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The first enantioselective synthesis of α-aminophosphinates

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Abstract—The first enantioselective synthesis of substituted α-aminophosphinic acids was carried out by the addition of ethyl phenylphosphinate to chiral imines in the absence of base or other catalyst. © 2003 Elsevier Science Ltd. All rights reserved.

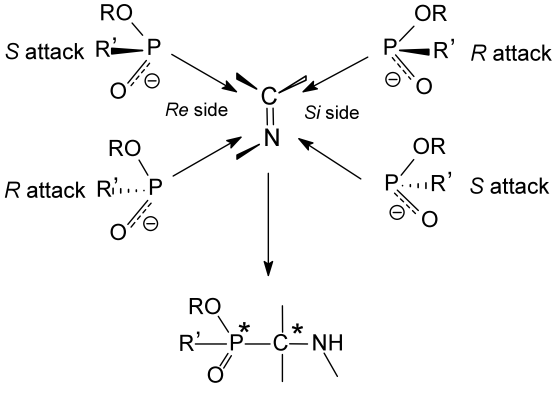
α-Aminophosphonic and phosphinic acids are the phosphorous analogues of α-aminocarboxylic acids, and therefore have biological importance both in themselves and as building blocks for peptides. Some are known as herbicides, such as glyphosate or glufosinate, and have commercial application. Others have promising enzyme inhibitory activity, or are neuroactive agents (e.g. NMDA receptor antagonists), HIV protease antagonists and collagenase inhibitors, etc.[1–4]

As building blocks of peptides, α-aminophosphinic acids seem to be even closer analogues of the α-aminocarboxylic acids than their α-aminophosphonic counterparts, due to their monobasic acidic character, and the higher stability of the P–C bond of phosphinic acids compared to the P–O bond of phosphonic acids.[5]

One can also suppose that the configuration at the α-carbon atom in the α-aminophosphinic acids plays a decisive role in the biological properties of these types of compound, as it does similarly in α-aminocarboxylic and phosphonic acids.[6] To the best of our knowledge, however, there have been no publications in the literature on the enantioselective synthesis of α-aminophosphinic acids.

Numerous methods have been developed for the preparation of optically active α-aminophosphonic acids. Typical examples include the addition of dialkyl phosphonate,[7] or its lithium salt[8,9] to an imine bearing a chiral auxiliary, with or without Lewis acid catalysis, respectively. A chiral phosphonate can also be used in the addition to nonchiral imines.[10] Heterobimetallic chiral catalysts such as lanthanoid-potassium BINOL[11] and others[12] were successfully used in asymmetric hydrophosphonylation of imines. Another method is the alkylation of suitably protected α-aminomethylphosphonic acid esters, which involves either a chiral auxiliary in the phosphonate,[13] or a chiral catalyst.[14] Stereoselective C–N bond formation is also a suitable method, by substitution of a chiral α-hydroxy function with an azido group, followed by hydrogenation, resulting in complete inversion of configuration at the α-carbon atom.[15]

The most obvious route for the synthesis of α-aminophosphinates seems to be the addition of H-phosphinates to a C=N double bond,[16] but contrary to the phosphonate synthesis, the addition results in a mixture of two diastereomeric pairs due to the attack of the prochiral phosphinate at the prochiral C-centre of the C=N bond[17] (Scheme 1).



Scheme 1.

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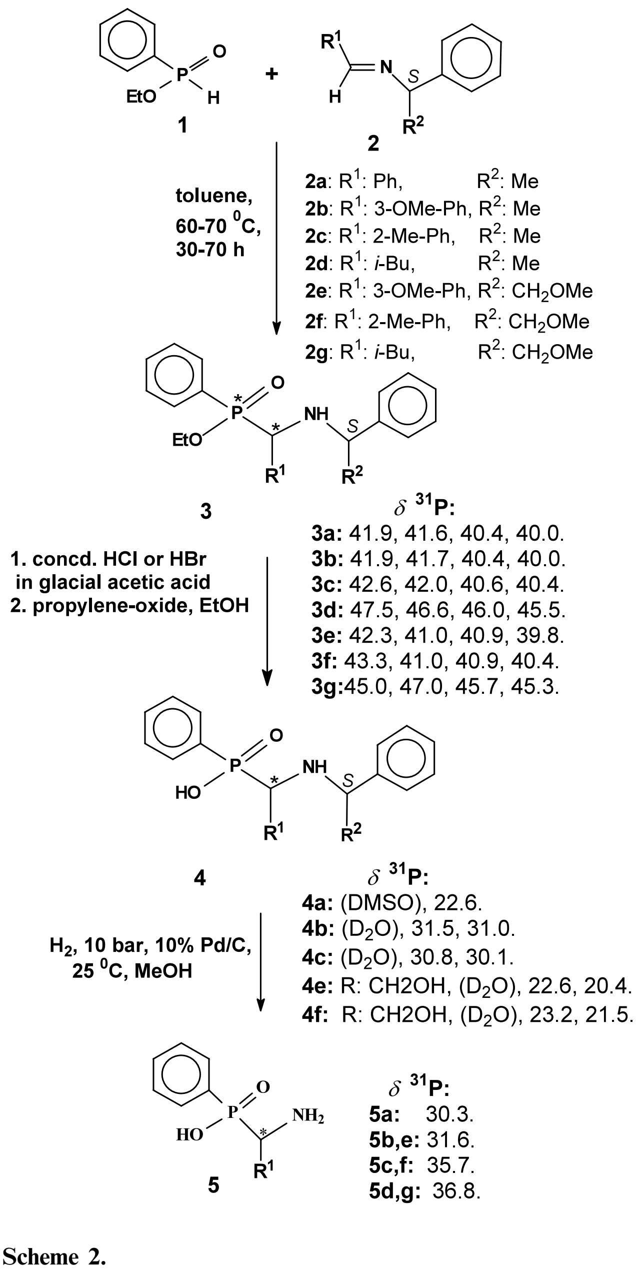
Despite its importance, only a single attempt to separate the enantiomers of aminophosphinic acid esters is known in the literature so far.[18] Belov and co-workers isolated the single (C_R,P_S)-enantiomer of ethyl α-benzylaminophenylphosphinate by repeated crystallisation of the diastereomeric mixture of esters followed by resolution, and then determined the absolute configuration by X-ray crystallography.

Here, we disclose a simple enantioselective synthesis of α-aminophosphinates **3** by the addition of ethyl phenylphosphinate **1** to chiral imines **2**, in the absence of a catalyst (Scheme 2). (For data on **3**, **4**, **5a**–**e** see Table 1.[19])

As model compounds we have chosen chiral imines **2** prepared from benzaldehyde and substituted benzaldehydes and chiral amines, such as (*S*)-α-methylbenzylamine and (*S*)-α-methoxymethylbenzylamine, respectively. We would like to point out, that the same auxiliaries were used as components of imines earlier in the synthesis of α-aminophosphonates using the complexing ability of a Lewis-acid catalyst or the chelating ability of lithium in a lithium salt.[7,8]



Scheme 2.

The imine **2** was heated with 1.5 equivalents of ethyl phenylphosphinate **1** at 70°C in toluene and the reaction was run until the imine was consumed (30–70 h).

Protected α-aminophosphinates **3** were isolated after flash chromatography. The diastereomeric ratio of **3** was determined by ^{31}P NMR without any purification apart from chromatography. It is noteworthy, that in products **3a**–**g** two diastereomers are dominant among the four.

To determine the enantioselectivity of the reaction on the Cα centre, **3** was hydrolysed using concd. HCl (**3a**–**c**), or HBr solution in glacial acetic acid (**3d**–**f**), respectively. The enantioselectivity was slightly decreased when the aminophosphinic acid had a substituent in the phenyl ring (Y = 2-Me, 3-OMe). The product crystallised spontaneously from the reaction mixture, which improved the optical purity (100% for **4a**) and at the same time decreased the yield (see **4a**–**c**,**e**,**f** in Table 1).

After the hydrolysis step the chirality of the phosphorus atom is lost and two chiral centres remain in the molecule **4**. Therefore the diastereomeric ratio in the protected aminophosphinic acid **4** corresponds to the enantiomeric ratio formed during the addition of **1** to **2**, as the carbon atom of the auxiliary does not change during the process and remains (*S*).

Deprotection of **4** was carried out by hydrogenolysis over a palladium on carbon catalyst in methanol resulting in α-aminophosphinic acids in an enantiomeric ratio of good to excellent (see **5a**–**g** in Table 1). Since the absolute configuration of **5a** is known, namely (*R*), one might assume the same configuration for **5b**,**e** and **5c**,**f** (*R*) as all these compounds, like **5a**, have a negative sign of optical rotation.

In summary, we have demonstrated that both the very simple chiral auxiliary α-methylbenzylamine and its methoxy derivative exert good/excellent chiral induction in the case of the addition of ethyl phenylphosphinate to imines. The *S* configuration in both types of chiral auxiliary induces the *R* configuration at the Cα centre by attack at the *Re*-side of the C=N plane of the imine carbon atom (Scheme 1); however, the enantiomeric ratio was nearly the same for both auxiliaries.

Surprisingly, we found that in our case the synthesis does not require the chelating effect of lithium, which is described for enantioselective addition in the case of the Li salt of diethyl phosphite. Moreover, in the case of ethyl phenylphosphinate, the reaction does not need the complexing ability of a Lewis acid catalyst for induction of enantioselectivity.

Table 1. Yield and isomeric ratio of α-aminophosphinates **3**, **4**, and α-aminophosphinic acids **5**

	R^1	R^2	**3**		**4**		**5**		
			Yield (%)	Diastereomeric ratio (%)[a]	Yield (%)	Diastereomeric ratio (%)	Yield (%)	Optical rotation $[\alpha]_D^{20}$	Enantiomeric ratio (%)[e]
a	Ph	Me	84	47:6:40:7	46	100:0[b]	60	−33[f]	100:0
b	3-OMe-Ph	Me	68	45:13:35:9	52	84:16[b]	23	−20[g]	90:10
c	2-Me-Ph	Me	48	30:14:40:16	27	83:17[b]	30	−19[g]	88:12
d	*i*-Bu	Me	60	45:39:11:5	–	–	20	−8[g]	80:20[c]
e	3-OMe-Ph	CH_2OMe	62	30:33:19:18	80	–[d]	40	−15[g]	79:21
f	2-Me-Ph	CH_2OMe	40	42:4:41:14	80	–[d]	42	−18[g,f]	86:14
g	*i*-Bu	CH_2OMe	60	42:10:35:13	–	–	50	−6.5[g]	70:30[c]

[a] After flash chromatography (the diastereomeric ratio had only changed slightly).

[b] After crystallisation.

[c] First hydrogenolysis, then hydrolysis.

[d] Oil, the diastereomeric ratio could not be determined by ^{31}P NMR because of diffuse peaks. The methoxy group is also hydrolysed to an OH group, according to FAB-MS.

[e] The enantiomeric ratio was determined by ^{31}P NMR after methylation of the phosphinic acid **5** to its methyl ester by means of diazomethane.

[f] Literature data: $[\alpha]_D^{20} = -28.8$ ($c = 1$, 1:1 HCl).[18]

[g] The optical rotation was determined in 20% NaOH solution ($c = 0.5$).

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19. Compound **3a**: oil. ^1H NMR ($CDCl_3$, 250 MHz) $\delta = 0.93$ (3H, t, $J_{HH} = 7.1$ Hz, $C\underline{H}_3CH_2O$, minor$_1$), 1.04 (3H, t, $J_{HH} = 7.1$ Hz, $C\underline{H}_3CH_2O$, major$_1$), 1.23 (3H, t, $J_{HH} = 7.1$

Hz, $\mathrm{C\underline{H}_3CH_2O}$, minor$_2$), 1.24 (3H, t, $J_{HH}=7.1$ Hz, $\mathrm{C\underline{H}_3CH_2O}$, major$_2$), 1.05 (3H, d, $J_{HH}=6.5$ Hz, $\mathrm{C\underline{H}_3CH}$, major$_1$), 1.18 (3H, d, $J_{HH}=6.5$ Hz, $\mathrm{C\underline{H}_3CH}$, major$_2$), 2.22 (1H, b, $\mathrm{N\underline{H}}$), 3.57 (1H, q, $J_{HH}=6.5$ Hz, $\mathrm{C\underline{H}_3CH}$), 3.62–3.82 (2H, m, $J_{PH}=14.2$ Hz, $\mathrm{CH_3C\underline{H}_2O}$, major$_1$), 3.97 (2H, dq, $J_{HH}=7.1$ Hz, $J_{PH}=14.2$ Hz, $\mathrm{CH_3C\underline{H}_2O}$, major$_2$), 4.08 (1H, d, $J_{PH}=16.1$ Hz, $\mathrm{PC\underline{H}}$, major$_1$), 4.11 (1H, d, $J_{HH}=16.1$ Hz, $\mathrm{PC\underline{H}}$, major$_2$), 6.98–7.11 (11H, m, $\mathrm{Ar\underline{H}}$), 7.20–7.45 (4H, m, $\mathrm{Ar\underline{H}}$). ^{13}C NMR δ: 16.47 (d, $J_{PC}=6.3$ Hz, $\mathrm{\underline{C}H_3CH_2O}$, major$_1$), 17.16 (d, $J_{PC}=6.3$ Hz, $\mathrm{\underline{C}H_3CH_2O}$, major$_2$) 22.10 (s, $\mathrm{\underline{C}H_3CH}$, major$_1$), 22.34 (s, $\mathrm{\underline{C}H_3CH}$, major$_2$), 55.27 (s, $\mathrm{CH_3\underline{C}H}$, major$_1$), 55.43 (s, $\mathrm{CH_3\underline{C}H}$, major$_2$), 60.61 (d, $J_{PC}=106.0$ Hz, $\mathrm{P\underline{C}H}$, major$_1$), 61.10 (d, $J_{PC}=106.0$ Hz, $\mathrm{P\underline{C}H}$, major$_2$), 61.40 (d, $J_{PC}=7.3$ Hz, $\mathrm{CH_3C\underline{H}_2O}$, major$_1$), 61.70 (d, $J_{PC}=7.3$ Hz, $\mathrm{CH_3C\underline{H}_2O}$, major$_2$), 125.38, 126.83, 127.47, 127.85 (d, $J_{PC}=98.0$ Hz, $\mathrm{P\underline{C}_{Ar}}$), 128.10, 128.31, 128.52, 128.73, 128.82, 129.10, 132.11, 132.22, 132.48, 132.63, 136.14, 136.26, 142.35, 145.35, $\mathrm{\underline{C}_{Ar}}$. Compound **3d**: oil. ^{1}H NMR δ: 0.26 (6H, d, $J_{HH}=6.4$ Hz, $\mathrm{C\underline{H}_3C\underline{H}_3CH}$, minor$_1$), 0.39 (6H, d, $J_{HH}=6.4$ Hz, $\mathrm{C\underline{H}_3C\underline{H}_3CH}$, major$_1$), 0.73 (6H, d, $J_{HH}=6.4$ Hz, $\mathrm{C\underline{H}_3C\underline{H}_3CH}$, minor$_2$), 0.80 (6H, d, $J_{HH}=6.4$ Hz, $\mathrm{C\underline{H}_3CH_3CH}$, major$_2$), 1.15 (3H, d, $J_{HH}=6.5$ Hz, $\mathrm{C\underline{H}_3CH}$), 1.22 (3H, t, $J_{HH}=7.0$ Hz, $\mathrm{C\underline{H}_3CH_2O}$, major$_1$), 1.29 (3H, t, $J_{HH}=7.0$ Hz, $\mathrm{C\underline{H}_3CH_2O}$, major$_2$), 1.28–1.35 (2H, m, $J_{HH}=2.0$ Hz, $\mathrm{C\underline{H}_2CH}$), 1.47–1.81 (1H, m, $\mathrm{CH_3CH_3C\underline{H}}$), 2.59 (1H, b, $\mathrm{N\underline{H}}$), 4.10 (1H, dd, $J_{PH}=17.0$ Hz, $J_{HH}=2.0$ Hz, $\mathrm{PC\underline{H}}$) 3.74–3.95 (2H, m, $J_{HH}=7.0$ Hz, $\mathrm{CH_3C\underline{H}_2O}$, major$_1$), 4.04–4.29 (2H, m, $J_{HH}=7.0$ Hz, $\mathrm{CH_3C\underline{H}_2O}$, major$_2$), 7.07–7.32 (7H, m, $\mathrm{Ar\underline{H}}$), 7.43–7.51 (2H, m, $\mathrm{Ar\underline{H}}$), 7.74–7.91 (1H, m, $\mathrm{Ar\underline{H}}$). Compound **4a**: mp: 223°C. ^{1}H NMR (DMSO, 250 MHz) $\delta=1.08$ (3H, d, $J_{HH}=6.4$ Hz, $\mathrm{C\underline{H}_3CH}$), 2.42 (1H, b, $\mathrm{N\underline{H}}$), 3.40 (1H, q, $J_{HH}=6.4$ Hz, $\mathrm{CH_3C\underline{H}}$), 3.71 (1H, d, $J_{PH}=15.8$ Hz, $\mathrm{PC\underline{H}}$), 6.99–7.26 (13H, m, $\mathrm{Ar\underline{H}}$), 7.47–7.53 (2H, m, $\mathrm{Ar\underline{H}}$). Compound **5a**: mp: 166°C. ^{1}H NMR (DMSO, 250 MHz) $\delta=2.82$ (1H, d, $J_{PH}=16.9$ Hz, $\mathrm{PC\underline{H}}$), 3.39 (3H, b, $\mathrm{O\underline{H}}$, $\mathrm{N\underline{H}_2}$), 6.99–7.24 (4H, m, $\mathrm{Ar\underline{H}}$), 7.27–7.38 (4H, m, $\mathrm{Ar\underline{H}}$), 7.47–7.53 (2H, m, $\mathrm{Ar\underline{H}}$). Compound **5b**,**e**: mp: 186°C. ^{1}H NMR ($\mathrm{D_2O}$, 250 MHz) $\delta=2.46$ (2H, b, $\mathrm{N\underline{H}_2}$), 3.09 (3H, s, $\mathrm{C_{Ar}OC\underline{H}_3}$), 3.42 (1H, d, $J_{PH}=20.6$ Hz, $\mathrm{PC\underline{H}}$), 6.58–7.20 (9H, m, $\mathrm{Ar\underline{H}}$). FAB-MS: m/z 278 $[M+1]^+$ (calcd 277.3). Compound **5c**,**f**: mp: 158°C. ^{1}H NMR ($\mathrm{D_2O}$, 250 MHz) $\delta=1.90$ (3H, s, $\mathrm{C_{Ar}C\underline{H}_3}$), 2.95 (1H, d, $J_{PH}=17.6$ Hz, $\mathrm{PC\underline{H}}$), 4.99 (2H, b, $\mathrm{N\underline{H}_2}$), 6.69–6.93 (2H, m, $\mathrm{Ar\underline{H}}$), 7.19–7.41 (7H, m, $\mathrm{Ar\underline{H}}$). FAB-MS: m/z 262 $[M+1]^+$ (calcd 261.3). Compound **5d**,**g**: mp: 124°C, ^{1}H NMR ($\mathrm{D_2O}$, 500 MHz) $\delta=0.49$ (3H, d, $J_{HH}=6.4$ Hz, $\mathrm{(C\underline{H}_3)_2CH}$), 0.56 (3H, d, $J_{HH}=6.4$ Hz, $\mathrm{(C\underline{H}_3)_2CH}$), 0.91–1.28 (2H, m, $\mathrm{C\underline{H}_2CH}$), 1.35–1.42 (1H, m, $\mathrm{(CH_3)_2C\underline{H}}$), 1.95 (2H, b, $\mathrm{N\underline{H}_2}$), 2.57–2.83 (1H, m, $J_{PH}=16.0$ Hz, $\mathrm{PC\underline{H}}$), 7.23–7.29 (3H, m, $\mathrm{Ar\underline{H}}$), 7.40–7.44 (2H, m, $\mathrm{Ar\underline{H}}$). FAB-MS: m/z 228 $[M+1]^+$ (calcd 227.3).