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Interesting by-products in the synthesis of chiral α-aminophosphinates from enantiopure sulfinimines

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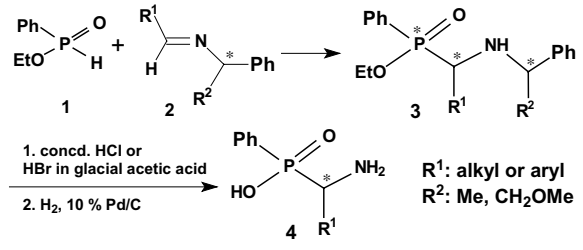
Abstract—A new reaction of enantiopure sulfinimines and ethyl phenylphosphinate is given. Several unexpected products were isolated and identified, their mechanism of formation is proposed.

α-Aminophosphonic and phosphinic acids are phosphorus analogues of α-aminocarboxylic acids, and therefore have biological importance.[1] Recently, we published a method for the enantioselective synthesis of substituted α-aminophosphinic acids **4** by the addition of ethyl phenylphosphinate **1** to imines **2** (Scheme 1).[2] The latter were prepared from an aldehyde and (*S*)-phenylethylamine or (*S*)-phenylglycinol methyl ether. These two simple chiral auxiliaries proved to be good to excellent in inducing asymmetry on the imine carbon atom resulting in enantiopure α-aminophosphinic acids **4** after deprotection of α-aminophosphinates **3**. It has to be pointed out that neither lithium as chelating metal, nor a Lewis acid catalyst are required for induction of the enantioselectivity in the phosphorylation reaction.



Scheme 1.

Keywords: α-Aminophosphinic acids; Ethyl phenylphosphonic acid; Side reaction of *p*-tolylsulfinimines.
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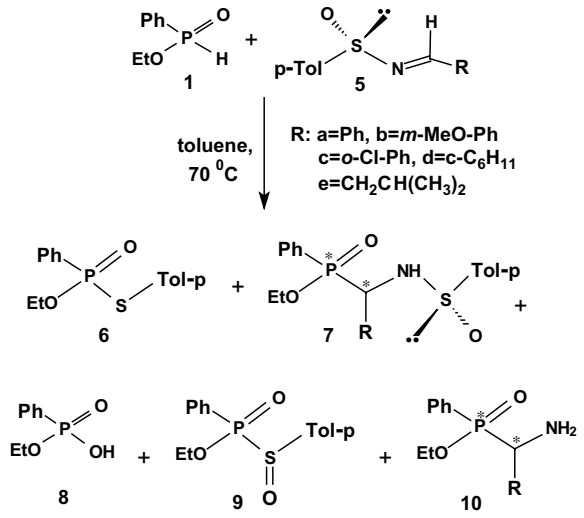
Continuing our work on the reactivity of phosphinate **1**, we decided to test sulfinamides as the chiral auxiliary, therefore several sulfinimine derivatives were synthesized in order to react them with ethyl phenylphosphinate.

Davis and co-workers successfully used enantiopure *p*-toluenesulfinimines as versatile chiral imine building blocks in the enantioselective synthesis of α- and β-aminoacids,[3,4] while others have used them in the synthesis of chiral primary amines.[5] This type of auxiliary was also used in the enantioselective synthesis of β- and α-amino-phosphonates[6] providing excellent enantiomeric excess using the lithium metal salt of methyl phosphonic acid diethyl ester and that of diethyl phosphite, respectively.

We chose (*S*)-sulfinimines **5** as the aminophosphinate precursors and prepared them by condensation of (*S*)-*p*-toluenesulfinamide with an aldehyde in dichloromethane with 4 Å molecular sieves at reflux temperature, according to a method in the literature.[7] After flash chromatography (hexane–ethyl acetate 9:1) the imines were isolated in moderate yields.[8] The imines **5a**–**e** and 2 equiv of ethyl phenylphosphinate **1** were kept at 70 °C in toluene and the reaction was run until the imine was consumed (50–100 h) (Scheme 2).

In the ^{31}P NMR spectra of the reaction mixtures several phosphorus containing products were always observed including thiophosphonic acid ester **6**,[9] phenylphosphonic acid monoethyl ester **8**, phosphonyl *p*-tolylsulfoxide **9**,[10] and the unprotected aminophosphinic acid ester **10**[11] besides the desired α-aminophosphinate **7**.[12]

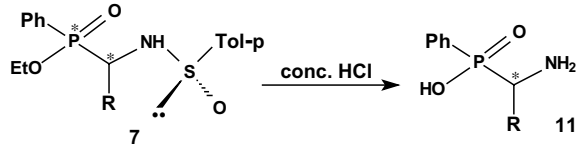


Scheme 2.

After separation of the products by column chromatography (on silica gel, eluent: toluene–acetone 17:3) we could isolate **6**, **7**, and **10** in pure form.

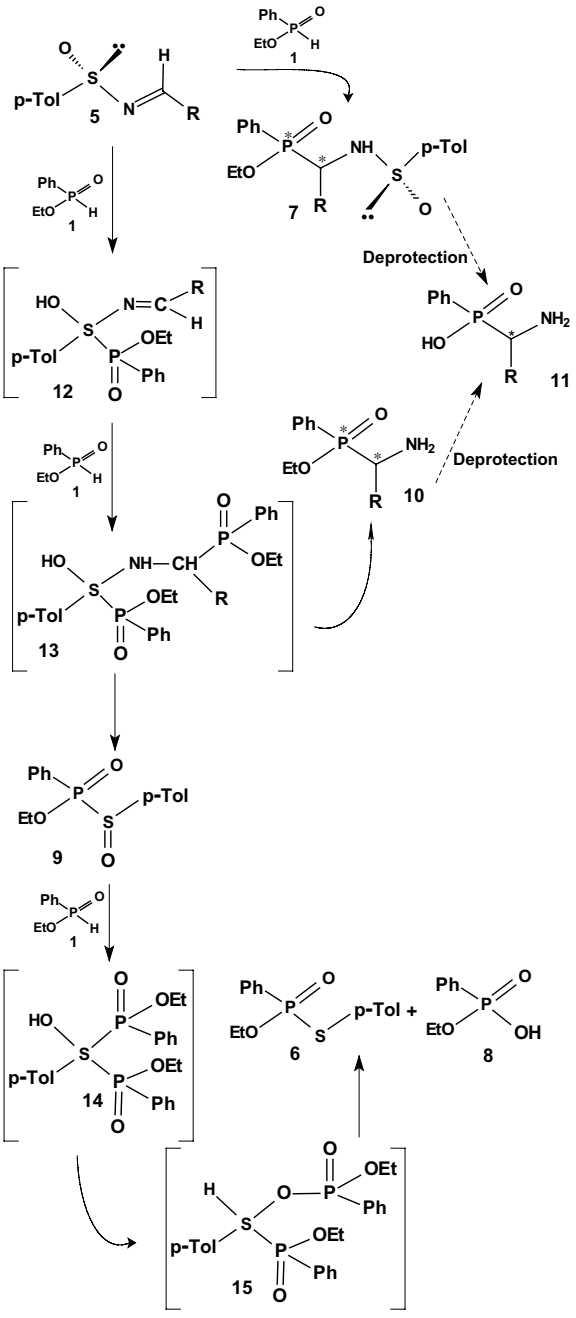
According to expectations, α-aminophosphinates **7** were obtained as four diastereomers although their yields were modest using imine derivatives **5a**–**c** prepared from aromatic aldehydes. We could not observe the formation of **7** at all for the aliphatic or alicyclic aldehydes **5d**–**e**. In all cases, thiophosphonic acid ester **6** was the main product. The phenylphosphonic acid monoethyl ester **8**, as well as **9** and **10**, was also detected in the reaction mixture, which indicated that the sulfur in **6** had been reduced; correspondingly the phosphorus in **8** had been oxidized.

Removal of the *N*-sulfinyl auxiliary and hydrolysis of the ethyl esters from the diastereomers of **7** were achieved in one step using concentrated hydrochloric acid under reflux (Scheme 3) to give the α-aminophosphinic acids[13] **11** with (−)-optical rotations (*R*).[14] The deprotection reactions occurred without racemization of the α-carbon,[2] still only modest enantiomeric excesses were observed (Table 2).



Scheme 3.

We assume, that the formation of **6**, **8**, **9**, and **10** can be explained by attack of the phosphorus nucleophile **1** on the sulfoxide moiety of **5** by a 1,2 addition causing loss of chirality and producing **12** as an intermediate in the first step of the reaction sequence (Scheme 4). In the cases of the aliphatic imines (**5d**, **5e**), this is the exclusive direction of the reaction due to the weaker electrophilicity of the carbon atom compared to that of the aromatic substituents (Table 1).



Scheme 4.

Table 1. Ratio (%) of compounds detected from ^{31}P NMR spectra

R	6[a]	7[b]	8[c,d]	9[c]	10[e]
a	41	19	15	11	14
b	37	35	3	7	18
c	35	22	6	7	30
d	55	—	31	14	—
e	83	—	13	4	—

[a] Yield after column chromatography (%): **6a**: 34, **6b**: 23, **6c**: 20, **6d**: 35, **6e**: 60.

[b] Mixture of four diastereomers.

[c] ^{31}P NMR ($CDCl_3$, 500 MHz) **8**: $\delta = 20.7$, **9**: $\delta = 1.1$ ppm.

[d] The ratio of **6/9** is not reliable because part of **9** separated in solid form from the NMR solution.

[e] ^{31}P NMR ($CDCl_3$, 500 MHz) **10a**: $\delta = 40.0, 39.9$; **10b**: $\delta = 39.8, 39.7$; **10c**: $\delta = 38.7, 38.5$ ppm.

Table 2. Enantiomeric excess (ee), yield, and chemical shifts of α-aminophosphinic acids **11**

R	11		
	Ee[a]	Yield (%)	δ^{31}P
a	20	52	30.3
b	40	48	31.6
c	30	58	37.9

[a] The enantiomeric ratio was determined by ^{31}P NMR after methylation of the phosphinic acid **5** by diazomethane.

A subsequent 1,2-addition of the phosphinate **1** to the C=N moiety in intermediate **12** results in the formation of **13**. Intermediate **13** can lose an aminophosphinate moiety **10** (in racemic form) and at the same time the side-product **9** is formed. Further transformation of **9** to side-products **6** and **8** needs another 1,2-addition of the phosphorus starting material to **9** supplying **14**. The latter intermediate—by an S–O phosphoryl migration—gives **15**, which splits into **6** and **8** by a redox process. A possible radical mechanism can be ruled out, because the same products were observed in the phosphorylation reaction carried out in the presence of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical trapping agent.[15]

This side reaction sequence is interesting because, according to our knowledge, there is only one example in the literature when the sulfur atom of a *p*-toluenesulfinimine, and not the carbon, was attacked. Moreau et al.[5b] aiming at the preparation of chiral amines also isolated an S-substituted product, that is tolyl methylsulfoxide, in a side reaction in the reaction of sulfinimine **5a** and methylmagnesium bromide.

Work to improve the regioselectivity and examination of the scope and limitation of these side-reactions is in progress.

Acknowledgements

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References and notes

1. Kuhkar, V. P.; Hudson, H. R. *Aminophosphonic and Aminophosphinic Acids*; John Wiley & Sons: Chichester, 2000.
2. Szabó, A.; Jászay, M. Z.; Hegedüs, L.; Töke, L.; Petneházy, I. *Tetrahedron Lett.* **2003**, *44*, 4603.
3. (a) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-H. *J. Org. Chem.* **1996**, *61*, 440; (b) Davis, F. A.; Fanelli, D. L. *J. Org. Chem.* **1998**, *63*, 1981.
4. (a) Davis, F. A.; Reddy, T. R.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387; (b) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913.
5. (a) Liu, G.; Cogan, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1997**, *119*, 9913; (b) Moreau, P.; Essiz, M.; Mérour, J.-Y.; Bouzard, D. *Tetrahedron: Asymmetry* **1997**, *8*, 591.
6. (a) Mikolajczyk, M.; Łyżwa, P.; Drabowicz, J. *Tetrahedron: Asymmetry* **1997**, *8*, 3991; (b) Mikolajczyk, M.; Łyżwa, P.; Drabowicz, J.; Wieczorek, M. W.; Błaszcyk, J. *Chem. Commun.* **1996**, 1503; (c) Lefebvre, I. M.; Evans, S. A. *J. Org. Chem.* **1997**, *62*, 7532.
7. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.
8. Compound **5c** is new, while the other sulfinimines are known. **5c**: ^{1}H NMR ($CDCl_3$, 250 MHz) $\delta = 2.40$ (s, 3H, C*H*$_3$), 7.33–7.67 (m, 4H, Ar*H*), 7.71–7.87 (m, 4H, Ar*H*), 9.08 (s, 1H, C*H*=N).
9. Compound **6**: ^{1}H NMR ($CDCl_3$, 250 MHz) $\delta = 1.38$ (t, $J_{HH} = 6.9$ Hz, 3H, C*H*$_3$CH$_2$O), 2.28 (s, 3H, C*H*$_{3Ar}$), 4.34 (dq, $J_{HH} = 6.9$ Hz, $J_{PH} = 14.1$ Hz, 2H, CH$_3$C*H*$_2$O), 6.99–7.14 (dd, 4H, Ar*H*), 7.17–7.50 (m, 3H, Ar*H*). 7.61–7.69 (m, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$) $\delta = 15.90$ (d, $J_{PC} = 6.6$ Hz, *C*H$_3$CH$_2$O), 20.69 (s, *C*H$_{3Ar}$), 61.88 (d, $J_{PC} = 6.6$ Hz, CH$_3$C*H*$_2$O), 122.31 (d, $J_{PC} = 5.5$ Hz), 127.63, 127.86, 129.52 (s, 2*C*$_{Ar}$), 130.86, 131.02, 131.10 (d, $J_{PC} = 150$ Hz, P*C*$_{Ar}$), 132.06 (d, $J_{PC} = 2.6$ Hz, *C*$_{Ar}$), 134.92 (d, $J_{PC} = 3.8$ Hz, 2*C*$_{Ar}$), 138.72 (d, $J_{PC} = 2.3$ Hz) *C*$_{Ar}$. ^{31}P NMR ($CDCl_3$) $\delta = 43.8$. FAB-MS: m/z 293 $[M+1]^+$ (calcd 292.3).
10. To give a chemical proof for the structure of **9**, **6** was oxidized by *m*-chloroperbenzoic acid. The product was monitored by FAB-MS, the fragmentation was identical with that of **9**.
11. Compound **10a**: ^{31}P NMR ($CDCl_3$) $\delta = 40.0$, 39.9 ppm. Compound **10b**: ^{31}P NMR ($CDCl_3$) $\delta = 39.8$, 39.7 ppm. Compound **10c**: ^{31}P NMR ($CDCl_3$) $\delta = 38.7$, 38.5 ppm.
12. Compound **7a**: oil. Yield: 15%. ^{1}H NMR ($CDCl_3$, 250 MHz) $\delta = 1.13$ (t, $J_{HH} = 7.1$ Hz), 1.24 (t, $J_{HH} = 7.1$ Hz), 3H, C*H*$_3$CH$_2$O, 2.15 (s, 3H, C*H*$_{3Ar}$), 4.14 (dq, $J_{HH} = 7.1$ Hz, $J_{PH} = 11.8$ Hz, 2H, CH$_3$C*H*$_2$O), 5.58 (d, $J_{PH} = 19.3$ Hz), 5.62 (d, $J_{HH} = 19.3$ Hz) 1H, PC*H*, 6.35 (b, 1H, N*H*), 6.98–7.32 (m, 11H, Ar*H*), 7.40–7.84 (m, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$) $\delta = 16.35$ (d, $J_{PC} = 5.8$ Hz, *C*H$_3$CH$_2$O), 21.58 (s, *C*H$_{3Ar}$), 62.85 (d, $J_{PC} = 19.7$ Hz, CH$_3$C*H*$_2$O), 69.23 (d, $J_{PC} = 110.0$ Hz, P*C*H), 122.47, 123.54, 125.02, 125.94, 126.57, 126.67, 127.02, 127.20, 127.57, 128.07, 128.60 (d, $J_{PC} = 93.6$ Hz, P*C*$_{Ar}$), 130.70, 131.40, 131.90, 132.30, 132.70, 133.70, 137.90 *C*$_{Ar}$. ^{31}P NMR ($CDCl_3$) $\delta = 41.3$, 40.8, 40.0, 38.9. Compound **7b**: oil. Yield: 31%. ^{1}H NMR ($CDCl_3$, 250 MHz) $\delta = 1.15$ (t, $J_{HH} = 7.1$ Hz), 1.20 (t, $J_{HH} = 7.1$ Hz), 3H, C*H*$_3$CH$_2$O, 2.26 (s, 3H, C*H*$_{3Ar}$), 3.53 (s), 3.56 (s), 3H, OC*H*$_3$, 3.93 (dq, $J_{HH} = 7.1$ Hz, $J_{PH} = 11.7$ Hz, 2H, CH$_3$C*H*$_2$O), 4.87 (b, 1H, N*H*), 5.03 (d, $J_{PH} = 19.6$ Hz), 5.07 (d, $J_{HH} = 19.6$ Hz) 1H, PC*H*, 6.64–6.72 (m, 2H, Ar*H*), 7.05–7.50 (m, 11H, Ar*H*). ^{13}C NMR ($CDCl_3$) $\delta = 16.65$ (d, $J_{PC} = 5.7$ Hz, *C*H$_3$CH$_2$O), 21.58 (s, *C*H$_{3Ar}$), 55.24 (s, O*C*H$_3$), 62.10 (d, $J_{PC} = 20.0$ Hz, CH$_3$C*H*$_2$O), 73.21 (d, $J_{PC} = 111.0$ Hz, P*C*H), 111.95, 112.29, 114.27, 114.42, 119.63, 119.91, 125.20 (d, $J_{PC} = 107.0$ Hz, P*C*$_{Ar}$), 125.44, 128.03, 128.24, 128.45, 128.93, 129.16, 132.67, 133.04, 133.19, 137.90, 138.17 *C*$_{Ar}$. ^{31}P NMR ($CDCl_3$) $\delta = 40.8$, 40.6, 39.8, 39.7. Compound **7c**: oil. Yield: 19%. ^{1}H NMR ($CDCl_3$, 250 MHz) $\delta = 1.14$ (t, $J_{HH} = 7.1$ Hz), 1.23 (t, $J_{HH} = 7.1$ Hz), 3H, C*H*$_3$CH$_2$O, 2.14 (s, 3H, C*H*$_{3Ar}$), 4.16 (dq, $J_{HH} = 7.1$ Hz, $J_{PH} = 12.0$ Hz, 2H, CH$_3$C*H*$_2$O), 5.68 (d, $J_{PH} = 19.2$ Hz), 5.72 (d, $J_{HH} = 19.2$ Hz) 1H, PC*H*, 6.42 (b, 1H, N*H*), 6.97–7.34 (m, 11H, Ar*H*), 7.39–7.81 (m, 2H, Ar*H*). ^{13}C NMR ($CDCl_3$) $\delta = 16.40$ (d, $J_{PC} = 5.6$ Hz, *C*H$_3$CH$_2$O), 21.56 (s, *C*H$_{3Ar}$), 62.80 (d, $J_{PC} = 20.0$ Hz, CH$_3$C*H*$_2$O), 69.21 (d, $J_{PC} = 109.0$ Hz, P*C*H), 125.47, 126.54, 127.02, 127.94, 128.57, 128.67, 129.02, 129.20,

129.57, 131.07, 131.60 (d, $J_{PC} = 93.6$ Hz, PC_{Ar}), 131.70, 132.40, 132.90, 133.30, 133.70, 134.70, 138.00 C_{Ar}. ^{31}P NMR ($CDCl_3$) $\delta = 40.3$, 39.4, 38.8, 38.5.

13. General procedure for α-aminophosphinic-acid **11**: α-Aminophosphinate **7** (1.5 Mmol) and 10 mL concentrated hydrochloric acid were refluxed for 8 h, then cooled and evaporated in vacuum. Ethanol (10 mL) and 0.5 mL propylene oxide were added to the residue, **11a–c** were isolated as crystals. Compound **11a**: mp: 166 °C. ^{1}H NMR (d_6-DMSO, 250 MHz) $\delta = 2.82$ (d, $J_{PH} = 16.9$ Hz, 1H, PC*H*), 3.39 (b, 3H, O*H*, NH_2), 6.99–7.24 (m, 4H, Ar*H*), 7.27–7.38 (m, 4H, Ar*H*), 7.47–7.53 (m, 2H, Ar*H*). Compound **11b**: mp: 186 °C. ^{1}H NMR (D_2O, 250 MHz) $\delta = 2.46$ (b, 2H, NH_2), 3.09 (s, 3H, $C_{Ar}OCH_3$), 3.42 (d, $J_{PH} = 20.6$ Hz, 1H, PC*H*), 6.58–7.20 (m, 9H, Ar*H*). FAB-MS: m/z 278 $[M+1]^+$ (calcd 277.3). Compound **11c**: mp: 178 °C ^{1}H NMR δ: (d_6-DMSO, 250 MHz) 3.23 (d, $J_{PH} = 17.6$ Hz, 1H, PC*H*), 3.74 (b, 2H, NH_2), 7.07–7.64 (m, 9H, Ar*H*). ^{13}C NMR (d_6-DMSO) δ: 37.96 (d, $J_{PC} = 92.6$ Hz, P*C*H), 125.87, 126.03, 127.86, 127.90, 127.96, 129.00 (d, $J_{PC} = 102.0$ Hz, PC_{Ar}), 129.87, 130.98, 131.14, 131.46, 132.8 (d, $J_{PC} = 16.5$ Hz, C_{Ar}–Cl), 133.10 C_{Ar}. ^{31}P NMR (d_6-DMSO) δ: 34.69.
14. The (*R*)-enantiomer of ethyl α-benzylamino-phenylphosphinic acid is known from the literature, and has been isolated by resolution and by repeated crystallization from the diastereomeric mixture of its ester. The absolute configuration was then determined by X-ray crystallography. See: Belov, Yu. P.; Rakhnovich, G. B.; Davankov, V. A.; Godovikov, N. N.; Aleksandrov, G. G.; Struchkov, Yu. T. *Izv. Akad. Nauk.* **1980**, *5*, 1125.
15. 2,2,6,6-Tetramethylpiperidine-1-oxyl (0.1 equiv), 1 equiv of imine **5a** or **5e** and 2 equiv of ethyl phenylphosphinate **1** were kept at 70 °C in toluene.