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

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Abstract: Nucleophilic addition of dialkylphosphites to N-tert-butanesulfinimines 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, α-chloro-α-aminophosphonate, α-phosphoryl-α-aminophosphonate

α-Aminoalkylyphosphonic 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 α-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-butanesulfinimine-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-butylsulfinimines12 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 α-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 phosphate 2 (Scheme 1). The results are shown in Table 1.

As shown in Table 1, the R2 group of dialkyl phosphites 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-donating 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 α-chloro-substituted ketosulfinimine 4 with dimethyl phosphate under similar reaction conditions.

Table 1 Synthesis of Chiral Acyclic Quaternary α-Aminophosphonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Ph</td>
<td>Me</td>
<td>24</td>
<td>85</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3b</td>
<td>Ph</td>
<td>Et</td>
<td>48</td>
<td>84</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3c</td>
<td>p-MeOC6H4</td>
<td>Et</td>
<td>72</td>
<td>82</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3d</td>
<td>p-NO2C6H4</td>
<td>Et</td>
<td>40</td>
<td>88</td>
<td>85</td>
</tr>
<tr>
<td>3e</td>
<td>Ph</td>
<td>n-Pr</td>
<td>72</td>
<td>81</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3f</td>
<td>p-MeOC6H4</td>
<td>n-Pr</td>
<td>72</td>
<td>70</td>
<td>91</td>
</tr>
<tr>
<td>3g</td>
<td>p-NO2C6H4</td>
<td>n-Pr</td>
<td>48</td>
<td>85</td>
<td>85</td>
</tr>
<tr>
<td>3h</td>
<td>Ph</td>
<td>i-Pr</td>
<td>72</td>
<td>&lt;20</td>
<td>–</td>
</tr>
<tr>
<td>3i</td>
<td>p-MeOC6H4</td>
<td>i-Pr</td>
<td>72</td>
<td>&lt;10</td>
<td>–</td>
</tr>
<tr>
<td>3j</td>
<td>p-NO2C6H4</td>
<td>i-Pr</td>
<td>48</td>
<td>74</td>
<td>18</td>
</tr>
<tr>
<td>3k</td>
<td>t-Bu</td>
<td>i-Pr</td>
<td>48</td>
<td>N.R.</td>
<td>–</td>
</tr>
</tbody>
</table>

a Isolated yield of two isomers.
b From the 31P NMR of the crude product.
c Detailed spectral data for 3a have been previously reported.

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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). 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 ɑ-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 K₂CO₃ as a base at room temperature. The diastereoselectivity improved dramatically through the use of KF instead of K₂CO₃ (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 K₂CO₃. When n = 2 and R = Ph, azetidinyl 2-phosphonate 6b was obtained in good yield and medium diastereoselectivity in the presence of K₂CO₃. However, 1,3-bis(O,O-dimethylphosphoryl)-1-butylsulfinylamino-1-phenylpropane (7b) was obtained in a poor diastereoselective excess when using Cs₂CO₃ 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 K₂CO₃ as a base; the reaction in the presence of Cs₂CO₃, gave only 2-phenyl-2-dimethylphosphorylpyrrolidine 6c (Scheme 5).

As indicated in Table 2, chiral cyclic three-, four- and five-membered ɑ-aminophosphonates, chiral ω-chloro-ɑ-aminophosphonates or chiral ω-phosphoryl-ɑ-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-

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**Scheme 2**

**Scheme 3**

**Scheme 4**

**Scheme 5**

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>R</th>
<th>Base</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>de (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Me</td>
<td>K₂CO₃</td>
<td>10</td>
<td>84</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Me</td>
<td>CsF</td>
<td>24</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Me</td>
<td>KF</td>
<td>30</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>H</td>
<td>K₂CO₃</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Ph</td>
<td>K₂CO₃</td>
<td>48</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>Ph</td>
<td>Cs₂CO₃</td>
<td>24</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Me</td>
<td>K₂CO₃</td>
<td>24</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>Ph</td>
<td>Cs₂CO₃</td>
<td>72</td>
<td>83</td>
<td>0</td>
</tr>
</tbody>
</table>

* Isolated yield.

b Determined by 31P NMR of the crude product.
ing the base used in the reaction. Unfortunately, the dia-
stereoisomers 5, 6 and 7 are inseparable by ordinary chromato-
graphy. The absolute configuration of the prod-
ucts 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 cyclic product 9 in medium chemical yield and diastereoselec-
tivity (Scheme 6).

![Scheme 6](image)

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

![Scheme 7](image)

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

In conclusion, a simple and efficient methodology involv-
ing nucleophilic addition of dialkylphosphites to N-tert-
butanesulfinimines leading to chiral acyclic α-amino-
phosphonates and chiral cyclic α-aminophosphonates has been developed in good chemical yields and modest to high diastereoselectivities under mild conditions using K₂CO₃ 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. ¹H NMR and ¹³C NMR spec-
tra were recorded at 300 MHz with CDCl₃ as solvent on a Varian EM 390 or a Bruker AM 300 spec-
trometer, and ¹³C NMR spectra were taken at 120 MHz with CDCl₃ as solvent on a Shimadzu IR 440 spectrometer, EI-MS measurements were per-
formed on an HP 5989A apparatus. HRMS data were recorded on a Finnigan MAT 8430 spectrometer. Elemental analyses were con-
ducted on a Heraeus Rapid CHNO apparatus.

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

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

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

¹H NMR (300 MHz, CDCl₃): 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).

¹³P NMR (120 MHz, CDCl₃): δ = 33.49.

IR (KBr): 3486, 2983, 1611, 1513, 1255, 1048, 838, 567 cm⁻¹.


**Diethyl (R)-1-[(S)-tert-Butylsulfinylamino]-(4-methoxyph-
eny lethylphosphonate (3c)**

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

¹H NMR (300 MHz, CDCl₃): δ = 0.91 (m, 6 H), 1.19 (s, 9 H), 1.25 (m, 6 H), 2.15 (d, J = 15.9 Hz, 3 H), 3.77 (s, 3 H), 4.03 (m, 4 H), 4.15 (m, 1 H), 7.68 (m, 2 H), 7.88 (m, 2 H).

¹³P NMR (120 MHz, CDCl₃): δ = 23.58.

IR (KBr): 3436, 2983, 1611, 1515, 1255, 1048, 838, 567 cm⁻¹.

MS (ESI): m/z = 414.1825 [M + Na]⁺.

Anal. Calcd for C₁₅H₂₇NO₄PS: 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]-(4-nitrophe-
ny lethylphosphonate (3d)**

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

¹H NMR (300 MHz, CDCl₃): δ = 0.91 (m, 6 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).

¹³P NMR (120 MHz, CDCl₃): 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 C₁₅H₂₇NO₄PS: 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]-(4-propyla-
ethylphosphonate (3e)**

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

¹H NMR (300 MHz, CDCl₃): δ = 0.91 (m, 6 H), 1.25 (m, 6 H), 2.15 (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).

¹³P NMR (120 MHz, CDCl₃): 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]+ calcld for C18H31N2O6PS: 412.1695; found: 412.1682.

Dimethyl (R)-1-[1-(S)-tert-Butylsulfinylamino]-1-(4-methoxyph-nyl)ethylphosphonate (3f)
Yield: 85%; colorless oil; de >95%.

IR (KBr): 3484, 2962, 1672, 1495, 1250, 1038, 845 cm–1.

Yield: 87%; colorless oil; de 22%.

Dimethyl (R)-1-[1-(S)-tert-Butylsulfinylamino]-1-(4-nitroph-nyl)ethylphosphonate (3g)
Yield: 85%; colorless oil; de 18%.

IR (KBr): 3500, 2971, 1702, 1223, 1060, 700 cm–1.

Yield: 86%; colorless oil; de >95%.

HRMS: m/z [M + H]+ calcld for C9H20NO4PS: 269.0851; found: 269.0862.

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

IR (KBr): 3420, 2975, 1702, 1237, 1002, 561 cm–1.

Yield: 85%; colorless oil; de 91%.

HRMS: m/z [M + Na]+ calcld for C18H32NO4PSNa: 412.1695; found: 412.1682.

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

IR (KBr): 3467, 2958, 1688, 1597, 1031, 693 cm–1.

Yield: 83%; colorless oil; de 42%.

HRMS: m/z [M + H]+ calcld for C16H27NO4PS: 360.1393; found: 360.1385.
$^{31}$P NMR (120 MHz, CDCl$_3$): $\delta = 35.84$ (s, 1 H), $J_{p,P} = 16.6$ Hz, $J_{P,H} = 21.1$ Hz.

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

HRMS: $m/z = 356.15$ [M + H]$^+$.

H$^1$ NMR (300 MHz, CDCl$_3$): $\delta = 1.22$ (s, 6 H), 1.96 (d, $J = 12.3$ Hz, 3 H), 1.96 (m, 1 H), 3.54 (m, 2 H), 3.67 (d, $J = 5.4$ Hz, 1 H), 3.82 (m, 6 H).

IR (KBr): 3420, 2961, 1640, 1459, 1227, 1034, 836 cm$^{-1}$.

Yield: 56%; colorless oil.

1H NMR (300 MHz, CDCl$_3$): $\delta = 1.22$ (s, 6 H), 1.71–2.20 (m, 8 H), 2.67 (m, 1 H), 3.83 (m, 6 H), 4.22 (s, 1 H).

13C NMR (75 MHz, CDCl$_3$): $\delta = 57.6, 54.4, 53.5, 45.1, 31.1, 25.2, 22.6, 19.5$.

$^{31}$P NMR (120 MHz, CDCl$_3$): $\delta = 32.95$ (s, 1 H), $J_{p,P} = 9.2$ Hz, $J_{P,H} = 75.1$ Hz.

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

HRMS: $m/z [M + Na]^+$ calc for C$_{12}$H$_{25}$ClNO$_4$PSNa: 216.0760; found: 216.0753.

Acknowledgment

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References


