

# Diastereomeric amides from *rac*-3,3',4,4'-tetramethyl-1,1'-diphosphaferrocene-2-carboxylic acid and (*S*)- $\alpha$ -phenylethylamine: separation and determination of absolute configuration

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Received 3 June 2000; received in revised form 3 August 2000; accepted 3 August 2000

## Abstract

Reaction of racemic 3,3',4,4'-tetramethyl-1,1'-diphosphaferrocene-2-carboxylic acid **1** with (*S*)- $\alpha$ -phenylethylamine in the presence of benzotriazol-1-yl-oxytris-(dimethylamino)phosphonium hexafluorophosphate and diisopropylethylamine leads to diastereomeric amides, (*S,R*)-**2** and (*S,S*)-**2**. The diastereomers were separated by column chromatography and their absolute configurations were determined from NMR data supported by molecular modeling. © 2001 Elsevier Science B.V. All rights reserved.

*Keywords:* Planar chirality; Central chirality; 1,1'-Diphosphaferrocene; Carboxylic acid; Amide; Absolute configuration

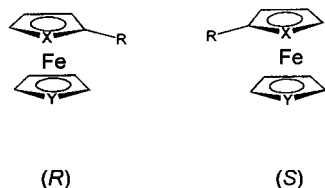
## 1. Introduction

Planar chiral ferrocenes having substituents able to bind to a metal center (e.g. 1,2-disubstituted with different donor groups) have attracted considerable attention as ligands in asymmetric catalysis [1]. This attention has recently turned to Group 15 heteroferrocenes such as azaferrocene, phospho- and 1,1'-diphosphaferrocene [2]. Such complexes contain heteroatoms with lone pairs of electrons in the cyclic  $\eta^5$ -ligands which provide good ligating properties [3] and their mono-substituted (in

this ligand) derivatives are also planar chiral (Scheme 1).

Among various derivatives of 1,1'-diphosphaferrocene synthesized up to now, readily accessible 3,3',4,4'-tetramethyl-1,1'-diphosphaferrocene-2-carboxylic acid **1** [4] seems to be the most appealing starting material for the development of chiral complexes based on this heteroferrocene system. We thought that the presence of the carboxylic function in the 2-position would result in the enhanced ability of the system to form P,O-chelate complexes with transition metals, and would facilitate introduction of additional stereogenic coordination centers, e.g. via coupling with chiral amines (most chiral ferrocenes that found application in asymmetric catalysis possess both planar chirality and stereogenic center in the lateral chain [1]).

We report herein on the coupling of **1** with a chiral amine, (*S*)- $\alpha$ -phenylethylamine ((*S*)- $\alpha$ -PEA) [5], and separation of the resulting diastereomeric amides by column chromatography. The absolute stereochemistry of these amides was assigned using NMR spectroscopy supported by molecular modeling.



Scheme 1. X, Group 15 element; Y, Group 15 element or CH.

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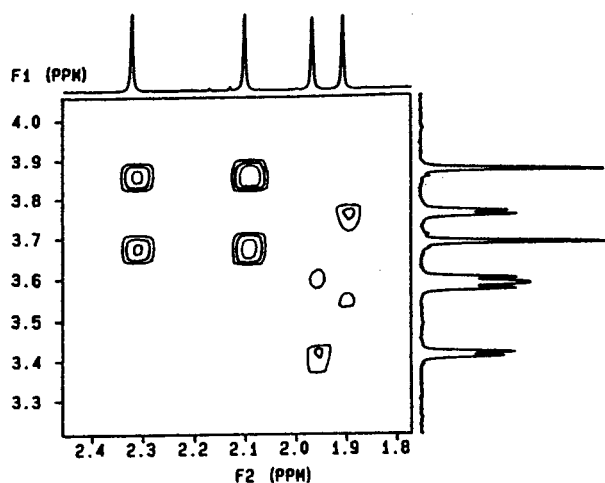
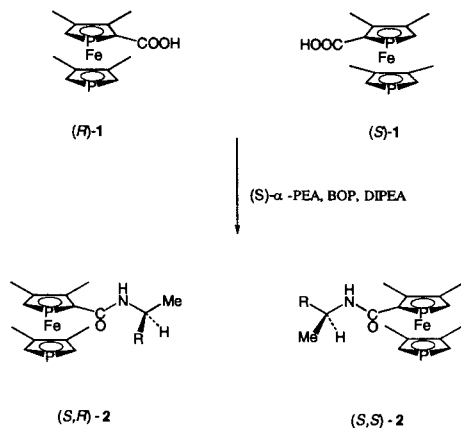


Fig. 1. The long-range COSY-45 contour plot of the less polar amide **2** showing correlation between methyl and phospholyl protons.

## 2. Results and discussion

We have found that *rac*-**1** reacts with (*S*)- $\alpha$ -PEA in the presence of benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) [6] and diisopropylethylamine (DIPEA) in acetonitrile to give the mixture of diastereomeric amides, (*S,R*)-**2** and (*S,S*)-**2** (the first stereodescriptor belongs to the central element of chirality, whereas the second describes planar heteroferrocene chirality according to the CIP rules [1b,2c]) in 95% yield (Scheme 2). These amides were separated by column chromatography on silica using a mixture of hexanes–benzene–acetone (15:5:1 v/v) as eluent. The total yield of separated diastereomers was 87%. The first eluted compound will be hereafter called as the less polar diastereomer.

Unfortunately, attempts to obtain X-ray quality crystals of either diastereomer failed. The configuration assignment was therefore based on the NMR data supported by the molecular modeling.

Comparison of the  $^1\text{H}$  chemical shifts of the methyl groups of both diastereomers (2.32, 2.10, 1.97, 1.91 and 2.33, 2.12, 2.10, 2.06 ppm for the less and more polar diastereomers, respectively) clearly indicate a shielding effect experienced by two of these groups in the less polar compound. Similar effect is observed for H-2' and H-5' resonances (3.67, 3.50 and 3.79, 3.70 ppm for the less and more polar compounds, respectively).

The long-range homonuclear COSY-45 (“COSY with delay”) spectrum (Fig. 1) showed that shielded methyl resonances at 1.97 and 1.91 ppm show correlations with H-2' and H-5' and therefore have to be assigned to methyl groups at C-3' and C-4'.

The observed differences of the  $^1\text{H}$  chemical shift of protons in the less substituted phospholyl ring are attributed to the phenyl ring current effect, different in each diastereomer. To confirm this hypothesis, amides (*S,R*)-**3** and (*S,S*)-**3** bearing cyclohexyl instead of phenyl rings have been synthesized. Thus, **1** was reacted with (*S*)- $\alpha$ -cyclohexylethylamine in the presence of BOP and DIPEA in acetonitrile at room temperature. The mixture of (*S,R*)-**3** and (*S,S*)-**3** was isolated by column chromatography. Although we were unable to separate these diastereoisomers, we have found that the  $^1\text{H}$ -NMR spectrum of their mixture showed methyl groups signals at 2.33, 2.12, 2.09, 2.08 and 2.06 ppm (some of the expected eight signals are overlapping). Thus, there are no signals for the methyl group at  $\delta < 2.00$  ppm, as expected in the absence of the ring current effect.

In order to find out in which of the two diastereoisomers the phenyl ring current effect should influence the less substituted phospholyl ligand, molecular modeling calculations were performed for various possible rotamers of (*S,R*)-**2** and (*S,S*)-**2** using the semiempirical ZINDO/1 MO method. The calculated geometries, corresponding to the global minima of the potential energy hypersurfaces, are shown in Fig. 2.

As can be seen, a shielding effect on the protons of the less substituted phospholyl ring is expected for (*S,R*)-**2** and this stereochemistry has been assigned for the less polar diastereoisomer. It is worth noting that the calculated value of dipole moment of this diastereoisomer (8.5 D) is slightly lower than that of its (*S,S*)- counterpart (9.0 D).

Chiroptical methods are very useful in determining the absolute configuration of organometallic complexes. It was therefore of interest to develop the application of these methods for chiral 1,1'-diphosphaferrocenes. The optical rotatory dispersion (ORD) curves for (*S,R*)-**2** and (*S,S*)-**2** are shown in Fig. 3.

The curves show the three distinct Cotton effects at ca. 320, 395, and 480 nm presumably due to d–d and charge-transfer transitions in the chiral heteroferrocene chromophore. (*S,R*)-**2** displays  $[\alpha]_{\text{D}}^{20} = -112^\circ$ , which nicely corroborates the negative value,  $[\alpha]_{\text{D}}^{25} = -158^\circ$ , reported by Ganter for (*R*)-2-formyl-3,4-dimethyl-1-

phoshaferrocene [2c], suggesting the same configuration of the heteroferrocene moiety in both compounds.

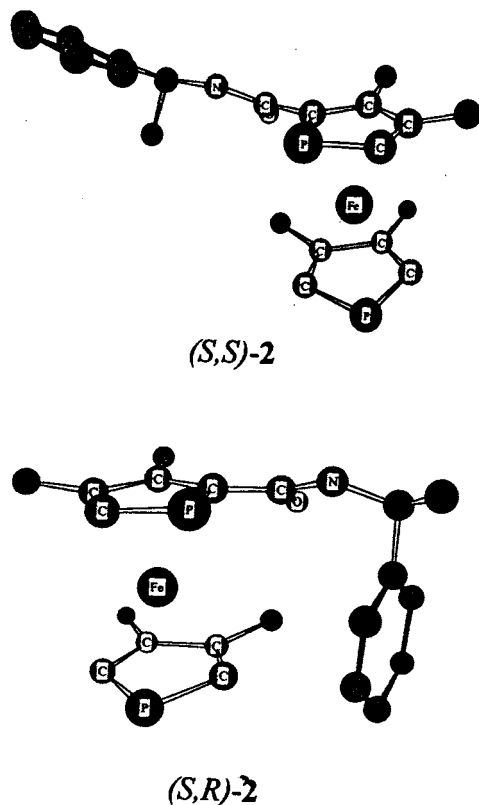


Fig. 2. Calculated geometries of (S,R)-2 and (S,S)-2.

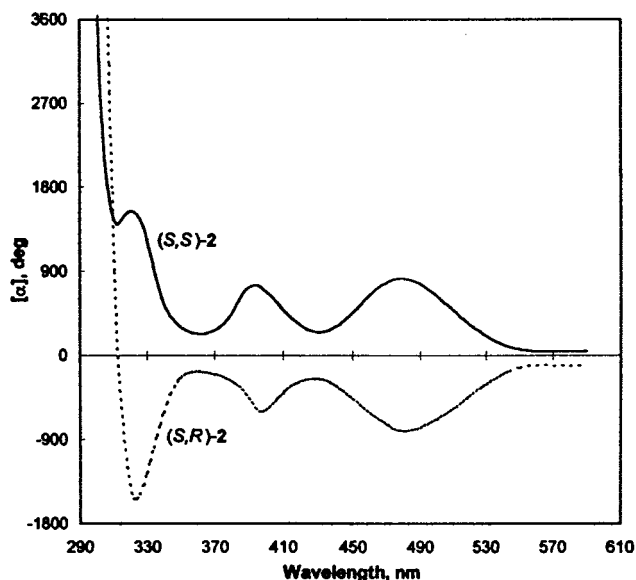


Fig. 3. ORD curves of (S,R)-2 and (S,S)-2.

### 3. Experimental

All operations were performed under an atmosphere of dry pure argon. Solvents were freshly distilled over the appropriate drying agents immediately prior to use. Compound **1** was prepared according to the literature method [4]. All other reagents were commercially available (Fluka, Aldrich) and were used as received. Chromatographic separations were carried out on Kieselgel 60 (230–400 mesh, ASTM) purchased from Merck. NMR spectra were recorded in  $\text{CHCl}_3$ -*d* solutions on a Varian Gemini 200 BB spectrometer (200 MHz for  $^1\text{H}$ ). ORD spectra were measured in  $\text{CHCl}_3$  solutions on a Perkin–Elmer 241PC polarimeter. The unconstrained geometry optimizations were done with the HyperChem 4.5 package implementation of the semiempirical ZINDO/1 method. Single state calculations were performed by a conjugate gradient Polak–Ribiere method using the overlap weighting factors  $p(\sigma-\sigma) = 1.00$  and  $p(\pi-\pi) = 1.00$ ; final RMS gradient  $< 0.05 \text{ kJ mol}^{-1} \text{ \AA}^{-1}$  was applied.

#### 3.1. Synthesis and separation of (S,R)-2 and (S,S)-2

A mixture of *rac*-3,3',4,4'-tetramethyl-1,1'-diphosphaferrocene-2-carboxylic acid, **1**, (96 mg, 0.3 mmol), BOP (144 mg, 0.33 mmol), (*S*)- $\alpha$ -PEA (40  $\mu\text{l}$ , 0.33 mmol) and diisopropylethylamine (120  $\mu\text{l}$ ) in acetonitrile (5 ml) was stirred at room temperature for 45 min, poured onto 2 M HCl and extracted with dichloromethane. The solvent was removed in vacuo and the residue was chromatographed on a short (2  $\times$  10 cm) column using benzene–chloroform (1:1 v/v) as eluent. The mixture of (S,R)-2 and (S,S)-2 was obtained as an orange solid in 95% yield. The diastereomers were separated by a subsequent chromatography on a longer column (2  $\times$  40 cm) using a mixture of hexanes–benzene–acetone as (15:5:1 v/v) eluent. Two orange, well-separated fractions were collected. Yield: first fraction 62 mg and second fraction 49 mg; total yield 111 mg (87%). Analytical samples were prepared by crystallization from dichloromethane–cyclohexane.

Analytical data: Found: first fraction C, 61.03; H, 6.34; N, 3.08; second fraction C, 61.19; H, 6.38; N, 3.08. Calc. for  $\text{C}_{23}\text{H}_{29}\text{FeNP}_2\text{O}$  (solvate with 1/3 molecule of cyclohexane): C, 60.94; H, 6.45; N, 3.08%.

Spectroscopic data — First fraction, (S,R)-2:  $^1\text{H}$ -NMR:  $\delta$  7.4–7.2 (m, 10H,  $\text{H}_{\text{ar}}$ ), 6.19 (br pt, 1H, NH), 5.08 (ddq, 1H,  $^3J_{\text{HCNH}} \approx 7.9 \text{ Hz}$ ,  $^3J_{\text{HCCH}} \approx 6.9 \text{ Hz}$ ,  $^5J_{\text{HP}} \approx 1.3 \text{ Hz}$ , NCHMe), 3.78 (d, 1H,  $^3J_{\text{HP}} = 37.2 \text{ Hz}$ , H-5), 3.67 (dd, 1H,  $^3J_{\text{HP}} = 36.1 \text{ Hz}$ ,  $^3J_{\text{HH}} = 1.9 \text{ Hz}$ , H-C2'), 3.50 (dd, 1H,  $^3J_{\text{HP}} = 36.2 \text{ Hz}$ ,  $^3J_{\text{HH}} = 1.9 \text{ Hz}$ , H-5'), 2.32 (s, 3H, Me-C3), 2.10 (s, 3H, Me-C4), 1.97 (s, 3H, Me-C4'), 1.91 (s, 3H, Me-C3'), 1.49<sub>s</sub> (d, 3H,  $^3J_{\text{HH}} = 6.9 \text{ Hz}$ , NCHMe).  $^{13}\text{C}$ -NMR:  $\delta$  170.17 (d,

$^2J_{\text{CP}} = 18.2$ , CO), 143.69 (s,  $C_{\text{ar}}$ ), 129.79 (d,  $^1J_{\text{CP}} = 104.65$  Hz, C2), 128.60, 127.21, 126.23 (3 s,  $C_{\text{ar}}$ ), 100.93 ( $^2J_{\text{CP}} = 7.5$  Hz), 99.40 ( $^2J_{\text{CP}} = 7.3$  Hz), 98.77 ( $^2J_{\text{CP}} = 7.3$  Hz), 97.73 ( $^2J_{\text{CP}} = 4.6$  Hz) (4 × d, C3, C3', C4, and C4'), 82.29, 82.29 (2 × d,  $^1J_{\text{CP}} \approx 60.4$  Hz, C2' and C5'), 79.80 (d,  $^1J_{\text{CP}} = 59.0$  Hz, C5), 49.13 (s, NCMe), 22.06 (s, NCMe), 15.42, 14.33, 13.97, 13.42 (4 × s, Me's).  $^{31}\text{P-NMR}$ :  $\delta$  -72.5 (ddd,  $^2J_{\text{PH}} = 37.2$  Hz,  $J_{\text{PP}} = 14.6$  Hz,  $^4J_{\text{PCCNH}} = 4.6$  Hz, P1), -76.6 (ddd,  $^2J_{\text{PH}} \approx ^2J_{\text{PH}} \approx 36.4$  Hz,  $J_{\text{PP}} = 14.6$  Hz, P1').

Second fraction, (*S,S*)-**2**:  $^1\text{H-NMR}$ :  $\delta$  7.4–7.2 (m, 10H,  $H_{\text{ar}}$ ), 6.22 (br pt, 1H, NH), 5.10 (dq, 1H,  $^3J_{\text{HCNH}} \approx 7.7$  Hz,  $^3J_{\text{HCCH}} \approx 6.9$  Hz, NCHMe), 3.80 (d, 1H,  $^3J_{\text{HP}} = 37.4$  Hz, H-5), 3.79 (dd, 1H,  $^3J_{\text{HP}} = 36.1$  Hz,  $^3J_{\text{HH}} = 1.95$  Hz, H-C2' or H-5'), 3.70<sub>s</sub> (dd, 1H,  $^3J_{\text{HP}} = 36.4$  Hz,  $^3J_{\text{HH}} = 1.95$  Hz, H-C2' or H-C5'), 2.33, 2.12, 2.10, 2.06 (4 × s, 4 3H, Me's), 1.53 (d, 3H,  $^3J_{\text{HH}} = 6.9$  Hz, NCHMe).  $^{13}\text{C-NMR}$ :  $\delta$  170.29 (d,  $^2J_{\text{CP}} = 18.2$  Hz, CO), 143.44 (s,  $C_{\text{ar}}$ ), 129.83 (d,  $^1J_{\text{CP}} = 104.9$  Hz, C2), 128.58, 127.12, 125.99 (3 × s,  $C_{\text{ar}}$ ), 101.05 ( $^2J_{\text{CP}} = 7.2$  Hz), 99.37 ( $^2J_{\text{CP}} = 6.8$  Hz), 98.51 ( $^2J_{\text{CP}} = 7.2$  Hz), 97.46 ( $^2J_{\text{CP}} = 4.5$  Hz) (4 × d, C3, C3', C4 and C4'), 83.23, 83.01 (2 × d,  $^1J_{\text{CP}} = 59.7$ , C2' and C5'), 80.09 (d,  $^1J_{\text{CP}} = 58.8$  Hz, C5), 48.99 (s, NCMe), 22.46 (s, NCMe), 15.40, 14.39, 14.15, 13.48 (4 s, Me's).  $^{31}\text{P-NMR}$ :  $\delta$  -71.7 (ddd,  $^2J_{\text{PH}} = 37.2$  Hz,  $J_{\text{PP}} = 13.7$  Hz,  $^4J_{\text{PCCNH}} = 4.5$  Hz, P1), -76.2 (ddd,  $^2J_{\text{PH}} \approx ^2J_{\text{PH}} \approx 36.2$  Hz,  $J_{\text{PP}} = 13.7$  Hz, P1').

### 3.2. Synthesis of (*S,R*)-**3** and (*S,S*)-**3**

A mixture of these diastereomers has been obtained in 82% yield by the same procedure using (*S*)- $\alpha$ -cyclohexylethylamine instead of (*S*)- $\alpha$ -PEA. Elemental analysis: Found: C, 58.15; H, 7.02; N, 3.16; P, 14.05. Calc.

for  $\text{C}_{21}\text{H}_{31}\text{FeNP}_2\text{O}$ : C, 58.48; H, 7.29; N, 3.29; P, 14.36.  $^1\text{H-NMR}$  (only methyl groups region): 2.33, 2.12, 2.09, 2.08, and 2.06.

### Acknowledgements

This work was financially supported by the Polish State Committee for Scientific Research (KBN), Grant 3T09A 027 16.

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