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Journal of Organometallic Chemistry 691 (2006) 3098–3102

Journal of Organometallic Chemistry

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Note

Diastereoselective addition of dimethyl phosphite to 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde

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Received 13 December 2005; received in revised form 23 February 2006; accepted 1 March 2006
Available online 6 March 2006

Abstract

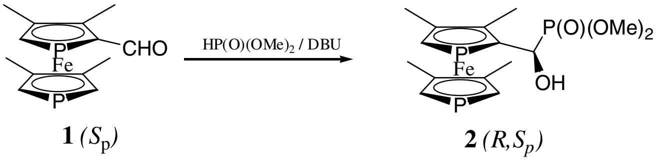
Addition of dimethyl phosphite to racemic 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde gives almost exclusively one diastereomer of the corresponding α-hydroxyphosphonate (d.r. ⩾96:4). Its absolute configuration (S,R_p)–(R,S_p) was established by X-ray diffraction.

Keywords: 1,1′-Diphosphaferrocene; α-Hydroxyphosphonate; Dimethylphosphite; Diastereoselective addition; X-ray structure

1. Introduction

During recent years there has been a growing interest in the stereoselective syntheses of hydroxyphosphonates [1] due to their biological activity [2–5] and wide application in syntheses of other functionalized phosphonates [6,7]. As biological activity of numerous ferrocene derivatives became well documented [8–10], we thought that it would be of interest to develop a stereocontrolled synthetic approach to ferrocenyl (or heteroferrocenyl) α-hydroxyphosphonates. Racemic ferrocenyl α-hydroxyphosphonates are accessible by the addition of dialkyl phosphites to ferrocenecarboxaldehyde [11]. We thought that by using planar chiral metallocene aldehydes it would be possible to control the stereochemistry of the α-hydroxyphosphonate carbon created in this reaction. In fact, some examples of a diastereoselective nucleophilic addition of organometallic reagents to planar chiral ferrocene and phosphaferrocene aldehydes have been reported [12–14].

In first attempts we used planar chiral (racemic) 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde **1** [15]. We report here that addition of dimethyl phosphite to this compound occurs with a high diastereoselectivity and leads to the hydroxyphoshonate **2**. The stereochemistry of this product was determined by X-ray diffraction.



1 (S_p) **2** (R,S_p)

(only one enantiomer of **1** is shown)

2. Results

2.1. Addition of dimethyl phospite to rac-1

The reaction of *rac*-**1** with dimethyl phosphite (excess) was carried out in a concentrated THF solution of reagents in the presence of a catalytic amount of DBU. (It has been noticed that this base is particularly efficient in closely related additions of dialkyl phosphites to aldehydes [16]).

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0022-328X/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jorganchem.2006.03.001

The ^{31}P NMR spectrum of the crude reaction mixture revealed a set of two signals in the region characteristic for the diphosphaferrocenyl moiety and two signals in the region of α-hydroxyphosphonates in the ratio of 96:4. The recrystallization of the sample from pentane gave material exhibiting only one signal in the phosphonate region (21.03 ppm) and two signals characteristic for the diphosphaferrocenyl group (−76.53 and −80.54 ppm). It is therefore possible that two diastereomers of **2** are formed in the 96:4 ratio, and recrystallization affords pure major diastereomer. However, one can not exclude a possibility that the second signal in the phosphonate region belongs to an impurity that not contain the heterometallocene group and only one diastereomer of **2** is formed exclusively. Therefore, we estimated d.r. ⩾96:4.

2.2. X-ray structure determination of 2

X-ray diffraction analysis of **2** allowed for determination of the configuration at the α-carbon of the α-hydroxyphosphonate chain. Crystals suitable for analysis were grown from layered dichloromethane–pentane. The crystal and structure refinement data are gathered in Table 1. Table 2 shows selected geometric parameters. The refinement revealed a positional disorder consisting in the presence of two components (A and B) with the occupancy factors 0.7 and 0.3, respectively. Because of the disorder the phospholyl rings of the diphosphaferrocene moiety are labeled in the following way: ring1 consists of the P2,C21,C22,C23,C24 atoms, ring2A consists of the P3A,C31A,C32A,C33A,C34A atoms (major component of the disorder part of the molecule) and ring2B is built of the atoms P3B,C31B,C32B,C33B,C34B (minor component of the disorder). Cg1, Cg2A and Cg2B correspond to the gravity centers of the mentioned rings, respectively. The structure of the major component is shown in Fig. 1.

Table 1
Experimental details of X-ray measurement for **2**

Empirical formula	$C_{15}H_{23}FeO_4P_3$
Formula weight	416.09
Crystal habit	plate
Crystal size (mm)	$0.8 \times 0.6 \times 0.1$
Crystal system	monoclinic
Space group	$P2_1/n$
Unit cell dimensions	
a (Å)	7.889(9)
b (Å)	22.740(9)
c (Å)	10.574(6)
β (°)	97.68(6)
V (Å^{-3})	1880(3)
Z	4
D_x (g cm^{-3})	1.470
T (K)	293(2)
λ (Å)	0.71073
θ Ranges for data collection (°)	2.64–25.00
Index ranges	$-9 \leqslant h \leqslant 9$ $0 \leqslant k \leqslant 26$ $0 \leqslant l \leqslant 12$
Data/parameters/restrains	3302/283/72
Final R indices for 1979 reflections [$I>2\sigma(I)$]	$R(F)^a = 0.0564$ $wR(F^2)^b = 0.1207$
R indices for all data	$R(F)^a = 0.1158$ $wR(F^2)^b = 0.1335$
Goodness-of-fit on F^2	0.902
Largest difference in peak and hole (e Å^{-3})	0.559 and −0.791

$w = 1/[\sigma^2(F_o^2) + (0.0726P)^2]$, where $P = [(F_o^2) + 2(F_c^2)]/3$.

[a] $R(F) = \Sigma(|F_o - F_c|)/\Sigma|F_o|$.

[b] $wR(F^2) = [\Sigma w(|F_o - F_c|)^2/\Sigma|F_o|^2]^{1/2}$.

Table 2
Selected bond lengths (Å) and angles (°) for **2**

P1–O1	1.468(4)
P1–O2	1.570(4)
P1–O3	1.574(4)
P1–C1	1.815(5)
C1–O4	1.431(5)
O2–C2	1.386(6)
O3–C3	1.441(6)
C1–C21	1.509(6)
C21–C22	1.425(6)
C22–C23	1.421(7)
C23–C24	1.414(7)
C24–P2	1.770(5)
C21–P2	1.791(5)
C22–C25	1.507(7)
C23–C26	1.530(6)
Fe–Cg1[a]	1.643(3)
Fe–Cg2A[a]	1.664(5)
P2···P3A	3.464(6)
O1–P1–O2	116.0(3)
O1–P1–O3	113.7(2)
O2–P1–O3	102.1(2)
O1–P1–C1	113.4(2)
O2–P1–C1	104.0(2)
O3–P1–C1	106.4(2)
P1–C1–O4	103.7(3)
P1–C1–C21	113.2(3)
O4–C1–C21	112.0(4)
C21–C22–C23	111.9(4)
C22–C23–C24	111.8(4)
C23–C24–P2	114.7(4)
C24–P2–C21	88.1(2)
P2–C21–C22	113.5(3)
Cg1–Fe1–Cg2A[a]	176.7(4)
O1–P1–C1–C21	170.8(3)
O1–P1–C1–O4	−67.6(4)
P2–Cg1···Cg2A–P3A[a]	25.2(3)

[a] Cg1 corresponds to the centroid of the ring P2–C21–C22–C23–C24; Cg2A corresponds to the centroid of the ring P3A–P31A–P32A–P33A–P34A.

The phospholyl ligands in the diphosphaferrocene moiety the rings are almost parallel to each other with dihedral angles between their calculated last-square planes equal to 2,1(4)° for the rings 1-2A and 3,0(9)° for the rings 1-2B. The rings are in almost eclipsed conformation with the P2–Cg2–Cg3–P3 dihedral angles equal to 25.2(3)° for the component A (rings 1-2A) and 2.7(5)° for the B one (rings 1-2B). In case of such a conformation the phosphorus atoms of the rings (P2 and P3) are much closer than the sum of van der Waals radii. The corresponding intramolecular P2···P3 distances are 3.464(6) Å for the P3A atom and 3.34(11) for the P3B atom. This suggests a "secondary bond" between phosphorus atoms [17].

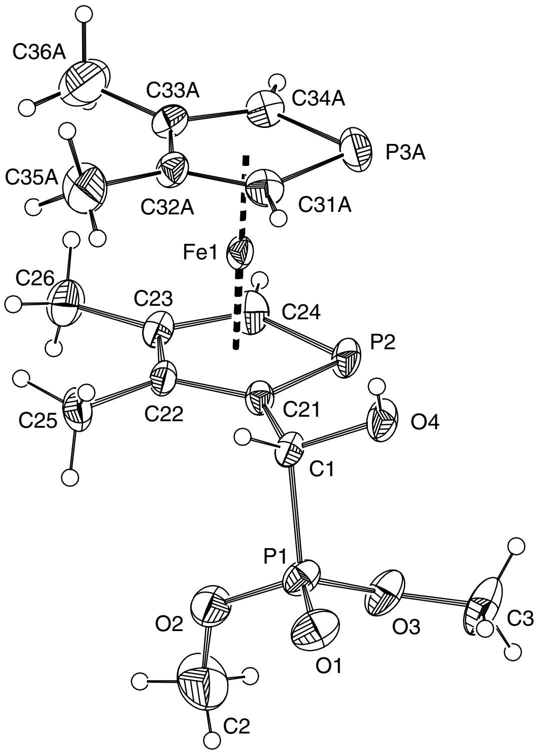

Fig. 1. Molecular structure of **2**. For clarity only the major component of disorder of one enantiomer is shown.

The phosphonyl group points away from the metallocene moieties as is expected on steric grounds.

In crystals the molecules of **2** forms hydrogen-bonded centrosymmetrical dimers between (S,R_p)- and (R,S_p)-enantiomers (Fig. 2). The geometry of the hydrogen bonds is described in Table 3.

3. Discussion

Table 3
Hydrogen bonding geometry in **2** (Å, °)

Scheme of hydrogen bond D–H···A	$d_{(D–H)}$ (Å)	$d_{(H\cdots A)}$ (Å)	$d_{(D\cdots A)}$ (Å)	∠(D–H···A) (°)
O4–H41···O1[a]	0.82(4)	1.92(4)	2.7356(5)	171.3(4)

[a] Symmetry code: $-x$, $-y$, $1-z$.

The results obtained in this work show that addition of a dialkyl phosphite to **1** proceeds in a highly diastereoselective manner. Diastereoselective nucleophilic additions of organometallic reagents to planar chiral ferrocenyl [12,13], phosphaferrocenyl [14], and other organometallic aldehydes [18] were already reported and rationalized in terms of an *exo*-addition to a preferred conformation of the aldehyde. However, in contrast to these reactions addition of dialkyl phosphites to the carbonyl group is usually reversible (Abramov and *retro*-Abramov reactions) [1]. Therefore, the stereochemistry of the addition may be governed by either kinetic or thermodynamic factors. An inspection of the molecular structure of **2** suggests that the diastereoisomer formed should be more stable (at least for steric reasons) than its (S,S_p)–(R,R_p) counterpart. On the other hand, the stereochemistry of **2** can be explained assuming a preferred *exo*-attack on the *s-cis* conformation of **1** (Fig. 3), which seems more stable than the *s-trans* one. It is worthy noting that the structurally related 3,3′,4,4′-tetramethyl phosphaferrocene-2-carboxaldehyde adopts the *s-cis* conformation in the solid state [19] and exhibits in the

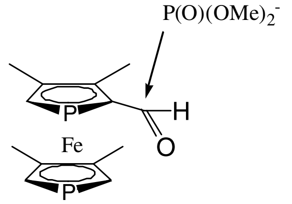

Fig. 3. The *exo*-attack of the phosphite anion on the *s-cis* conformation of **1**.

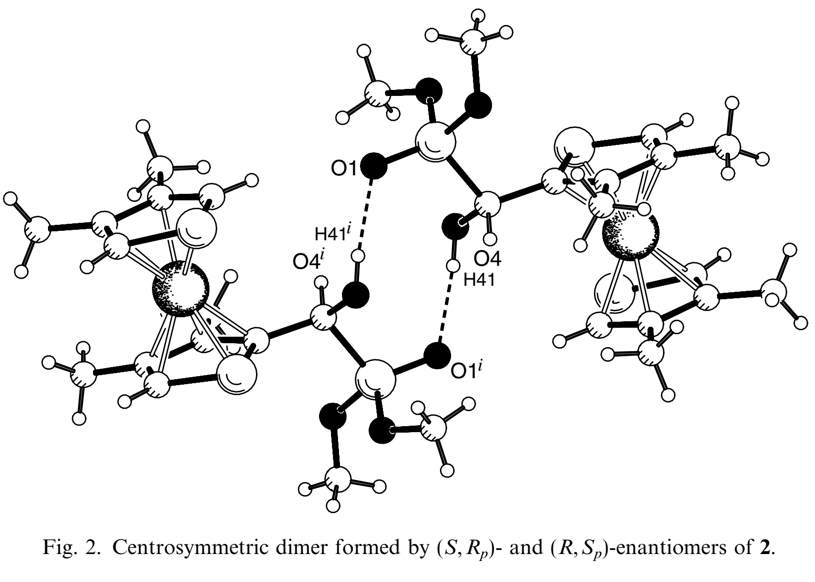

Fig. 2. Centrosymmetric dimer formed by (S,R_p)- and (R,S_p)-enantiomers of **2**.

^{1}H NMR spectrum the coupling constant between the CHO proton and the nearest phosphorus atom similar to that in **1** (4.4 and 4.5 Hz, for this compound and **1**, respectively). It is therefore possible that in this reaction both thermodynamic and kinetic factors cooperate, favoring formation of the (S,R_p)–(R,S_p) diastereomer.

In this preliminary study racemic **1** has been used and therefore racemic **2** was obtained. However, an efficient method of resolution of **1** was recently reported [20], which opens the route to both enantiomers of **2**. This route, as well as reactions at the stereogenic α-carbon in this compound, which may constitute a useful method of general interest in preparation of chiral 1,1′-diphosphaferrocenes, are currently under investigation in the Laboratory and will be reported in due course.

4. Experimental

*4.1. Addition of dimethyl phosphite to **1***

To an argon-saturated solution of **1** [15] (0.1 mmol) and dimethyl phosphite (0.1 ml, 1.14 mmol) in THF (0.2 ml) DBU (5 μl, 0.033 mmol) was added at −78 °C and the mixture was kept at this temperature for 20 h. After pouring into water, extraction with ether and chromatography (SiO_2/ ethyl acetate) the product **2** was isolated as a yellow solid in quantitative yield. Crystallization from pentane afforded diastereomerically pure **2**. ^{31}P NMR (81 MHz, $CDCl_3$, δ ppm): 21.03, −76.53, −80.54. ^{1}H NMR (200 MHz, $CDCl_3$, δ ppm): 4.50 (1H, td (t after addition of D_2O), $J = 9.3$ Hz, $J = 3.1$ Hz), 4.14 (1H, d, $J = 36.1$ Hz), 3.79 (3H, d, $J = 10.3$ Hz), 3.77 (3H, d, $J = 10.3$ Hz) 3.59 (1H, dd (d after addition of D_2O), $J = 36.4$, $J = 1.7$ Hz), 3.56 (1H, d, $J = 37.1$ Hz), 2.95 (1H, m, disappears after addition of D_2O), 2.13(s, 3H), 2.10(s, 6H), 2.07(s, 3H). HRMS (EI): Anal. Calc. for $C_{15}H_{23}FeO_4P_3$: 416.01586. Found: 416.01576.

*4.2. X-ray structure determination of **2***

A single red crystal mounted on a glass fiber was used for measurements at room temperature on a Rigaku AFC5S diffractometer [21] using Mo Kα X-ray source and a graphite monochromator. The unit cell dimensions were determined from a least-squares fit to setting angles of 25 reflections. Monitoring of 3 standard reflections measured after each group of 150 reflections showed no significant decays under X-ray irradiation. Reflection intensities were corrected for Lorentz and polarization effects and absorption corrections were also applied [22].

The structure was solved by direct methods using SHELXS-86 [23] and refined by full-matrix least square method on F^2 using SHELXL-97 [24]. After the refinement with isotropic displacement parameters, refinement was continued with anisotropic displacement parameters for all non-hydrogen atoms. Relatively high anisotropic parameters and inaccurate bond lengths of one phosphacyclopentadienyl ring (P3, C31, C32, C33, C34, C35 and C36 atoms) gave the reason for modeling positional disorder. The mentioned atoms are refined as a disorder group consisting of two components A and B. The occupancy factors are equal to 0.7 for major component of disorder (A) and 0.3 for the minor one (B). Some constrains were included to order the geometry of the rings A and B in this way that the distances between corresponding atom pairs of different components were treated to be equal.

All hydrogen atoms except for the one (H41) atom taking part in hydrogen bond were introduced in calculated positions with idealized geometry and refined using rigid body model with C–H distances equal to 0.97 Å (CH_3) or 0.93 Å (aromatic CH). They were given isotropic displacement parameters equal to 1.2 (in case of secondary or aromatic C parent atom) or 1.5 (tertiary C parent atom) of the equivalent displacement parameters of the C atoms they are attached. The position of the H41 atom was found on the Fourier difference map and its parameters have been refined. In the final step of refinement all the non-hydrogen atoms were refined with anisotropic displacement parameters.

The molecular geometry was calculated by WinGX [25]. The drawings were made by PLATON [26]. The standard uncertainties calculated for the geometry parameters of the disorder group are large, about 0.01 Å for bond lengths and 0.01° for angles.

5. Supplementary materials

Experimental details, atoms' coordinates and displacement parameters are deposited with the Cambridge Crystallographic Data Centre, CCDC 292487. Copies of this information can be obtained free of charge from The Director, CCDC, 12, Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Acknowledgements

We are grateful to Dr. Arkadiusz Kłys for providing the sample of **1**. This work was financially supported by a research grant from University of Łódź.

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