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Resolution and determination of the absolute configuration of 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde

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Abstract—Racemic 3,3′,4,4′-tetramethyl-1,1′-diphosphaferrocene-2-carboxaldehyde **1** was resolved via the formation of diastereomeric dioxolanes with (*S*)-(+)-1-phenyl-1,2-ethanediol. Four stereoisomers were separated by column chromatography. The absolute configuration of one of them (2″*R*, 4″*S*,1*R*) was established by X-ray diffraction. Acid hydrolysis of the dioxolanes afforded quantitatively (*R*)- and (*S*)-enantiomers of **1**. Optical rotatory dispersion (ORD) spectra of both enantiomers are also reported.

1. Introduction

Planar chiral heterometallocenes have attracted considerable attention as novel ligands for asymmetric catalysis[1] and materials displaying bulk second order non-linear optical properties.[2] There have been reports of the resolution or enantioselective syntheses of planar chiral azaferrocenes,[3] phosphaferrocenes[4] and 1,1′-diphoshaferrocenes.[5,6] The latter system is of particular interest because it is readily available, relatively stable and displays a varied coordination chemistry.[7]

We have briefly reported the resolution of racemic 3,3′,4,4′-tetramethyl-1,1′-diphoshaferrocene-2-carboxaldehyde **1** via diastereomeric imines formed in the reaction with (*S*)-(−)-2-amino-3-phenylpropanol.[2] Unfortunately, this method is not very convienient as the chromatographic separation of imines is poor and the yields of pure diastereomers are low (partial overlapping of the bands on the column).

Herein we report an efficient method for the resolution of **1** based on the formation of diastereomeric acetals with (*S*)-(+)-1-phenyl-1,2-ethanediol (Scheme 1). Although apparently more complicated (4 diastereomers are formed because of the creation of a new stereogenic centre on the formyl carbon) it offers a particularly efficient chromatographic separation and quantitative conversion of separated diastereomers of **2** into enantiomers of **1**.

2. Results and discussion

Racemic **1** was reacted with (*S*)-(+)-1-phenyl-1,2-ethanediol in the presence of a catalytic amount of *p*-toluenesulfonic acid and activated molecular sieves at room temperature and left overnight to afford a mixture of diastereomeric dioxolanes **2** in 83% yield along with 13% of unreacted **1**. These were separated by chromatography on a short silica column. HPLC analysis showed that, as expected, because of creation of the stereogenic center at the C-2″, four diastereomers are formed in a roughly 1:1:1:1 ratio (Scheme 1).

This was confirmed by ^{1}H NMR spectroscopy which did not show the formyl proton signal, but instead four doublets of equal intensity at 5.7–6.0 ppm; assignable to H-2″ were observed ($^3J_{PH}$ = 6.4–6.9 Hz). The diastereomers were separated by column chromatography. Three of them were obtained as orange oils, but one (third in the order of elution) formed on evaporation of the solvent crystals suitable for X-ray analysis, which established its absolute configuration, (2″*R*, 4″*S*,1*R*)-**2** (Fig. 1). In this structure, similarly as in other structures of 1,1′-diphosphaferrocenes determined in our laboratory,[8] the distance between the phosphorus atoms, 3.646 (1) Å, is shorter than the sum of their van der Waals radii, 1.9 Å. The dihedral angle between the planes normal to each phospholyl ring that contain both iron and phosphorus atoms is 48.4 (2)°.

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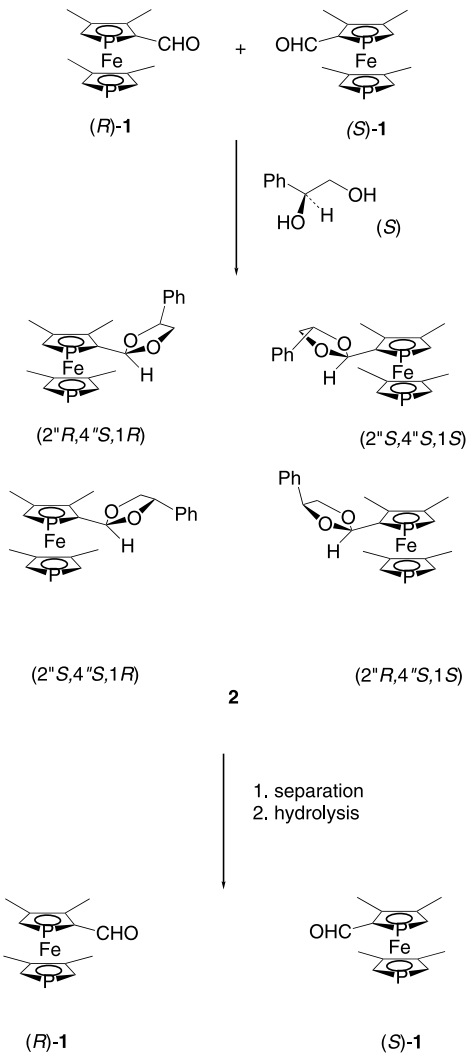
Acid hydrolysis of this compound afforded **1** in a quantitative yield. We assumed that the planar chirality of the metallocene moiety did not change in this reaction and that we obtained (*R*)-**1**. Its enantiomeric purity was checked by ^{31}P NMR spectroscopy using the chiral shift reagent, europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]. We estimated an e.e. >99%. The three other fractions were also hydrolysed and the configuration of the acid controlled by ^{31}P NMR in the presence of the chiral shift reagent. It was found that (*R*)-**1** was also obtained from the second fraction. Consequently, its absolute configuration must be (2″*S*, 4″*S*,1*R*)-**2**. The H2″ proton signal in the ^{1}H NMR spectra of these compounds appears at a lower field than the analogous signal in (2″*R*, 4″*S*,1*R*)-**2** (5.93 ppm versus 5.74 ppm). We attributed this deshielding to the phenyl ring current effect. In the former compound the phenyl ring is *trans* to H2″, whereas in the latter they are mutually *cis*.

The (*S*) enantiomer of **1** was obtained by hydrolysis of the first and fourth fractions. On the basis of the chemical shift of the H2″ protons we can tentatively assign their stereochemistry: (2″*S*, 4″S,1S)-**2** (first fraction) and (2″*R*, 4″*S*,1*S*)-**2** (fourth fraction).



Scheme 1.

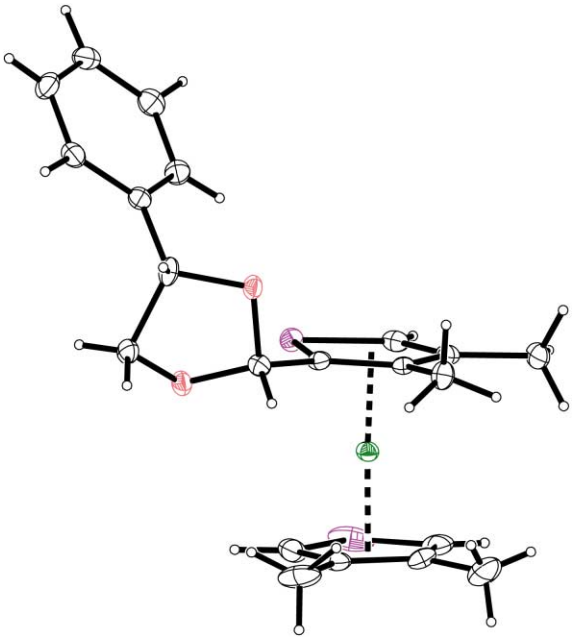


Figure 1. X-Ray structure of (2″*R*, 4″*S*,1*R*)-**2**.

We have also measured the optical rotatory dispersion (ORD) spectra of (*R*)-**1** and (*S*)-**1** (Fig. 2). They confirmed the enantiomeric relationship between these compounds. (*R*)-**1** was levorotatory, similarly as (*R*)-3,4-dimethyl-phosphaferrocenecarboxaldehyde.[4a]

3. Experimental

All operations were performed under an atmosphere of pure dry argon. Solvents were freshly distilled over the appropriate drying agents immediately prior to use. Racemic **1** was prepared according to the literature method.[9] Molecular sieves 4 Å were activated by heat-

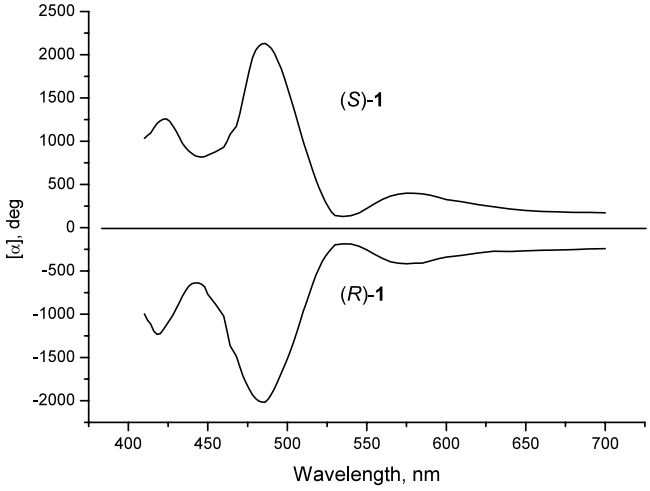


Figure 2. ORD spectra of (*R*)-**1** and (*S*)-**1**.

ing to 300°C at 0.1 Tr for 3 h. All other reagents were commercially available (Aldrich) and were used as received. Chromatographic separations were carried out on silica gel 60 (230–400 mesh ASTM) purchased by Fluka. NMR spectra were recorded in $CDCl_3$ solutions on a Varian Gemini 200 BB spectrometer (200 MHz for ^1H). ORD spectra were measured in $CHCl_3$ on a Perkin-Elmer 241 PC polarimeter.

3.1. Synthesis and separation of the diasteromers of 2

A mixture of *rac*-3,3,4,4′-tetramethyl-1,1′-diphosphaferrocene-2carboxaldehyde, **1**, (250 mg, 0.82 mmol), (*S*)-(+)-1-phenyl-1,2-ethandiol (170 mg, 1.22 mmol), a catalytic amount of *p*-toluenosulfonic acid and freshly activated molecular sieves 4 Å (4 g) in dichloromethane was stirred at rt overnight. The solvent was removed in vacuo and the residue chromatographed on a short (2×7 cm) column using hexane–chloroform (1:1 v/v) as eluent. Unreacted **1** (32 mg, 13%) and a mixture of 4 diastereomers of **2** (290 mg, 83%) were obtained. The diastereomers were separated by a subsequent chromatography on a longer column (2×45 cm) using a mixture of either hexane–ethyl acetate (10.5:1 v/v) or petroleum ether–ethyl acetate (12:1 v/v) as the eluent. Four orange, well-separated fractions were collected.

Fraction 1. Yield 55 mg. ^1H NMR: δ 7.31–7.37 (m, 5H, H_{Ar}), 5.95 (d, 1H, $^3J_{HCCP}=6.9$ Hz, H2″), 5.10 (dd, 1H, $^3J_{HCCH}=6.1$ Hz, $^3J_{HCCH}=8.2$ Hz, H4″ or H5″), 4.48 (dd, 1H, $^3J_{HCCH}=6.2$ Hz, $^3J_{HCCH}=8.2$ Hz, H4″ or H5″), 3.5–4.0 (m, 4H, phospholyl and H4″ or H5″), 2.27 (s, 3H, Me), 2.20 (s, 3H, Me), 2.12 (s,3H, Me), 2.11 (s, 3H, Me).

Fraction 2. Yield 53 mg. ^1H NMR: δ 7.39–7.33 (m, 5H, H_{Ar}), 5.94 (d, 1H, $^3J_{HCCP}=6.8$ Hz, H2″), 5.21 (dd, 1H, $^3J_{HCCH}=6.9$ Hz, $^3J_{HCCH}=6.5$ Hz, H4″ or H5″), 4.41 (dd, 1H, $^3J_{HCCH}=6.5$ Hz, $^3J_{HCCH}=8.2$ Hz, H4″ or H5″), 3.5–4.0 (m, 4H, phospholyl and H4″ or H5″), 2.25 (s, 3H, Me), 2.21 (s, 3H, Me), 2.12 (s, 6H, 2×Me).

Fraction 3. Yield 60 mg.^1H NMR: δ 7.3–7.4 (m, 5H, H_{Ar}), 5.74 (d, 1H, $^3J_{HCCP}=6.4$ Hz, H2″), 5.06 (dd, 1H, $^3J_{HCCH}=6.9$ Hz, $^3J_{HCCH}=6.8$ Hz, H4″ or H5″), 4.23 (dd, 1H, $^3J_{HCCH}=6,9$ Hz, $^3J_{HCCH}=7.9$ Hz, H4″ or H5″), 3.5–4.0 (m, 4H, phospholyl and H4″ or H5″), 2.24 (s, 3H, Me), 2.21 (s, 3H, Me), 2.12 (s, 6H, 2×Me).

Fraction 4. Yield 65 mg.^1H NMR: δ 7.3–7.5 (m, 5H, H_{Ar}), 5.78 (d, 1H, $^3{}_{JHCCP}=6.7$ Hz, H2″), 5.03 (dd, 1H, $^3J_{HCCH}=7,6$ Hz, $^3J_{HCCH}=6.5$ Hz, H4″ or H5″), 4.20 (dd, 1H, $^3J_{HCCH}=7,6$ Hz, $^3J_{HCCH}=7,1$ Hz, H4″ or H5″), 3.5–4.0 (m, 4H, phospholyl and H4″ or H5″), 2.28 (s, 3H, Me), 2.21 (s, 3H, Me), 2.12 (s, 3H, Me), 2.11 (s, 3H, Me).

3.2. Hydrolysis of acetals

Fractions 1–4 were dissolved in THF (3ml), after which one drop of conc. HCl was added and the resulting solution stirred 0.5 h at rt. The solvent was removed in vacuo and the residue chromatographed (silica gel, chloroform) to afford **1** in a quantitative yield.

^1H NMR: 9.83 (d, $J=4.6$ Hz, 1H, CHO), 4.21 (d, $J=36.5$ Hz, 1H, H5), 3.82 (d, $J=36.3$ Hz, 2H, H2′ and H5′), 2.42 (s, 3H, Me), 2.18 (s, 3H, Me); 2.10 (s, 3H, Me), 2.06 (s, 3H, Me). IR ($CHCl_3$): 1664 cm^{-1}(CO).

The absolute configurations and enantiomeric purity were determined by ^{31}P NMR in the presence of europium tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorate]. The spectral assignment was verified by the addition to the sample a small amount of racemic **1**, which resulted in the appearance of a signal of the other enantiomer. The ^{31}P NMR signals of (*R*)-**1** in the presence of an equimolar amount of the europium complex appeared as doublets at −46.2 ppm and −65.0 ppm ($^2J_{PP}=7.7$ Hz), whereas those of (*S*)-**1** at −46.2 ppm and −65.3 ppm.

First fraction: (*S*)-**1**; e.e. >99%; $[\alpha]_D^{20}$+395 ($c=0.028$, $CHCl_3$).

Second fraction: (R)-**1**; e.e. >98%.

Third fraction: (*R*)-**1**; e.e. >99%;$[\alpha]_D^{20}$ −403 ($c=0.036$, $CHCl_3$).

Fourth fraction: (*S*)-**1**; e.e. >99%.

4. Supplementary material

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 214292. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax +44 (0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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