butylsulfinyl aldimines or ketimines occurs successfully at room temperature with potassium carbonate as base to afford \( \alpha \)-amino- and \( \alpha \)-alkyl-\( \alpha \)-amino-\( \textit{N} \)-(\textit{tert}-butylsulfinyl)phosphonates in good to excellent chemical yield and diastereoselectivity. The major diastereomers were separated and smoothly converted into enantiopure \( \alpha \)-amino- and \( \alpha \)-alkyl-\( \alpha \)-aminophosphonic acids.

Key words: \( \alpha \)-aminophosphonic acids, \( \alpha \)-alkyl-\( \alpha \)-aminophosphonic acids, \( N \)-\textit{tert}-butylsulfinyl imines, asymmetric synthesis, nucleophilic addition.

Optically active \( \alpha \)-aminophosphonic acids are compounds with significant biological activities which have found widespread use as surrogates for \( \alpha \)-amino acids and enzyme inhibitors. They also show antibacterial and antifungal activities. It is well known that the biological activities of \( \alpha \)-aminophosphonic acids depend strongly on the absolute configuration of the stereogenic carbon atom bearing the amino group. Therefore, investigations aimed at convenient and effective routes leading to enantiopure \( \alpha \)-aminophosphonic acids and their derivatives have received considerable attention. The methods so far available for the preparation of such molecules include direct resolutions, both chemical and enzymatic, and asymmetric synthesis using either a chiral auxiliary or an organocatalyst. In fact, the asymmetric addition of dialkyl or trialkyl phosphites to chiral aldimines or ketimines has proved to be one of the facile approaches. Gilmore and McBride reported the first synthesis of optically active \( \alpha \)-aminophosphonic acids in 1972 using a diastereoselective addition of diethyl phosphate to chiral imines. As reported by our group, such an asymmetric nucleophilic addition is remarkably influenced by the electronic and steric effects of the substrates. Recently, asymmetric synthesis using \( N \)-tolyssulfinyl imines as chiral auxiliary has aroused the interest of organic chemists. These enantiopure sulfinimines, pioneered by Davis, are versatile chiral imine building blocks which have been employed in the asymmetric synthesis of amines, \( \alpha \)- and \( \beta \)-amino acids, \( \alpha \)- and \( \beta \)-aminophosphonates, and heterocycles. These experimental data demonstrate that enantiopure \( N \)-tolyssulfinyl imines have found wide application in the asymmetric synthesis of chiral molecules.

More recently, Ellman introduced \( N \)-\textit{tert}-butylsulfinyl imines as nucleophilic addition acceptors. The \( N \)-\textit{tert}-butylsulfinyl group activates the imines for the nucleophilic addition, serves as a powerful chiral directing group, and after the addition reaction is readily cleaved upon treatment of the product with acid. Most importantly, competitive nucleophilic attack at sulfur should be minimized for addition to \( N \)-\textit{tert}-butylsulfinyl versus \( N \)-\( p \)-tolylsulfinyl imines due to the greater steric hindrance and reduced electronegativity of the \( p \)-butyl group relative to the \( p \)-tolyl moiety.

Nevertheless, asymmetric synthesis of \( \alpha \)- and \( \beta \)-aminophosphonic acids has been reported based on the nucleophilic addition of dialkyl phosphites to \( N \)-tolyssulfinyl aldimes or ketimines. In this paper we describe our results using \( N \)-\textit{tert}-butylsulfinyl aldimes and ketimines as chiral auxiliaries in order to compare the chemical behavior of these two sulfinimine types during the nucleophilic addition reactions of dialkyl phosphites.

The required \( (S) \)-(\textit{tert}-butylsulfinyl)imine 1 or 3 was readily prepared by adding aldehyde or ketone to \( (S) \)-(\textit{tert}-butanesulfinamidate in the presence of 2 equivalents of titanium(IV) ethoxide at room temperature to 60 °C in tetrahydrofuran. Optically active \( \alpha \)-aminophosphonates were obtained by the reaction of imines with dialkyl phosphites under various reaction conditions. For optimization of the reaction, the structural effect of the corresponding aldime or ketimine and dialkyl phosphate, as well as the influence of various bases on the diastereoselectivity of this nucleophilic addition was briefly examined (Table 1).

As indicated in Table 1, the base used in the addition has a crucial impact on the diastereoselectivity of the reaction. When dimethyl or diethyl phosphate was employed, the \( \alpha \)-(\textit{tert}-butylsulfinylamino)phosphonates 4a were obtained in excellent chemical yield but the diastereoselectivity was poor (Table 1, entries 1–3). Since the reaction proceeded very rapidly even at –78 °C (<1 h) in the presence of LiHMDS, it is obvious that LiHMDS is not a suitable base for use in this reaction. To our delight, the reaction was successful when potassium carbonate was employed; the diastereoselectivity improved dramatically with the de of the reaction increasing from 38.9% to 81.8% (Table 1,
entry 2 vs 11). The solvent also has an influence on the reaction rate and the diastereoselectivity (Table 1, entries 9–11). The best result was obtained when potassium carbonate was used and the reaction was carried out at room temperature using dichloromethane as solvent.

The optimized protocol was then expanded to a variety of sulfinimines derived from aldimines and ketimines. The results are summarized in Table 2.

The data in Table 2 indicate that the reaction of N-tert-butylsulfinyl ketimines generally results in a much higher diastereoselectivity than reaction of the corresponding aldimines (Table 2, entries 8–16 vs 1–7). The electronic effect of the R group in either aldimine or ketimine has no significant effect on either the chemical yield or diastereoselectivity.

Thus, the optimized protocol was applied to the asymmetric synthesis of quaternary α-aminophosphonates using N-sulfinyl ketimines. The phosphorus analogues of quaternary α-amino acids are of considerable value because it has been found that incorporation of such molecules into peptides results in increased rigidity and resistance to protease enzymes and therefore enhanced bioactivity. Fairly good diastereoselectivities were obtained not only for aromatic but also for aliphatic N-sulfinyl ketimines in the presence of potassium carbonate at room temperature (Table 2, entries 8–16). The electronic effect of the R group has no significant influence on the selectivity as only one isomer was detected in the 31P NMR spectra of the reaction mixtures, except for entry 14 (72.4% de) probably because of a 6.5:1 ratio of E/Z-isomers in the starting (−)-3g (R1 = Et) where phosphate addition to both isomers results in the lower diastereoselectivity.

During the course of the reaction, the potassium cation is probably chelated to the sulfinyl and phosphonate oxygens. Nucleophilic attack of the phosphite anion takes place from the least hindered n-face (anti to the tert-butyl group at sulfur, TS-1) (Figure 1).

### Table 1 Screening Dialkyl Phosphites and Optimization of the Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>LiHMDS</td>
<td>–78 °C</td>
<td>THF</td>
<td>1</td>
<td>85</td>
<td>37.6</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>LiHMDS</td>
<td>–78 °C</td>
<td>THF</td>
<td>1</td>
<td>83</td>
<td>38.9</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>CaH₂</td>
<td>0 °C</td>
<td>THF</td>
<td>3</td>
<td>80</td>
<td>40.4</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>Et₂N</td>
<td>0 °C</td>
<td>Et₂O</td>
<td>10</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>KF</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>30</td>
<td>&lt;10% conversion</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>CsF</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>30</td>
<td>&lt;30% conversion</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>Li₂CO₃</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>30</td>
<td>&lt;10% conversion</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>Na₂CO₃</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>30</td>
<td>&lt;30% conversion</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>K₂CO₃</td>
<td>r.t.</td>
<td>Et₂O</td>
<td>15</td>
<td>85</td>
<td>69.4</td>
</tr>
<tr>
<td>10</td>
<td>Me</td>
<td>K₂CO₃</td>
<td>r.t.</td>
<td>benzene</td>
<td>20</td>
<td>85</td>
<td>70.9</td>
</tr>
<tr>
<td>11</td>
<td>Me</td>
<td>K₂CO₃</td>
<td>r.t.</td>
<td>CH₂Cl₂</td>
<td>30</td>
<td>81</td>
<td>81.8</td>
</tr>
</tbody>
</table>

*a* Isolated total yield of two isomers.

*b* From the 31P NMR spectrum of the crude reaction mixture.

**Figure 1**

The major diastereomers of the (tert-butylsulfinylamino) methylphosphonates 4a–g were isolated by flash column chromatography on silica gel. Then, the N-tert-butylsulfinyl group in 4a, 4d, 4g, and 5a was selectively removed in excellent yield to give the corresponding enantiopure benzoxycarbonyl-protected aminomethylphosphonates (R)-6a–d.

Free aminomethylphosphonic acids (R)-7 were obtained upon refluxing enantiopure phosphonates 4 and 5 in 10 N
hydrochloric acid and isolation in the usual manner by the addition of propylene oxide (Table 3).

The absolute configuration of the aminomethylphosphonic acids 7 thus obtained was established based on a comparison of the sign of the optical rotation with that reported in the literature.14

In summary, we have shown that nucleophilic addition of dialkyl phosphites to N-tert-butylsulfinyl aldimines or ketimines, followed by subsequent deprotection and hydrolysis, constitutes a new synthetic route leading to chiral α-amino- and α-alkyl-α-aminophosphonic acids in good to excellent chemical yield and enantioselectivity. As found by us, N-tert-butylsulfinyl imines behave much better as chiral Michael addition acceptors than N-tolylsulfinyl imines. Furthermore, nucleophilic addition takes place under milder conditions, i.e. at room temperature with potassium carbonate as base, than for Davis’ sulfinimines where such additions have to be carried out under rather complicated reaction conditions, i.e. at ~78 °C in the presence of LiHMDS as base. Studies on the fields of application of such a reaction system are now ongoing in our laboratory.

All solvents used throughout these experiments were dried using standard procedures. IR spectra were measured on a Shimadzu IR 440 spectrometer. 1H NMR spectra were recorded at 300 MHz with CDCl3 as solvent (unless otherwise indicated) on a Bruker Avance 440 spectrometer, 1H NMR spectra were recorded at 300 MHz with CDCl3 or a Varian Mercury 300 spectrometer, and 31P NMR spectra with that reported in the literature.

### Table 2  Addition of Dimethyl Phosphite to N-tert-Butylsulfinyl Imines (S)-1, (S)-3

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>Ph</td>
<td>CH2Cl2</td>
<td>30</td>
<td>81</td>
<td>81.8</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4-MeOC6H4</td>
<td>CH2Cl2</td>
<td>30</td>
<td>78</td>
<td>85.2</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>4-MeC6H4</td>
<td>CH2Cl2</td>
<td>20</td>
<td>81</td>
<td>80.2</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>4-CIC6H4</td>
<td>CH2Cl2</td>
<td>20</td>
<td>82</td>
<td>72.4</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>Et</td>
<td>CH2Cl2</td>
<td>20</td>
<td>80</td>
<td>77.0</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>i-Pr</td>
<td>CH2Cl2</td>
<td>30</td>
<td>79</td>
<td>85.1</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>t-Bu</td>
<td>CH2Cl2</td>
<td>30</td>
<td>77</td>
<td>86.9</td>
</tr>
<tr>
<td>8</td>
<td>5a</td>
<td>Ph</td>
<td>Et2O</td>
<td>24</td>
<td>85 &gt;95</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5b</td>
<td>4-MeC6H4</td>
<td>Et2O</td>
<td>24</td>
<td>82 &gt;95</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5c</td>
<td>4-CIC6H4</td>
<td>Et2O</td>
<td>20</td>
<td>85 &gt;95</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>5d</td>
<td>4-NO2C6H4</td>
<td>Et2O</td>
<td>20</td>
<td>81 &gt;95</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5e</td>
<td>1-C10H7</td>
<td>Et2O</td>
<td>24</td>
<td>83 &gt;95</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>5f</td>
<td>4-PhC6H4</td>
<td>Et2O</td>
<td>24</td>
<td>80 &gt;95</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>5g</td>
<td>Et</td>
<td>CH2Cl2</td>
<td>30</td>
<td>73</td>
<td>72.4</td>
</tr>
<tr>
<td>15</td>
<td>5h</td>
<td>n-Bu</td>
<td>CH2Cl2</td>
<td>30</td>
<td>75 &gt;95</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5i</td>
<td>t-Bu</td>
<td>CH2Cl2</td>
<td>40</td>
<td>73 &gt;95</td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yield of the mixture of diastereomers.

*From the 31P NMR spectrum of the crude reaction mixture.

### Table 3  Removal of the N-tert-Butylsulfinyl Group

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>31P (δ)</th>
<th>[α]D 20°</th>
<th>Config</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>Ph</td>
<td>84</td>
<td>24.41</td>
<td>10.6d</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td>4-CIC6H4</td>
<td>H</td>
<td>85</td>
<td>23.86</td>
<td>14.0d</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td>t-Bu</td>
<td>H</td>
<td>81</td>
<td>27.87</td>
<td>20.3d</td>
</tr>
<tr>
<td>4</td>
<td>6d</td>
<td>Ph</td>
<td>Me</td>
<td>83</td>
<td>27.14</td>
<td>20.1d</td>
</tr>
<tr>
<td>5</td>
<td>7a</td>
<td>Ph</td>
<td>H</td>
<td>81</td>
<td>18.06</td>
<td>20.9°</td>
</tr>
<tr>
<td>6</td>
<td>7b</td>
<td>Ph</td>
<td>Me</td>
<td>83</td>
<td>21.60</td>
<td>51.1°</td>
</tr>
<tr>
<td>7</td>
<td>7c</td>
<td>4-CIC6H4</td>
<td>Me</td>
<td>88</td>
<td>21.25</td>
<td>53.9°</td>
</tr>
<tr>
<td>8</td>
<td>7d</td>
<td>4-NO2C6H4</td>
<td>Me</td>
<td>84</td>
<td>20.57</td>
<td>82.6°</td>
</tr>
<tr>
<td>9</td>
<td>7e</td>
<td>1-C10H7</td>
<td>Me</td>
<td>85</td>
<td>18.59</td>
<td>50.7°</td>
</tr>
<tr>
<td>10</td>
<td>7f</td>
<td>4-PhC6H4</td>
<td>Me</td>
<td>83</td>
<td>21.38</td>
<td>75.9°</td>
</tr>
<tr>
<td>11</td>
<td>7g</td>
<td>Et</td>
<td>Me</td>
<td>84</td>
<td>16.71</td>
<td>0.1°</td>
</tr>
</tbody>
</table>

*Reaction conditions: (a) 4 N HCl, MeOH, r.t., 6 h; (b) 5% NaHCO3, CH2Cl2, CbzCl, 0 °C, 4 h; (c) 10 N HCl, reflux, 18 h; (d) propylene oxide, EtOH.

*Isolated yield.

*Established based on a comparison of the sign of the optical rotation with that reported in the literature.

* Determined in CHCl3.

* Determined in 1 N NaOH.

(S)-N-tert-Butylsulfinyl Ketimines (S)-3; General Procedure

In a 20-mL, single-necked, round-bottom flask equipped with a magnetic stirrer bar was placed (S)-(−)-tert-butanesulfinamide (1.212 g, 10.0 mmol) in THF (5 mL), and then a mixture of the corresponding ketone (12 mmol) and Ti(OEt)4 (4.565 g, 20 mmol) was
added into the solution. The reaction mixture was then stirred at 60 °C for 6 h and finally was quenched with H2O (5 mL). At this time EtOAc (10 mL) was added to the mixture. The H2O phase was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (20 mL) and dried (Na2SO4). The solvent was removed and the residue was subjected to column chromatography on silica gel (PE–CH2Cl2, 2:1).

(S)-(−)-N-(1-Phenylethylidene)-tert-butanesulfinamidine (3a, R1 = Ph)

Yield: 85%.

1H NMR (CDCl3): δ = 1.32 (s, 9 H), 2.77 (s, 3 H), 7.45 (m, 3 H), 7.89 (d, J = 7.5 Hz, 2 H), 7.72 (d, J = 8.4 Hz, 2 H), 7.78 (d, J = 8.1 Hz, 2 H).

ESI-MS: m/z = 258.2 [M + H+].

IR (KBr): 2962, 1596, 1567, 1277, 1186, 1068, 823 cm−1.

Anal. Calcd for C12H16N2O3S: C, 53.71; H, 6.01; N, 10.44. Found: C, 53.65; H, 6.18; N, 10.33.

Yield: 80%; yellow solid; mp 138–149 °C.

(S)-(−)-N-[1-(4-Methylphenyl)ethylidene]-tert-butanesulfinamide (3c, R1 = 4-MeC6H4)

Yield: 83%; colorless oil.

1H NMR (CDCl3): δ = 8.7 Hz, 2 H).

ESI-MS: m/z = 274.2 [M + H+].

Anal. Calcd for C12H15NOS: C, 70.29; H, 7.00; N, 10.44. Found: C, 70.18; H, 6.99; N, 4.79.

(S)-(−)-N-[1-(1-Naphthyl)ethylidene]-tert-butanesulfinamide (3e, R1 = 1-Ph)

Yield: 88%; yellow solid; mp 120–122 °C.

[α]D20 = −16.7 (c 1.0, CHCl3).

IR (KBr): 2956, 1689, 1592, 1258, 1091, 1019, 827 cm−1.

1H NMR (CDCl3): δ = 1.36 (s, 9 H), 2.89 (s, 3 H), 7.56 (m, 2 H), 7.84–8.06 (m, 5 H).

ESI-MS: m/z = 274.2 [M + H+].

Anal. Calcd for C16H19NOS: C, 70.92; H, 7.04; N, 5.12. Found: C, 70.18; H, 6.99; N, 4.79.

Synthesis 2007, No. 24, 3779–3786 © Thieme Stuttgart · New York
Dimethyl (S,R)-(+)-(tert-Butylsulfinylamino)(4-methylphenyl)methylphosphonate (4e)

Yield: 81%; 80.2% de; colorless oil.

$[\alpha]_D^{20} = +63.19$ (c 1.0, CHCl$_3$).

IR (KBr): 3450, 2964, 1468, 1243, 1018, 837, 578 cm$^{-1}$.

HRMS: $m/z$ calcld for C$_{14}$H$_{24}$NO$_4$PSNa [M + Na$^+$/]: 372.1216; found: 372.1212.

Dimethyl (S,S,R)-(+)-(1-tert-Butylsulfinylamino)-1-phenylethylphosphonate (5a)

Yield: 85%; >95% de; colorless oil.

$[\alpha]_D^{20} +67.8$ (c 1.0, CHCl$_3$).

IR (KBr): 3480, 2958, 1458, 1244, 1032, 830, 570 cm$^{-1}$.

HRMS: $m/z$ calcld for C$_{16}$H$_{26}$NO$_5$PSNa [M + Na$^+$/]: 396.1209; found: 396.1207.

Dimethyl (S,R)-(+)-(1-tert-Butylsulfinylamino)-1-phenylethylphosphonate (5b)

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

$[\alpha]_D^{20} +85.2$ (c 1.0, CHCl$_3$).

IR (KBr): 3477, 2984, 1458, 1245, 1031, 833, 751, 564 cm$^{-1}$.

MS (El): $m/z = 348$ [M + H$^+$].

HRMS: $m/z$ calcld for C$_{15}$H$_{26}$NO$_4$PSNa [M + Na$^+$/]: 370.1210; found: 370.1212.

Dimethyl (S,S,R)-(+)-(1-tert-Butylsulfinylamino)-1-(4-methylphenylethyl)phosphonate (5c)

Yield: 85%; >95% de; colorless oil.

$[\alpha]_D^{20} +68.5$ (c 1.0, CHCl$_3$).

IR (KBr): 3478, 2959, 1466, 1245, 1060, 840, 562 cm$^{-1}$.

MS (El): $m/z = 368$ [M + H$^+$].

Anal. Calcd for C$_{16}$H$_{26}$NO$_5$PSNa: C, 50.81; H, 7.32; N, 3.93. Found: C, 50.81; H, 7.32; N, 3.93.
Dimethyl (S,R)-(++)-(tert-Butylsulfinylamino)-1-(1-naphthyl)ethylphosphonate (5e)

Yield: 83%; >95% de; colorless oil.

\[
[a]_{D}^{20} +37.9 (c 1.0, CHCl_3).
\]

IR (KBr): 3467, 2957, 1461, 1238, 1035, 827, 560 cm⁻¹.

1H NMR (CDCl₃): \( \delta = 1.19 \) (s, 9 H), 2.13 (d, \( J = 15.9 \) Hz, 3 H), 3.56 (d, \( J_{P} = 10.5 \) Hz, 6 H), 4.02 (s, 1 H), 7.41 (m, 2 H), 7.65–7.80 (m, 4 H), 7.94 (s, 1 H).

31P NMR (CDCl₃): \( \delta = 25.71. \)

ESI-MS: \( m/z = 406.2 \) [M + Na⁺].

HRMS: \( m/z \) calcd for C₁₂H₂₉NO₄PSNa [M + Na⁺]: 406.1262; found: 406.1262.

Anal. Calcd for C₁₂H₂₉NO₄PSNa: C, 56.45; H, 7.43; N, 2.94. Found: C, 56.45; H, 7.43; N, 2.94.

Dimethyl (S,R)-(++)-1-(1,1-Diphenyl-4-yl)-(1-tert-butylsulfinylamino)ethylphosphonate (5f)

Yield: 80%; >95% de; colorless oil.

\[
[a]_{D}^{20} +97.2 (c 1.0, CHCl_3).
\]

IR (KBr): 3480, 2958, 1489, 1365, 1243, 1031, 847, 577 cm⁻¹.

1H NMR (CDCl₃): \( \delta = 1.19 \) (s, 9 H), 2.06 (d, \( J = 15.6 \) Hz, 3 H), 3.58 (d, \( J_{P} = 10.5 \) Hz, 6 H), 4.01 (s, 1 H), 7.30 (m, 3 H), 7.53 (m, 6 H).

31P NMR (CDCl₃): \( \delta = 24.74. \)

ESI-MS: \( m/z = 432.3 \) [M + Na⁺].

HRMS: \( m/z \) calcd for C₂₂H₃₉NO₄PSNa [M + Na⁺]: 432.1371; found: 432.1369.

Anal. Calcd for C₂₂H₃₉NO₄PSNa: C, 58.66; H, 6.89; N, 3.42. Found: C, 58.89; H, 6.18; N, 3.51.

Dimethyl (S,R)-(++)-1-(tert-Butylsulfinylamino)-1-methylproplyphosphonate (5g)

Yield: 73%; 72.4% de; colorless oil.

\[
[a]_{D}^{20} +22.6 (c 1.0, CHCl_3).
\]

IR (KBr): 3467, 2957, 1461, 1238, 1035, 827, 560 cm⁻¹.

1H NMR (CDCl₃): \( \delta = 0.95 \) (t, \( J = 7.5 \) Hz, 3 H), 1.16 (s, 9 H), 1.42 (d, \( J = 15.6 \) Hz, 3 H), 1.80 (m, 2 H), 3.58 (m, 1 H), 3.73 (d, \( J_{P} = 13.5 \) Hz, 3 H), 3.78 (d, \( J_{P} = 10.5 \) Hz, 3 H).

31P NMR (CDCl₃): \( \delta = 30.25. \)

MS (EI): \( m/z = 286 \) [M + H⁺].

Anal. Calcd for C₁₂H₂₀NO₃PS: C, 42.09; H, 8.48; N, 4.91. Found: C, 42.26; H, 8.28; N, 4.51.

Dimethyl (S,R)-(++)-1-(tert-Butylsulfinylamino)-1-methylpentlyphosphonate (5h)

Yield: 75%; >95% de; colorless oil.

\[
[a]_{D}^{20} +45.9 (c 1.0, CHCl_3).
\]

IR (KBr): 3467, 2957, 1461, 1238, 1035, 827, 560 cm⁻¹.

1H NMR (CDCl₃): \( \delta = 0.83 \) (m, 3 H), 1.15 (s, 9 H), 1.24–1.43 (m, 7 H), 1.70 (m, 2 H), 3.52 (m, 1 H), 3.75 (m, 6 H).

31P NMR (CDCl₃): \( \delta = 29.80. \)

ESI-MS: \( m/z = 336.2 \) [M + Na⁺].

HRMS: \( m/z \) calcd for C₁₃H₁₉NO₃PS [M + H⁺]: 314.1558; found: 314.1549.

Anal. Calcd for C₁₃H₁₉NO₃PS: C, 45.99; H, 9.01; N, 4.47. Found: C, 46.79; H, 9.22; N, 3.84.

Dimethyl (S,R)-(++)-1-(Benzyloxy carbamylamino) methylphosphonates (6): General Procedure

In a 20-mL, single-necked, round-bottom flask equipped with a magnetic stirrer bar, a solution of 5 (1.0 mmol) in MeOH (5 mL) was added into the solution. The reaction mixture was then stirred at r.t. for 6 h. After that, the resulting mixture was concentrated under reduced pressure for 0.5 h. At this time, CH₃Cl (10 mL) was added to the flask and the solution was cooled to 0 °C in an ice bath. This was followed by the addition of Et₂N until pH 7. Then, 5%aq NaHCO₃ (5 mL) was added in sequence. The reaction mixture was stirred at 0 °C for 4 h, which was followed by the addition of H₂O (5 mL). The aqueous phase was extracted successively with Et₂O (5 mL) and EtOAc (2 × 5 mL). The combined organic layers were washed with brine (20 mL) and dried (Na₂SO₄). The solvent was removed and the residue was subjected to column chromatography on silica gel (PE:EtOAc, 1:1).

Dimethyl (R)-(++)-1-(Benzyloxy carbamylamino)phenylmethylphosphonate (6a)

Yield: 84%; >99% ee; white powder; mp 129–130 °C.

\[
[a]_{D}^{20} +10.6 (c 1.0, CHCl₃).
\]

IR (KBr): 3222, 3033, 2957, 1415, 1552, 1254, 1041, 698 cm⁻¹.

1H NMR (CDCl₃): \( \delta = 3.55 \) (d, \( J_{P} = 10.5 \) Hz, 3 H), 3.73 (d, \( J_{P} = 11.1 \) Hz, 3 H), 5.08–5.17 (m, 3 H), 5.72 (m, 1 H), 7.26–7.41 (m, 10 H).

31P NMR (CDCl₃): \( \delta = 24.41. \)

ESI-MS: \( m/z = 372.1 \) [M + Na⁺].

Anal. Calcd for C₁₄H₁₅NO₃PS: C, 58.45; H, 5.77; N, 4.01. Found: C, 58.72; H, 5.93; N, 3.61.

Dimethyl (R)-(++)-1-(Benzyloxy carbamylamino)4-chlorophenylmethylphosphonate (6b)

Yield: 85%; >99% ee; white powder; mp 119–120 °C.

\[
[a]_{D}^{20} +41.4 (c 1.0, CHCl₃).
\]

IR (KBr): 3242, 3038, 2957, 1720, 1547, 1250, 1031, 564 cm⁻¹.

1H NMR (CDCl₃): \( \delta = 3.55 \) (d, \( J_{P} = 10.5 \) Hz, 3 H), 3.73 (d, \( J_{P} = 10.8 \) Hz, 3 H), 5.00–5.21 (m, 3 H), 5.68 (m, 1 H), 7.20–7.40 (m, 9 H).
**Dipropylphosphonate (6c)**  
Yield: 81%; >99% ee; colorless oil.

**Dimethyl (R)-(++)-1-Benzoxycarbonylamino-1-phenylethylphosphonic Acid (7b)**  
Yield: 83%; white solid; mp 260–262 °C.

**3-Pentylphosphonate (6d)**  
Yield: 83%; >99% ee; colorless oil.

**3-Pentylphosphonate (6d)**

Yield: 83%; >99% ee; colorless oil.

**Yield: 81%; >99% ee; colorless oil.**

**ESI-MS:** m/z = 234.6 [M – 1].

HRMS: m/z calcd for C_{17}H_{24}NO_{5}P Na [M + Na^+]: 258.0058; found: 258.0057.

**R-(++)-1-Amino-1-(4-nitrophenyl)ethylphosphonic Acid (7d)**  
Yield: 84%; white solid; mp 230–235 °C.

**Yield: 88%; white solid; mp 225–230 °C.**

**Yield: 83%; >99% ee; colorless oil.**

**ESI-MS:** m/z = 250.1 [M – 1].

HRMS: m/z calcd for C_{8}H_{12}NO_{3}P Na [M + Na^+]: 224.0455; found: 224.0447.

**Yield: 88%; white solid; mp 225–230 °C.**

**Yield: 84%; white solid; mp 249–253 °C.**

**ESI-MS:** m/z = 258.0058; found: 258.0057.

**ESI-MS:** m/z = 245.2 [M – 1].

HRMS: m/z calcd for C_{12}H_{14}NO_{3}PNa [M + Na^+]: 274.0616; found: 274.0616.

**ESI-MS:** m/z = 250.1 [M – 1].

HRMS: m/z calcd for C_{18}H_{22}NO_{5}P Na [M + Na^+]: 274.0616; found: 274.0603.

**ESI-MS:** m/z = 276.2 [M – 1].

HRMS: m/z calcd for C_{17}H_{19}ClNO_{5}P [M + Na^+]: 378.0235; found: 378.0233.

**ESI-MS:** m/z = 200.2 [M – 1].

HRMS: m/z calcd for C_{8}H_{12}NO_{3}PNa [M + Na^+]: 224.0455; found: 224.0447.

**ESI-MS:** m/z = 200.2 [M – 1].

HRMS: m/z calcd for C_{8}H_{12}NO_{3}P Na [M + Na^+]: 224.0455; found: 224.0447.
$^{31}\text{P} \text{NMR (D}_2\text{O, 0.5 N NaOH): } \delta = 16.71.$

ESI-MS: $m/z = 152.2$ [M – 1].

HRMS: $m/z$ calcld for C$_4$H$_{12}$NO$_3$PNa [M + Na$^+$]: 176.0453; found: 176.0447.

Acknowledgment

This project was supported by the National Natural Science Foundation of China (Grant No. 20372706, 20672132).

References


