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Tetrahedron Letters 45 (2004) 4245–4248
Tetrahedron Letters

Diastereoselective carbonyl phosphonylation using chiral *N*,*N*′-bis-[(*S*)-α-phenylethyl]-bicyclic phosphorous acid diamides

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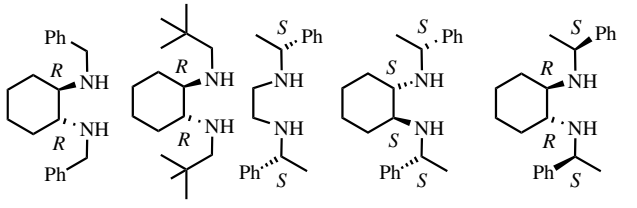
Received 9 December 2003; revised 31 March 2004; accepted 7 April 2004

Abstract—Addition of aldehydes to the *P*-anion derivatives of chiral phosphorous acid diamides (1*S*,2*S*,1′*S*,1″*S*)-**2** and (1*R*,2*R*,1′*S*,1″*S*)-**2** in THF gave α-hydroxyphosphonamides in good yield (64–100%) and moderate diastereoselectivities.

1. Introduction

The Pudovik reaction is a well known phosphonylation process that involves the addition of organophosphorous compounds containing a labile P–H bond to unsaturated systems.[1] During the last decade, the asymmetric Pudovik reaction of aldehydes, in the presence of chiral diols, amino alcohols and diamines as catalysts or chiral auxiliaries have been successfully reported.[2]

Spilling and co-workers[3] reported the use of phosphorous acid diamides derived from *N*,*N*′-dibenzyl- and *N*,*N*′-dineopentyl-*trans*-(1*R*,2*R*)-1,2-cyclohexanodiamine, **A** and **B**, with moderate to good diastereoselectivity (Chart 1).[3] Additionally, Kee and co-workers reported the use of *N*,*N*′-bis-[(*S*)-α-phenylethyl]-1,2-ethylendiamine **C** with moderate results (Chart 1).[4] Herein, we report the use of (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1′*S*,1″*S*)-*trans*-*N*,*N*′-bis[(*S*)-α-phenylethyl]-1,2-diaminocyclohexane,[5] (1*S*,2*S*,1′*S*,1″*S*)-**1** and (1*R*,2*R*,1′*S*,1″*S*)-**1**, which incorporate both the *trans*-1,2-cyclohexanediamine and the α-phenylethyl group. These 1,2-diamines, which are structurally related to compounds **A**–**C**, are used in the asymmetric phosphonylation of aldehydes. Also, analyses of X-ray crystallography data of some derivatives are presented in this report.



A **B** **C** (1*S*,2*S*,1′*S*,1″*S*)-**1** (1*R*,2*R*,1′*S*,1″*S*)-**1**

Chart 1.

2. Results and discussion

The condensation of diamines (1*S*,2*S*,1′*S*,1″*S*)-**1** and (1*R*,2*R*,1′*S*,1″*S*)-**1** with PCl_3 and Et_3N in toluene followed by filtration of the resulting $Et_3N{\cdot}HCl$ gives the crude chlorodiazaphospholes, which are not isolated. The subsequent addition of 1 equiv of water, and 1 equiv of Et_3N to the crude reaction mixture affords the diazaphosphole oxides **2**. Both diastereoisomers of **2** are purified by column chromatography and evaluated in the addition of aldehydes to their lithium salts in THF, affording α-hydroxyphosphonamides **3a**–**k** (Table 1). In all cases, the reaction is quite clean, and conversions are good to high (65–100%). Since starting material and all diastereoisomeric pairs **3a**–**k** are easily distinguishable by ^{31}P NMR spectroscopy, this provides a suitable method for the determination of conversions and isomeric ratios.

Keywords: Pudovik reaction; 1,2-Diamines; Phosphoramides; α-Hydroxyphosphonamides.
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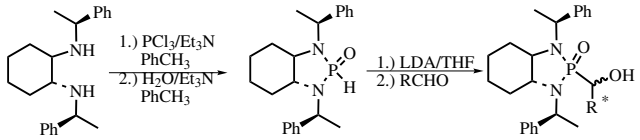
doi:10.1016/j.tetlet.2004.04.027

Table 1. Reaction of (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1*S*,1″*S*)-*N*,*N*″-(α-phenylethyl)-substituted phosphorous acid diamide with aldehydes



(1*S*,2*S*,1′*S*,1″*S*)-**1** (1*S*,3*S*,1′*S*,1″*S*)-**2** (1*S*,3*S*,1′*S*,1″*S*,α*SR*)-**3a-f**

(1*R*,2*R*,1′*S*,1″*S*)-**1** (1*R*,3*R*,1′*S*,1″*S*)-**2** (1*R*,3*R*,1′*S*,1″*S*,α*SR*)-**3g-k**

Entry	Diamine	Aldehyde	Product	Conversion[a] (%)	δ,[a] ppm major/minor	Δδ,[a] ppm	Isomeric ratio[a]	Conf.[b]
1	(1*S*,2*S*,1′*S*,1″*S*)-**1**	Benzaldehyde	**3a**	92	36.3/34.7	+1.6	1.8:1	*R*[c]
2	(1*S*,2*S*,1′*S*,1″*S*)-**1**	*p*-Anisaldehyde	**3b**	87	36.9/34.7	+2.2	1.6:1	*R*
3	(1*S*,2*S*,1′*S*,1″*S*)-**1**	*p*-Bromobenzaldehyde	**3c**	65	36.1/33.5	+2.6	2.6:1	*R*
4	(1*S*,2*S*,1′*S*,1″*S*)-**1**	1-Naphthaldehyde	**3d**	100	36.6/34.5	+2.0	1.9:1	*R*[d]
5	(1*S*,2*S*,1′*S*,1″*S*)-**1**	Isobutyraldehyde	**3e**	99	36.8/38.2	−1.4	1.6:1	*S*
6	(1*S*,2*S*,1′*S*,1″*S*)-**1**	Isovaleraldehyde	**3f**	100	37.6/39.8	−2.2	1.5:1	*S*[e]
7	(1*R*,2*R*,1′*S*,1″*S*)-**1**	Benzaldehyde	**3g**	98	35.6/34.9	+0.7	1.3:1	*S*[d]
8	(1*R*,2*R*,1′*S*,1″*S*)-**1**	*p*-Anisaldehyde	**3h**	100	35.8/34.9	+0.9	1.8:1	*S*
9	(1*R*,2*R*,1′*S*,1″*S*)-**1**	*p*-Bromobenzaldehyde	**3i**	100	35.2/34.6	+0.6	2.0:1	*S*
10	(1*R*,2*R*,1′*S*,1″*S*)-**1**	Isobutyraldehyde	**3j**	97	36.9/38.9	−2.0	1.7:1	*R*
11	(1*R*,2*R*,1′*S*,1″*S*)-**1**	Isovaleraldehyde	**3k**	100	37.7/38.5	−0.8	2.6:1	*R*

[a] Conversion and diastereoisomeric ratios were determined from ^{31}P NMR spectra of the crude products, which were recorded in $CDC1_3$.

[b] In each case, the assignment of configuration on the new stereogenic centre of the major epimer was determined by cross reference of Δδ values, and based on the structure of compounds **3a**,**d**,**f** and **g**.

[c] Mixed crystals of the diastereoisomers were obtained, and X-ray diffraction analysis was performed.[6]

[d] In both cases, the absolute configuration of the major diastereoisomers were determined by single crystal X-ray diffraction.[7]

[e] The absolute configuration of the minor diastereoisomer was determined by single crystal X-ray diffraction.[7]

Diastereoisomeric ratios are moderate, and stereoselectivities are found to be strongly dependent on the nature of the aldehyde and the chiral diamines **1**. The major and minor diastereoisomers of the carbinols prepared from aromatic aldehydes were reversed in their positions in the ^{31}P NMR (Table 1, entries 1–4 and 7–9), relative to the products prepared from the aliphatic aldehydes (Table 1, entries 5–6 and 10–11). In consequence, we surmise that the major epimers of compounds **3a**–**d** (Table 1, entries 1–4), which give rise to a positive Δδ value, have an opposite configuration at C_α in comparison with the major epimers of compounds **3e** and **3f** (Table 1, entries 5 and 6). By the same token, compounds **3g**–**i** (Table 1, entries 7–9) derived from aromatic aldehydes present positive Δδ value. Thus, we assume that the opposite configuration on C_α is present in compounds **3j** and **3k** (entries 10 and 11), in contrast to compounds **3g**–**i**. Such a crossover in stereoselectivity due to the nature of the aldehyde, that is aromatic versus aliphatic, was previously observed by Spilling and co-workers when diamine **B** was used as a chiral auxiliary.[3] Also, Kee and co-workers reported a crossover in stereoselectivity due to contrasting steric requirements on the aldehyde.[4]

We also observe that the diastereoselectivity is higher when diamine *all-S*-**1** reacts with aromatic aldehydes (Table 1, entries 1–6), while the aliphatic aldehydes give higher selectivities with diamine (1*R*,2*R*,1′*S*,1″*S*)-**1** (Table 1, entries 4 and 5). In order to assign the absolute configuration from carbinols **3a**–**k**, we were able to obtain single crystals of one of the diastereoisomers from α-hydroxyphosphonamides **3d**,**f** and **g**, which were fully characterized.[7] The assignment of the actual absolute configuration for these compounds, through the refinement of a Flack parameter, allowed us to know the configuration of the new stereogenic centre at the major isomer formed (Table 1).[8]

Table 2 presents a comparison of the data reported in the literature for some diastereoisomeric carbinols by Spilling and co-workers[3a] (Table 2, entries 1, 2 and 6)

Table 2. Comparative data of some diastereoisomeric carbinols using diamines **A**, **B**, **C**, (1*S*,2*S*,1′*S*,1″*S*)-**1** and (1*R*,2*R*,1′*S*,1″*S*)-**1** as chiral auxiliaries

Entry	Diamine	Aldehyde	δ,[a] ppm major/minor	Δδ,[a] ppm	Isomeric ratio[a]	Conf.[b]	Lit.
1	**A**	Benzaldehyde	36.9/35.9	+1.0	1.1:1	*R*	3a
2	**B**	Benzaldehyde	39.0/38.1	+0.9	25:1	*S*	3a
3	**C**	Benzaldehyde	34.0/34.5	−0.5	1.8:1	—	4
4	(1*S*,2*S*,1′S,1″*S*)-**1**	Benzaldehyde	36.3/34.7	+1.6	1.8:1	*R*	
5	(1*R*,2*R*,1′S,1″*S*)-**1**	Benzaldehyde	35.6/34.9	+0.7	1.3:1	*S*	
6	**A**	Isovaleraldehyde	42.6/42.3	+0.3	3.4:1	*R*	3a
7	(1*S*,2*S*,1′S,1″*S*)-**1**	Isovaleraldehyde	37.6/39.8	−2.2	1.5:1	*S*	
8	(1*R*,2*R*,1′S,1″*S*)-**1**	Isovaleraldehyde	37.7/38.5	−0.8	2.6:1	*R*	

[a] ^{31}P NMR spectra of the crude products were recorded in $CDCl_3$.

[b] The configuration of the major diastereoisomer were reported.

and Kee and co-workers[4] (Table 2, entry 3) with our results (Table 2, entries 4, 5, 7 and 8).

In conclusion, we obtain moderate diastereoselectivities on the carbonyl phosphonylation of aldehydes using the *N*,*N*′-bis-[(*S*)-α-phenylethyl]-bicyclic phosphorous acid diamides **2** prepared from the (1*S*,2*S*,1′*S*,1″*S*)- and (1*R*,2*R*,1′*S*,1″*S*)-*trans*-*N*,*N*′-bis[(*S*)-α-phenylethyl]-1,2-diamino-cyclohexane **1**. Contrary to our expectations, the conformational preferences of the α-phenylethyl group have no influence over the stereochemistry of the newly generated α-stereocentre.

Acknowledgements

We thank CONACYT for financial support (Project No 39500-Q and Grant No 91276).

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7. *(3aS,7aS)-(Naphthalen-2-yl)-[2-oxo-1,3-bis-[(S)-α-phenylethyl]-octahydro-2λ⁵-benzo[1,3,2]diazaphosphol-2-yl]-methanol*, **3d** *major isomer*. Colourless crystals, mp = 192–194 °C, $[\alpha]_D$ + 131.0 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz) δ = 8.26 (d, *J* = 8 Hz, 1H), 7.93–7.14, 16 H), 5.75 (d, *J* = 9.2 Hz, 1H), 4.43 (c, *J* = 6.8 Hz, 1H), 4.07 (m, 1H), 3.61 (s, 1H), 2.29 (m, 2H), 2.17 (m, 1H), 1.78 (d, *J* = 7.2 Hz, 3H), 1.76 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.34 (m, 1H), 1.25 (m, 1H). ^{13}C NMR (400 MHz) δ = 134.5, 133.3, 130.8, 128.8–123.7, 70.9 (d, J_{CP} = 123.0 Hz), 62.3 (d, J_{CP} = 9.1 Hz), 60.8 (d, J_{CP} = 6.0 Hz), 54.8 (d, J_{CP} = 4.5 Hz), 52.3, 30.8 (d, J_{CP} = 7.6 Hz), 29.7 (d, J_{CP} = 6.1 Hz), 24.4 (d, J_{CP} = 4.6 Hz), 23.16, 19.7 (d, J_{CP} = 7.6 Hz). ^{31}P NMR δ = 36.6. Mass spectra $(M + Na)^+$ calcd 547.2490, found 547.2495 (ES+). X-ray structure: colourless needle, 0.65×0.24×0.20 mm^3, $C_{33}H_{37}N_2O_2P$, monoclinic, $P2_1$, *a* = 11.1340(12), *b* = 10.092(2), *c* = 13.1275(15) Å, β = 96.716(8)°, *Z* = 2, *Z*′ = 1. Bruker P4 diffractometer using Mo K_α radiation (λ = 0.71073 Å), *T* = 296(1) K, 7514 reflections measured up to 2θ = 55°, 3937 independent data (R_{int} = 2.60%) for 434 refined parameters. The structure was solved and refined using standard methods[8] with data corrected for absorption effect (transmission factors: 0.623 to 0.662). Final *R* indices: R_1 = 3.87% for 2903 reflections having $F_o > 4\sigma(F_o)$ and wR_2 = 11.07% for all data. Absolute configuration from the refinement of a Flack parameter: *x* = −0.01(11). The crystallographic data have been deposited with the CCDC (number 226194).
(3aS,7aS)-3-Methyl-1-[2-oxo-1,3-bis-[(S)-α-phenylethyl]-octahydro-2λ⁵-benzo[1,3,2]diazaphosphol-2-yl]-butan-1-ol, **3f** *minor isomer*. Colourless crystals, mp = 194–196 °C, $[\alpha]_D$ + 13.10 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz) δ: 7.67–7.17 (m, 10H), 4.74 (sext, *J* = 7.2 Hz, 1H), 4.35 (sext, *J* = 7.2 Hz, 1H), 3.92 (m, 1H), 2.94 (m, 1H), 2.60 (m, 1H), 2.46 (m, 1H), 1.96 (m, 1H), 1.87 (m, 1H), 1.69 (d, *J* = 1.7 Hz, 3H), 1.66 (d, *J* = 1.7 Hz, 3H), 1.56 (m, 4H), 1.46 (m, 3H), 0.99 (d, *J* = 1.7 Hz, 3H), 0.93 (d, *J* = 1.7 Hz, 3H), 0.83 (m, 1H), 0.80 (m, 1H). ^{13}C NMR (75.4 MHz) 147.1, 139.3, 128.7–126.3, 68.5 (d, J_{CP} = 128.3 Hz), 64.2 (d, J_{CP} = 8.0 Hz), 60.7 (d, J_{CP} = 4.6 Hz), 54.7 (d, J_{CP} = 5.7 Hz), 51.2, 39.6, 31.1 (d, J_{CP} = 10.3 Hz), 30.1 (d, J_{CP} = 6.9 Hz), 24.9, 24.6 (d, J_{CP} = 13.7 Hz), 24.4, 23.8, 23.7, 21.1, 20.0 (d, J_{CP} = 6.9 Hz). ^{31}P NMR δ = 39.8. IR: 3261, 2952, 2867, 1170, 699 cm^{-1}. Mass spectra (M^+) calcd 455.2827, found 455.2835. X-ray structure: crystallized from petroleum ether/EtOAc. Colourless prism, 0.56×0.38×0.16 mm^3, $C_{27}H_{39}N_2O_2P$, monoclinic, *C*2, *a* = 23.905(2), *b* = 10.4523(13), *c* = 10.6764(8) Å, β = 96.477(5)°, *Z* = 4, *Z*′ = 1. Bruker P4 diffractometer using Mo K_α radiation (λ = 0.71073 Å), *T* = 297(1) K, 4484 reflections measured up to 2θ = 52.5°, 4201 independent data (R_{int} = 1.77%) for 290 refined parameters. The structure was solved and refined using standard methods[8] using nonabsorption-corrected data. Final *R* indices: R_1 = 4.02% for 3281 reflections having $F_o > 4\sigma(F_o)$ and wR_2 = 10.15% for all data. Absolute configuration from the refinement of a Flack parameter: *x* = 0.02(10). The crystallographic data have been deposited with the CCDC (number 226195).
(3aR,7aR)-[2-Oxo-1,3-bis[(S)-α-phenylethyl]-octahydro-2λ⁵-benzo[1,3,2]diazaphosphol-2-yl]-phenyl-methanol, **3g** *major isomer*. Colourless crystals, mp = 192–194 °C, $[\alpha]_D$ − 118.76 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz) δ: 7.63–7.17, (m, 15H), 5.30 (dd, *J* = 4.4 Hz, J_{CP} = 11.4 Hz, 1H), 4.69–4.66 (m, 1H), 4.35–4.31 (m, 1H), 3.66 (dd, *J* = 5.5 Hz, *J* = 11.9 Hz, 1H), 2.8 (d, *J* = 8.4 Hz, 2H), 1.6 (d, *J* = 7.0 Hz, 3H), 1.51 (d, *J* = 7.3 Hz, 3H), 1.59–1.38 (m, 5H), 1.25–0.57 (m, 3H). ^{13}C NMR (100 MHz) 144.5, 143.5 (d, J_{CP} = 6.2 Hz), 128.2–126.3, 72.6, 71.4, 61.3 (d J_{CP} = 5.4 Hz), 60.8 (d, J_{CP} = 7.7 Hz), 53.3, 49.5 (d, J_{CP} = 5.4 Hz), 30.4 (d, J_{CP} = 6.2 Hz), 30.2 (d, J_{CP} = 9.3 Hz), 24.3, 19.2, 16.8. ^{31}P NMR δ = 35.6. IR: 3423, 3238, 3059, 2940, 2867,

1197, 702 cm^{-1}. Mass spectra (M^+) calcd 475.2514 found 475.2499. X-ray structure: crystallized from petroleum ether/EtOAc. Colourless prism, $0.7\times0.4\times0.2\,mm^3$, $C_{29}H_{35}N_2O_2P$, monoclinic, $P2_1$ $a = 9.6504(12)$, $b = 17.3532(14)$, $c = 15.9951(15)$ Å, $\beta = 95.621(11)°$, $Z = 4$, $Z' = 2$. Bruker P4 diffractometer using Mo K_α radiation ($\lambda = 0.71073$ Å), $T = 300(2)$ K, 11946 reflections measured up to $2\theta = 55°$, 6734 independent data ($R_{int} = 3.02\%$) for 614 refined parameters. The structure was solved and refined using standard methods[8] using data corrected for absorption effect (transmission factors: 0.681 to 0.759). Final R indices: $R_1 = 4.30\%$ for 4862 reflections having $F_o > 4\sigma(F_o)$ and $wR_2 = 11.00\%$ for all data. Absolute configuration from the refinement of a Flack parameter: $x = -0.04(8)$. The crystallographic data have been deposited with the CCDC (number 226196).

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