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Synthesis of chiral β-aminophosphonates via Rh-catalyzed asymmetric hydrogenation of β-amido-vinylphosphonates

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ABSTRACT

The Rh-catalyzed asymmetric hydrogenation of prochiral β-*N*-acetylamino-vinylphosphonates allows the preparation of chiral β-*N*-acetylamino-phosphonates with excellent yields (up to 100%) and high enantioselectivities (up to 92% ee). The reaction is strongly dependent on the chiral bidentate phosphorus ligand and the solvent employed. In several cases an inversion of the induced chirality was noted by using the corresponding *E*- or *Z*-isomeric substrates.

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1. Introduction

Phosphorus analogues of amino acids display highly interesting properties in biochemistry and medicine. By replacement of natural α- or β-amino acids in proteins by the corresponding aminophosphonic acids structure and binding properties are significantly altered, hence new insights in biochemical process are possible as well as new medicinal applications emerge.[1] In this view, β-aminophosphonic acids are isosters of β-amino acids.[2] Up to now they have seen applications as antibacterial agents,[3] enzyme inhibitors,[4] haptens for catalytic antibodies[5] und anti-HIV agents.[6]

Recently, Palacios[1] and Ma[7] summarized methods for the preparation of β-aminophosphonates. These compounds can be prepared via formation of C–C–, C–N–, and C–P–bonds, ring opening reactions or rearrangements. Other venues are based on the selective reduction of unsaturated functionalities such as amides[8] or thioamides[9] with boranes or the hydrogenation of oximes with molecular hydrogen in the presence of Raney-nickel[10] and Pd/C,[11] respectively. Further methods rely on the reduction of azides, nitriles, or nitro compounds.[1]

In most cases β-aminophosphonates are chiral.[7] Therefore, in recent time growing research activities are dedicated to the enantioselective preparation of synthetic precursors, which can be easily transformed into β-aminophosphonates.[12] For example, Kolodiazhnyi et al. reported on the diastereoselective reduction of chiral β-keto phosphonates with the $NaBH_4$/tartaric acid system to afford the corresponding β-hydroxy phosphonates with high diastereoselectivity.[13]

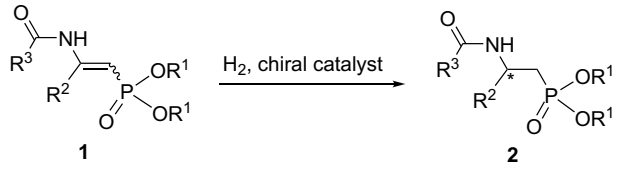

Figure 1. Asymmetric hydrogenation of prochiral β-enamidophosphonates.

In spite of these results up to now there is no report for the asymmetric hydrogenation of prochiral enamidophosphonates of type **1** which would directly lead to the formation of chiral β-amidophosphonates **2** (Fig. 1). The only known examples of a hydrogenation approach concern the diastereoselective reduction of optically active β-enaminophosphonates with $NaBH_4$ or H_2/Pd/C to give diastereomeric 2-amino-2-alkyl-ethan-1-ylphosphonates in 20–90% de.[14]

This situation is quite astonishing since the asymmetric hydrogenation of pertinent dehydroamino acid derivatives with chiral transition metal catalysts, preferentially based on Rh-, Ru-, or Ir-complexes, is one of the most established methods for the preparation of chiral α-[15] and β-amino acids.[16] Moreover, the reduction of these olefins is usually employed as a benchmark reaction to test the catalytic performance of chiral catalysts, and therefore is the focus of numerous mechanistic investigations.[17,18] Also the asymmetric hydrogenation of α-dehydroamino phosphonates is known to proceed with high enantioselectivity with Rh-catalysts based on phosphorus ligands.[7,19]

2. Results and discussion

Herein, we report our results on the first enantioselective hydrogenation of β-enamidophosphonates generating chiral

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β-amidophosphonates with a huge potential for biochemical and medicinal applications. Moreover, reaction products can be used as coupling reagents in Horner–Wadsworth–Emmons-reactions, hence those chiral amines can be derived which are not easily accessible by other methods.[20]

The required prochiral substrates for asymmetric hydrogenation can be prepared by different pathways. For example, reaction of α-halo ketones with trialkylphosphites affords β-ketophosphonates which can be converted by condensation with ammonia or primary amines into enaminophosphonates.[21] Final acetylation affords the desired enamides as a mixture of *E*- and *Z*-isomers.[22] The composition of the mixture is dependent on the substitution pattern and the solvent used.[23] The addition of primary amines or ammonia to unsaturated phosphonates (1-alkenylphosphonates[24] or allenyl-phosphonates[14,25]) likewise yields prochiral enamides.

We followed the route suggested by the groups of Palacios and Oh.[26a–c] In their approach nitriles **4** are reacted with methyldiethylphosphonate **3** in the presence of *n*-BuLi (Fig. 2). Subsequent hydrolysis gives 2-amino-alkenylphosphonates **5**, which are acylated with acetic anhydride or acetyl chloride to give the desired dehydroamidophosphonates of type **6**.

According to these conditions, we obtained *E*/*Z*-mixtures of compounds **6a,b** which were subsequently separated into the individual isomers by flash chromatography.

Preliminary individual trials of the asymmetric hydrogenation under conditions usually successful in the hydrogenation of α- and β-dehydroacetamido acid derivatives (e.g., ambient pressure)[15,16] gave disappointing results. In order to speed up the screening process in the next stage, we investigated the reaction in a high-throughput (HTS) approach considering 20 chiral Rh-complexes in three solvents at an initial hydrogen pressure of 35–40 bar (0.1 mmol substrate in 0.5 mL solvent, S/C = 100) (Fig. 3). Precatalysts were prepared in situ by mixing $[Rh(COD)_2]BF_4$ with an equimolar amount of the bidentate phosphorus ligand. Among these 240 trials Rh-catalysts based on ligands **8**–**11** performed best. Superior results were achieved in both dichloromethane and THF as solvent.[27,28] Subsequent up-scal-

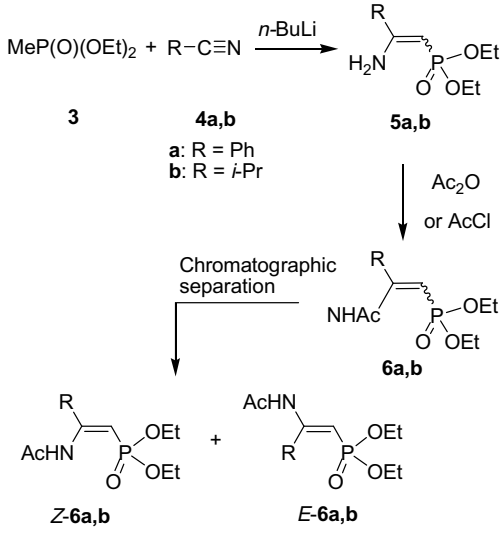

Figure 2. Synthesis of isomeric β-enamidophosphonates **6**.

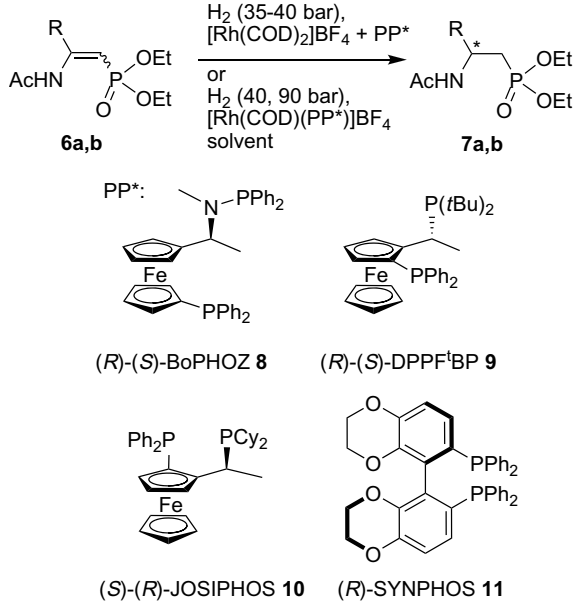

Figure 3. Rh-catalyzed asymmetric hydrogenation and the best ligands.

Table 1
Results of the asymmetric hydrogenation of β-enamidophosphonates *Z*-**6a**,**b** and *E*-**6a**,**b**[a]

Entries	Substr.	PP*	40 bar, THF		40 bar, CH_2Cl_2		90 bar, THF		90 bar, CH_2Cl_2	
			Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)	Conv.[b] (%)	ee[c] (%)
1	*Z*-**6a**	**8**	100	67 (−)	100	72 (−)	100	71 (−)	100	67 (−)
2	*Z*-**6a**	**9**	100	35 (−)	80	78 (−)	100	36 (−)	100	79 (−)
3	*Z*-**6a**	**10**	100	**90** (+)	100	**83** (+)	100	**89** (+)	100	77 (+)
4	*Z*-**6a**	**11**	100	22 (−)	57	23 (−)	100	10 (−)	100	23 (−)
5	*E*-**6a**	**8**	100	**82** (−)	100	76 (−)	100	**82** (−)	91	76 (−)
6	*E*-**6a**	**9**	100	14 (+)	100	32 (+)	100	17 (+)	100	35 (+)
7	*E*-**6a**	**10**	92	24 (+)	100	42 (+)	100	25 (+)	90	41 (+)
8	*E*-**6a**	**11**	62	70 (+)	65	**92** (+)	71	73 (+)	66	**90** (+)
9	*Z*-**6b**	**8**	92	62 (+)	80	**86** (+)	85	71 (+)	78	**91** (+)
10	*Z*-**6b**	**9**	69	59 (+)	75	84 (+)	52	68 (+)	87	**90** (+)
11	*Z*-**6b**	**10**	100	**89** (−)	93	72 (−)	100	**91** (−)	100	75 (−)
12	*Z*-**6b**	**11**	100	22 (−)	57	23 (−)	100	10 (−)	100	23 (−)
13	*E*-**6b**	**8**	100	65 (+)	100	61 (+)	100	66 (+)	100	67 (+)
14	*E*-**6b**	**9**	100	50 (−)	100	**78** (−)	100	56 (−)	100	69 (−)
15	*E*-**6b**	**10**	100	29 (−)	100	58 (−)	100	34 (−)	100	63 (−)
16	*E*-**6b**	**11**	100	70 (−)	100	55 (−)	100	63 (−)	100	**81** (−)

[a] 0.33 mmol of substrate, 0.0033 mmol of $[Rh(PP^*)(COD)]BF_4$ at 25 °C, 24 h in 4 mL of solvent.
[b] The determination of the conversion was carried out by ^1H- or ^{31}P NMR spectroscopy.
[c] The enantiomeric excess was determined by HPLC (CHIRALPAK AD-H, 15 cm), **6a**: hexane/ethanol = 95:5, 1.5 mL/min, t_R = 10.9 min for (−)-enantiomer, t_R = 17.5 min for (+)-enantiomer; **6b**: hexane/ethanol = 92:8, 0.8 mL/min, t_R = 5.0 min for (+)-enantiomer, t_R = 6.1 min for (−)-enantiomer; in brackets the sign of the specific rotation of the hydrogenation product.

ing experiments were carried out with isolated precatalysts of the type [Rh(COD)(PP*)]BF_4 at 40 and 90 bar, respectively, initial hydrogen pressure. No differences in the catalytic results in dependence on the nature of the precatalyst preparation (in situ vs isolated precatalyst) were noted.

Results of the optimized trials, which were performed with 0.5 mmol of the substrate are listed in Table 1.[29] Our results give evidence that Rh-catalyzed asymmetric hydrogenation is a powerful methodology for the preparation of the desired chiral target compounds. With the exception of a few trials, most reactions were complete after 24 h. In dependence on the catalyst, solvent and hydrogen pressure used up to 92% ee could be achieved (entry 8, 40 bar, CH_2Cl_2). In contrast to most asymmetric hydrogenations of related β-dehydroacylamido acid derivatives also with *Z*-β-acetylamido-vinylphosphonates as substrates, good ee-values can be achieved (up to 91% ee). It is remarkable to note that the application of ligands **9** and **10** gave in the hydrogenation of *Z*-substrates products with the opposite configuration in the product. In contrast by employment of *E*-olefins the same configuration was induced. There is no uniform correlation between H_2-pressure and enantioselectivity, neither with *E*- nor with *Z*-substrates. Moreover, a comparison of results obtained with different substrates is not possible. Small changes in the structure of the substrate or ligand structure influence the catalytic result significantly. This finding is in contrast to the tendencies noted several times with related unsaturated β-amino acid substrates in hand.[17b]

3. Conclusions

In conclusion for the first time the asymmetric hydrogenation of β-acetylamido-vinylphosphonates was successfully performed to give the chiral β-acetylamido phosphonates in up to 92% ee. Further work is in progress to elucidate the mechanism of the reaction.

4. Experimental

4.1. General procedure

Solvents were dried and freshly distilled under argon before use. All reactions were performed under an argon atmosphere. Thin-layer chromatography was performed on precoated TLC plates (silica gel). Flash chromatography was carried out with Silica Gel 60 (particle size 0.040–0.063 mm). Melting points are uncorrected. NMR spectra were recorded at a Bruker ARX 400 spectrometer at the following frequencies: 400.13 MHz (^{1}H), 100.63 MHz (^{13}C), 161.98 MHz (^{31}P). Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield from TMS as internal standard. Chemical shifts of ^{31}P NMR spectra are referred to H_3PO_4 as external standard. Signals are quoted as s (singlet), d (doublet), br (broad) and m (multiplet). The chiral ligands were purchased from STREM and ALFA AESAR.

4.2. (*Z*)-Diethyl-2-amino-2-phenylvinylphosphonate 5a

A 250 mL flask was charged with diethylmethylphosphonate (33 mmol, 5.02 g) in dry THF (90 mL). At −78 °C, a 1.6 M *n*-BuLi/hexane-solution (36.3 mmol, 22.7 mL) was slowly added and the solution was stirred for 1 h. After addition of 1 equiv of benzonitrile (33 mmol, 3.41 g), stirring was continued for 15 min at this temperature and further 2 h at 0 °C. After quenching the reaction with water (25 mL), the mixture was evaporated on a rotavapor to remove the THF. The aqueous residue was extracted with dichloromethane (3 × 30 mL), the combined extracts were dried (Na_2SO_4), and concentrated to yield **5a** as a pale yellow oil (7.90 g, 94%). ^{1}H NMR (acetone-d_6) δ 7.62 (m, 2H, arom. H), 7.43 (m, 3H, arom. H), 6.63 (s (br), 2H, NH_2); 4.08 (m, J = 11.9 Hz, 1H, =CH), 4.00 (m, 4H, OCH_2), 1.27 (d, J = 6.9 Hz, 6H, CH_3); ^{13}C NMR (acetone-d_6) δ 163.4 (N–C=), 139.7 (arom. C), 127.0, 129.3, 130.6 (arom. CH), 73.9 (d, J = 191 Hz, =CH), 61.2 (OCH_2), 16.7 (CH_3); ^{31}P NMR (acetone-d_6) δ +28.0; Anal. Calcd for $C_{12}H_{18}NO_3P$ (255.25): C, 56.47; H, 7.11; N, 5.49. Found: C, 56.28; H, 7.01; N, 5.29.

4.3. (*Z*)-Diethyl-2-amino-2-isopropylvinylphosphonate 5b

The compound was prepared by the same procedure as described for **5a** using isobutyronitrile (2.28 g, 33 mmol). After evaporation of solvent, **5b** was obtained as white solid in analytically pure form (5.60 g, 77%). Mp = 58–60 °C; ^{1}H NMR (acetone-d_6) δ 6.28 (s (br), 2H, NH_2), 3.91 (q, J = 7.1 Hz, 4H, OCH_2), 3.57 (d, J = 13.0 Hz, =CH), 2.37 (m, 1H, CH), 1.23 (d, J = 7.1 Hz, 6H, CH_3), 1.13 (d, J = 7.1 Hz, 6H, CH_3); ^{13}C NMR (acetone-d_6) δ 172.4 (d, J = 5 Hz, N–C=), 68.7 (d, J = 192 Hz, =CH), 60.8 (d, J = 5 Hz, OCH_2), 36.6 (d, J = 19 Hz, CH), 21.7 (CH_3), 16.7 (d, J = 6 Hz, CH_3); ^{31}P NMR (acetone-d_6) δ +29.0; Anal. Calcd for $C_9H_{20}NO_3P$ (221.23): C, 48.86; H, 9.11; N, 6.33. Found: C, 49.2; H, 9.29; N, 6.30.

4.4. Diethyl 2-acetamino-2-phenylvinylphosphonate 6a

To a solution of the enamide phosphonate **5a** (25 mmol, 6.38 g) in dry THF (100 mL) were added pyridine (50 mmol, 3.96 g) and acetic acid anhydride (125 mmol, 12.76 g). The solution was refluxed for 24 h. After cooling to ambient temperature, a saturated aq Na_2CO_3 solution (100 mL) was added and the solution was extracted with ethyl acetate (3 × 100 mL). The combined organic phases were washed with saturated aq Na_2CO_3 solution and brine (100 mL, respectively). The solvents were removed under vacuo, and the residue was separated and purified by column chromatography (AcOEt/EtOH = 15:1). *Z*-Isomer ***Z*-6a**: R_f-value 0.70; m = 7.20 g (65%) of pale yellow oil; ^{1}H NMR (acetone-d_6) δ 10.18 (s (br), 1H, NH); 7.43 (m, 2H, arom. H), 7.35 (m, 3H, arom. H), 5.02 (d, J = 11.3 Hz, 1H, =CH), 4.08 (m, 4H, OCH_2), 2.04 (s, 3H, CH_3), 1.30 (dt, J = 7,0 Hz, 0.5 Hz, 6H, CH_3); ^{13}C NMR (acetone-d_6) δ 168.5 (C=O), 157.2 (d, J = 3 Hz, N–C=), 138.3 (d, J = 18 Hz, arom. C), 130.0, 128.7, 127.7 (arom. CH), 97.8 (d, J = 182 Hz, =CH), 62.4 (d, J = 5 Hz, OCH_2), 24.3 (CH_3), 16.6 (d, J = 5 Hz, CH_3); ^{31}P NMR (acetone-d_6) δ +19.1; Anal. Calcd for $C_{14}H_{20}NO_4P$ (297.29): C, 56.56; H, 6.78; N, 4.71. Found: C, 56.79; H, 6.73; N, 4.44; *E*-isomer ***E*-6a**: R_f-value 0.55; m = 2.00 g (18%) of white crystals; mp = 118–121 °C; ^{1}H NMR (acetone-d_6) δ 8.88 (s (br), 1H, NH); 7.49 (m, 2H, arom. H), 7.39 (m, 3H, arom. H), 6.89 (d, 1H, J = 11.8 Hz, =CH), 3.72 (m, 4H, OCH_2), 2.10 (s, 3H, CH_3), 1.29 (dt, J = 6.9, 0.5 Hz, 6H, CH_3); ^{13}C NMR (acetone-d_6) δ 170.7 (C=O), 151.9 (d, J = 16 Hz, N–C=), 137.5 (arom. C), 130.1, 129.9, 128.7 (arom. CH), 99.9 (d, J = 200 Hz, =CH), 61.3 (d, J = 6 Hz, OCH_2), 24.7 (CH_3), 16.4 (d, J = 6 Hz, CH_3); ^{31}P NMR (acetone-d_6) δ +19.5; Anal. Calcd for $C_{14}H_{20}NO_4P$ (297.29): C, 56.56; H, 6.78; N, 4.71; Found: C, 56.70; H, 6.67; N, 4.41.

4.5. Diethyl 2-acetamino-2-isopropylvinylphosphonate 6b

The compound was prepared by the same procedure as described for **6a** using enamide **5b** (25 mmol, 5.53 g). The purification and isolation were realized by column chromatography (AcOEt/EtOH = 9:1). *Z*-Isomer ***Z*-6b**: R_f-value 0.80; m = 4.2 g (59%) of a colorless oil; ^{1}H NMR ($CDCl_3$) δ 10.53 (s (br), 1H, NH); 4.45 (d, J = 9.9 Hz, 1H, =CH), 4.01 (m, 4H, OCH_2), 3.85 (m, 1H, CH), 2.07 (s, 3H, CH_3), 1.30 (dt, J = 7.0, 0.5 Hz, 6H, CH_3), 1.08 (d, J = 6.8 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.3 (C=O), 167.6 (N–C=), 85.9 (d, J = 186 Hz, =CH), 61.7 (d, J = 5 Hz, OCH_2), 30.2 (d, J = 16 Hz, CH), 25.4 (CH_3), 21.4 (CH_3), 16.2 (d, J = 6 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ +22.7; Anal. Calcd for $C_{11}H_{22}NO_4P$ (263.27): C, 50.18; H, 8.42; N,

5.32. Found: C, 50.08; H, 8.19; N, 5.20; *E*-isomer ***E*-6b**: R_f-value 0.50; *m* = 0.7 g (10%) of white crystals, mp = 151–155 °C; ^{1}H NMR ($CDCl_3$) δ 7.07 (s (br), 1H, NH); 6.54 (d, *J* = 12.3 Hz, 1H, =CH), 4.00 (m, 4H, OCH_2), 3.68 (m, 1H, CH), 2.11 (s, 3H, CH_3), 1.27 (d, *J* = 7.0 Hz, H, CH_3), 1.10 (d, *J* = 7.0 Hz, 6H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.9 (C=O), 157.2 (d, *J* = 20 Hz, N–C=), 95.4 (d, *J* = 199 Hz, =CH), 61.2 (d, *J* = 5 Hz, OCH_2), 30.5 (d, *J* = 6 Hz, CH), 25.0 (CH_3), 20.2 (CH_3), 16.2 (d, *J* = 6 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ +21.6; Anal. Calcd for $C_{11}H_{22}NO_4P$ (263.27): C, 50.18; H, 8.42; N, 5.32. Found: C, 49.89; H, 8.28; N, 5.19.

4.6. General procedure for the asymmetric hydrogenation

4.6.1. High-throughput hydrogenations[27]

The screening was performed in a reactor hosting 24 GC-vials. In a glovebox under argon successively in each vessel 100 μL of CH_2Cl_2, 1 mmol of $[Rh(COD)_2]BF_4$ (100 μL 0.01 M in CH_2Cl_2), and 1.1 μmol of ligand (110 μL 0.01 M in CH_2Cl_2) were mixed. Then the solvent was evaporated. To each vessel 0.5 mL of a freshly prepared solution of 0.1 mmol of vinylphosphonate in the solvent was added. The reactor was placed in an autoclave. Hydrogen with an initial pressure of 40 bar was added and the vessels stirred for 24 h. After depressurizing the reaction solutions were filtered through a short pad of silica gel and analyzed.

4.6.2. Optimization

The asymmetric hydrogenation was carried out with an automatic hydrogenation device hosting 8 autoclaves (HP-ChemScan HEL-Group). The Rh-catalyst (3.3 μmol) and the substrate (0.33 mmol) were transferred into the autoclaves and kept under argon. The solvent (4 mL) was added and the autoclaves were pressurized with hydrogen to the appropriate pressure after reaching the temperature of 25 °C. The gas uptake was monitored over a period of 24 h.

4.7. *rac*-Diethyl 2-acetamino-2-phenylethylphosphonate *rac*-7a

Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.30–7.12 (m, 5H, arom. H), 5.30 (1H, m, CH–N), 3.97 (m, 2H, OCH_2), 3.69 (m, 2H, OCH_2), 2.36 (s (br), 1H, NH); 2.36–2.12 (2H, m, CH_2-P), 1.95 (s, 3H, CH_3), 1.22 (t, 3H, *J* = 7.1 Hz, CH_3), 1.00 (t, 3H, *J* = 7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.2 (C=O), 141.2 (d, *J* = 8 Hz, arom. C), 128.3, 127.2, 126.0 (arom. CH), 61.7 (d, *J* = 7 Hz, OCH_2), 61.4 (d, *J* = 6 Hz, OCH_2), 48.2 (d, *J* = 5 Hz, CH–N), 32.1 (d, *J* = 139 Hz, CH_2P), 23.1 (CH_3), 16.2 (d, *J* = 6 Hz, CH_3), 15.9 (d, *J* = 6 Hz, CH_3); ^{31}P NMR ($CDCl_3$) δ +27.9; Anal. Calcd for $C_{14}H_{22}NO_4P$ (299.30): C, 56.18; H, 7.41; N, 4.68. Found: C, 56.63; H, 7.53; N, 4.32.

4.8. *rac*-Diethyl 2-acetamino-2-isopropylethylphosphonate *rac*-7b

Pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.32 (d (br), 1H, NH); 4.10–3.88 (m, 5H, CH–N, OCH_2), 2.02–1.80 (3H, m, CH, CH_2P), 1.91 (s, 3H, CH_3), 1.24 (dt, *J* = 7.1, 3.1 Hz, 6H, CH_3), 0.85 (d, *J* = 6.8 Hz, 3H, CH_3), 0.83 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.4 (C=O), 61.6 (d, *J* = 7 Hz, OCH_2), 61.1 (d, *J* = 6 Hz, OCH_2), 49.7 (d, *J* = 4 Hz, CH–N), 31.9 (d, *J* = 10 Hz, CH), 27.2 (d, *J* = 140 Hz, CH_2P), 23.0 (CH_3), 18.5 (CH_3), 18.3 (CH_3), 16.1 (d, CH_3, $J_{C,P}$ = 6 Hz); ^{31}P NMR ($CDCl_3$) δ +30.1; Anal. Calcd for $C_{11}H_{24}NO_4P$ (265.29): C, 49.80; H, 9.12; N, 5.28. Found: C, 50.18; H, 9.23; N, 5.07.

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References

1. Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899–931. and references cited therein.
2. *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Soloshonok, V., Eds., 2nd ed.; John Wiley & Sons: Hoboken, 2005.
3. Allen, J. G.; Arthenton, F. R.; Hall, M. J.; Hassall, C. H.; Holmes, S. W.; Lambert, R. W.; Nisbert, L. J.; Ringrose, P. S. *Nature* **1978**, *272*, 56–58.
4. (a) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *15*, 3295–3340; (b) Smith, W. W.; Bartlett, P. A. *J. Am. Chem. Soc.* **1998**, *120*, 4622–4628; (c) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652–1661.
5. Hirschmann, R.; Smith, A. B., III; Talor, C. M.; Benkovic, P. A.; Taylor, C. D.; Yager, K. M.; Sprengler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.
6. Alonso, E.; Alonso, E.; Solis, A.; del Pozo, C. *Synlett* **2000**, 698–700.
7. Ma, J.-A. *Chem. Soc. Rev.* **2006**, *35*, 630–636.
8. Wasilewski, C.; Demblowski, L.; Topolski, M. *Synthesis* **1989**, 52–53.
9. Roy-Gourvennec, S.; Lemarie, M.; Masson, S. *Phosphorus, Sulfur, Silicon* **1997**, *123*, 247–254.
10. (a) Maier, L.; Diel, P. J. *Phosphorus, Sulfur, Silicon* **1996**, *109–110*, 341–344; (b) Maier, L.; Diel, P. J. *Phosphorus, Sulfur, Silicon* **1995**, *107*, 245–255.
11. Isbell, A. F.; Englert, L. F.; Rosenberg, H. *J. Org. Chem.* **1969**, *34*, 755–756.
12. Xu, C.; Yuan, C. *Eur. J. Org. Chem.* **2004**, 4410–4415.
13. Nesterov, V. V.; Kolodiazhnyi, O. I. *Synlett* **2007**, 2400–2404.
14. (a) Bosco, M.; Bisseret, P.; Bouix-Peter, C.; Eustache, J. *Tetrahedron Lett.* **2001**, *42*, 7949–7952; (b) Sauveur, F.; Collignon, N.; Guy, A.; Savignac, P. *Phosphorus, Sulfur* **1983**, *14*, 341–346.
15. (a) Au-Yeung, T. T.-L.; Chan, S.-S.; Chan, A. S. C. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004; pp 14–28; (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley-VCH: New York, 2000; pp 9–17.
16. (a) Enthaler, S.; Erre, G.; Junge, K.; Holz, J.; Börner, A.; Alberico, E.; Nieddu, I.; Gladiali, S.; Beller, M. *Org. Process Res. Dev.* **2007**, *11*, 568–577; (b) Monti, C.; Gennari, C.; Piarulli, U.; de Vries, J. G.; de Vries, A. H. M.; Lefort, L. *Chem. Eur. J.* **2005**, *11*, 6701–6717; (c) Dai, Q.; Yang, W.; Zhang, X. *Org. Lett.* **2005**, *7*, 5343–5345; (d) Reetz, M. T.; Li, X. *Angew. Chem., Int. Ed.* **2005**, *44*, 2959–2962. and references cited therein.
17. (a) Brown, J. M. In *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007; pp 1073–1103. Chapter 31; (b) Drexler, H.-J.; You, J.; Zhang, S.; Fischer, C.; Baumann, W.; Spannenberg, A.; Heller, D. *Org. Process Res. Dev.* **2003**, *7*, 355–361.
18. For the preparation of other functionalized phosphonates by Rh- and Ru-catalyzed asymmetric hydrogenation, see: (a) Wang, D.-Y.; Hu, Y.-P.; Huang, J.-D.; Deng, J.; Yu, S.-B.; Duan, Z.-D.; Xu, X.-F.; Zeng, Z. *Angew. Chem., Int. Ed.* **2007**, *46*, 8002–8005; (b) Badkar, P. A.; Rath, N. P.; Spilling, C. D. *Org. Lett.* **2007**, *9*, 3619–3622.
19. (a) Wang, D.-Y.; Huang, J.-D.; Hu, X.-P.; Deng, J.; Yu, S.-B.; Duan, Z.-C.; Zheng, Z. *J. Org. Chem.* **2008**, *73*, 2011–2014; (b) Gridnev, I. D.; Yasutake, M.; Imamoto, T.; Beletskaya, I. P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5385–5390; (c) Holz, J.; Stürmer, R.; Schmidt, U.; Drexler, H.-J.; Heller, D.; Krimmer, H.-P.; Börner, A. *Eur. J. Org. Chem.* **2001**, 4615–4624; (d) Burk, M. J.; Stammers, T. A.; Straub, J. A. *Org. Lett.* **1999**, *1*, 387–390; (e) Dwars, T.; Schmidt, U.; Fischer, C.; Grassert, I.; Kempe, R.; Froehlich, R.; Drauz, K.; Oehme, G. *Angew. Chem., Int. Ed.* **1998**, *27*, 2851–2853; (f) Schmidt, U.; Oehme, G.; Krause, H.-W. *Synth. Commun.* **1996**, *26*, 777–781.
20. For example: (a) Rozalski, M.; Krajewska, U.; Panczyk, M.; Mirowski, M.; Rozalska, B.; Wasek, T.; Janecki, T. *Eur. J. Med. Chem.* **2007**, *42*, 248–255; (b) Wasek, T.; Olczak, J.; Janecki, T. *Synlett* **2006**, 1507–1510; (c) Okada, Y.; Minami, T.; Miyamoto, M.; Tsuneyuki, O.; Sumiko, S.; Junji, S. *Heteroatom Chem.* **1995**, *6*, 195–210.
21. (a) Johnson, A.-L.; Slaett, J.; Janosik, T.; Bergman, J. *Heterocycles* **2006**, *68*, 2165–2170; (b) Pietruszka, J.; Witt, A. *Synthesis* **2006**, 4266–4268.
22. Sakhibullina, V. G.; Polezhaeva, N. A.; Bagautdinova, D. A.; Arbuzov, B. A. *Zh. Obshch. Khim.* **1991**, *61*, 2421–2427.
23. (a) Sakhibullina, V. G.; Polezhaeva, N. A.; Bagautdinova, D. A.; Arbuzov, B. A. *Zh. Obshch. Khim.* **1989**, *59*, 983–986; (b) Alikin, A. Yu.; Liorber, B. G.; Sokolov, M. P.; Razumov, A. I.; Zykova, T. V.; Salakhutdinov, R. A. *Zh. Obshch. Khim.* **1982**, *52*, 316–322.
24. Panarina, A. E.; Dogadina, A. V.; Ionin, B. I. *Russ. J. Gen. Chem.* **2001**, *71*, 147–148.
25. (a) Khusainova, N. G.; Mostovaya, O. A.; Berdnikov, E. A.; Litvinov, I. A.; Krivolapov, D. B.; Cherkasov, R. A. *Russ. J. Org. Chem.* **2005**, *41*, 1260–1264; (b) Palacios, F.; Aparicio, D.; Garcia, J. *Tetrahedron* **1996**, *52*, 9609–9628.
26. (a) Palacios, F.; Ochoa De Retana, A. M.; Pascual, S.; Oyarzabal, J. *J. Org. Chem.* **2004**, *69*, 8767–8774; (b) Palacios, F.; Garcia, J.; Ochoa de Retana, A. M.; Oyarzabal, J. *Heterocycles* **1995**, *41*, 1915–1922; (c) Shin, W. S.; Lee, K.; Oh, D. Y. *Tetrahedron Lett.* **1995**, *36*, 281–282.
27. All results of the HTS can be obtained from the authors on request.
28. It should be noted, however, when in an individual trial 3 mmol of *Z*-**6b** was hydrogenated with $[Rh((R)\text{-SYNPHOS})(COD)]BF_4$ in methanol, the chiral product was obtained in quantitative yield and in 94% ee. Obviously in some cases the HTS-approach can give some misleading results. Currently, this aspect is under investigation.
29. Up to now correlation of the sign of the specific rotation with the absolute configuration cannot be given. A comparison with the specific rotation of known chiral β-substituted β-amino-ethan-1-ylphosphonates indicates that a positive sign correlates with an (*S*)-configuration.