Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 15, pp. 2607–2611, 1997

Printed in Great Britain
PII: S0957-4166(97)00273-5
0957-4166/97 $17.00 + 0.00

Enantiomerically pure phosphaferrocenes with planar chirality

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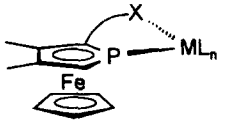
Abstract: Enantiomerically pure 2-formyl-3,4-dimethylphosphaferrocene **1** was prepared straightforwardly by resolution of rac-**1** via column chromatography on silica of diastereomeric aminals formed of **1** and (*R*),(*R*)-1,2-di(*N*-methylamino)cyclohexane **2**. Both enantiomers (*S*)-**1** and (*R*)-**1** are obtained in 94% yield with ee>99%. The amine **2** is recycled in 89% yield. The absolute configuration of (*S*)-**1** has been determined by X-ray crystallography. © 1997 Elsevier Science Ltd

Planar chiral ferrocenes have attracted considerable attention as ligands in asymmetric catalysis.[1] The classical route to these compounds based on the resolution of a racemate was developed by Ugi.[2] However, diastereo- and enantioselective syntheses of enantiomerically pure ferrocene derivatives have meanwhile been devised.[3] Planar chiral tricarbonylchromium complexes of disubstituted benzene derivatives are accessible in enantiopure form as well and have been successfully applied in asymmetric synthesis.[4] In contrast, comparatively little is known about the preparation of planar chiral π complexes of heterocycles. Non-racemic 2-methylazaferrocene was synthesized by Schlögl as early as 1969 and has been examined regarding its chiroptical properties. However, the enantiomeric purity of the compound was not determined.[5] Fu recently reported on the utilization of enantiomerically pure azaferrocene compounds in asymmetric catalysis.[6] We have been interested in the application of donor substituted phosphaferrocenes as bidentate chelate ligands for a while. These ligands coordinate to a metal center via the phosphorus atom of the phospholyl ring and the donor group X on the substituent (Scheme 1).[7] In order to investigate the potential of this new chiral metal–ligand arrangement it is essential to have access to the enantiomerically pure ligands. We report here an efficient method which makes planar chiral phosphaferrocenes available in enantiomerically pure form for the first time.



Scheme 1.

Results

The starting point for our ligand syntheses[7] is the aldehyde **1** which is obtained in a Vilsmeyer reaction from 3,4-dimethylphosphaferrocene as racemate **1a,b**.[8] Thus, having access to the enantiopure aldehydes **1a** and **1b** allows the preparation of a set of enantiomerically pure ligands by subsequent transformations. Treatment of *rac*-**1** with 1.05 equivalents of (*R*),(*R*)-1,2-di(*N*-methylamino)cyclohexane **2**[9] in ether at room temperature affords the 1:1 mixture of the diastereomeric aminals **3a** and **3b** in quantitative yield which can easily be separated by column chromatography on silica (Scheme 2). Remarkable differences are observed for the elution of the two isomers: aminal **3a** is obtained with hexane/ether 3:1 whereas more polar aminal **3b** requires hexane/ether 1:1 to be eluted. This different elution behaviour ensures an efficient separation and high capacity. Using a 20

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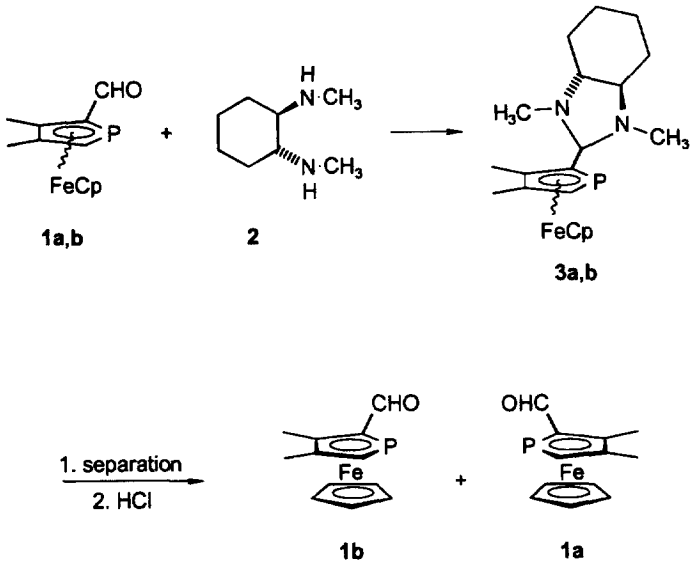
cm column a 5 g mixture of **3a** and **3b** can easily be separated into the analytically pure components which are obtained in >96% yield. Cleavage of the aminals is successfully performed in the two-phase system CH_2Cl_2/HCl leading to the enantiomerically pure aldehydes **1a** and **1b** in >97% yield. From the aqueous phase the amine auxiliary **2** can be recycled in 89% isolated yield after extraction with CH_2Cl_2 and sublimation. The enantiomeric purity of the aldehydes **1a** and **1b** was determined by HPLC and exceeds the 99% level in both cases. The respective opposite enantiomer can not be detected in the chromatograms of **1a** and **1b** respectively. Thus, the aldehydes are configurationally stable for days in the presence of 2 N HCl. An X-ray crystal structure determination was carried out in order to elucidate the absolute configuration of aldehyde **1a**. Suitable crystals were obtained from hexane/THF at 4°C. To make use of the large contribution of anomalous dispersion to the atomic scattering factor of iron the structure determination was carried out with $Cu_{K\alpha}$ radiation. This allowed the unambigous determination of the absolute configuration of the molecule. Figure 1 shows the molecular structure of **1a** in the crystal which is found to have (*S*)-configuration.[10] The formyl group is oriented coplanar with the phospholyl ring and the phosphorus and oxygen atoms in a cis arrangement. The geometric parameters of the structure are within the range observed for other phosphaferrocenes.[11]



Scheme 2.

The simple and efficient separation of enantiomeric aldehydes **1a** and **1b** provides for the first time a straightforward access to enantiomerically pure phosphaferrocenes with planar chirality. Synthetic implications of the new chiral compounds are currently under investigation.

Experimental section

All manipulations were carried out under dry N_2 in Schlenk glassware. Solvents were dried and purified by standard methods and were stored under N_2. NMR spectra were recorded on a Varian Unity 500 spectrometer (500 MHz, ^1H, int. TMS; 126 MHz, $^{13}C\{^1H\}$, APT, int. TMS; 202 MHz, $^{31}P\{^1H\}$, ext. 85% H_3PO_4). Mass spectra were recorded on a Finnigan MAT 95. Elemental analysis (C, H, N) was performed with a Carlo-Erba elemental analyzer, Modell 1106. $[\alpha]_D$ were recorded on a Perkin Elmer 241 polarimeter. Silica was modified by the addition of 20 ml triethylamine to 100 g silica and subsequent drying in high vacuum.

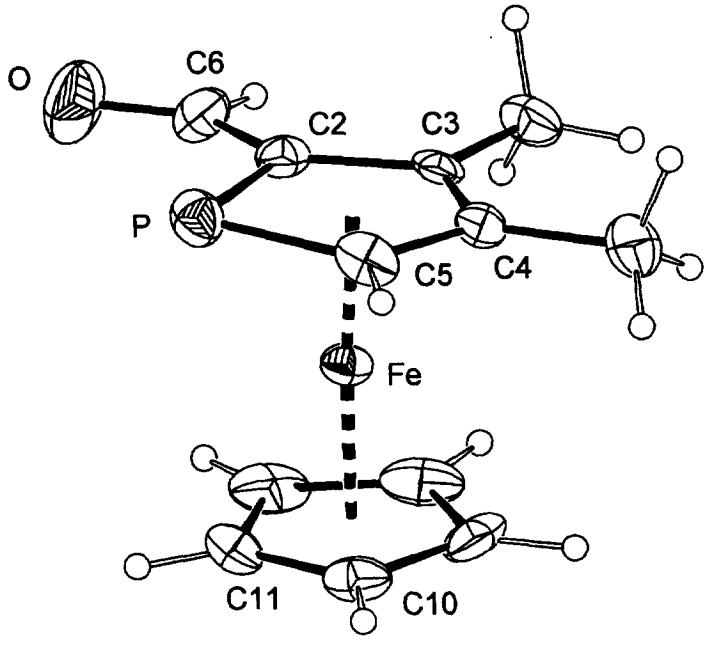


Figure 1. Molecular structure of (*S*)-**1a** in the crystal.

Preparation of aminals 3a and 3b

3.27 g (12.6 mmol) **1a,b** and 1.88 g (13.2 mmol) **2** were stirred in 40 mL of ether in the presence of molecular sieves (3 Å) for 3 d at room temperature. After filtration and removal of the solvent under vacuum the residue is chromatographed on 80 g of modified silica. Aminal **3a** is eluted first with hexane/ether 3:1 followed by **3b** using hexane/ether 1:1.

3a: 2.32 g, 96%; ^{1}H NMR ($CDCl_3$): δ=1.2–1.4 (m, 4 H, C_6H_{10}), 1.7–2.1 (m, 5 H, C_6H_{10}), 2.17, 2.25, 2.31, 2.37 (4 s, 12 H, CH_3), 2.80 (m, 1 H, C_6H_{10}), 3.59 (d, ^3J(HP)=8.9 Hz, 1 H, N_2CH), 3.70 (d, ^2J(HP)=35.2 Hz, 1 H, α-CH), 4.16 (s, 5 H, Cp); ^{13}C NMR ($CDCl_3$): δ=15.3 (CH_3), 16.9 (CH_3), 24.4 (CH_2), 25.2 (CH_2), 27.2 (CH_2), 29.8 (CH_2), 38.2 (NCH_3), 39.2 (NCH_3), 66.2 (NCH), 67.9 (NCH), 72.0 (Cp), 76.9 (d, ^1J(CP)=58 Hz, α-CH), 90.2 (d, ^2J(CP)=16 Hz, N_2CH), 91.5 (d, ^2J(CP)=5 Hz, β-C), 96.7 (d, ^2J(CP)=6 Hz, β-C), 104.7 (d, ^1J(CP)=55 Hz, α-C); ^{31}P NMR ($CDCl_3$): δ=−75.8; $C_{18}H_{29}FePN_2$, calcd.: 384.14118, found: 384.14121 (HRMS).

3b: 2.34 g, 97%; ^{1}H-NMR ($CDCl_3$): δ==1.1–1.3 (m, 4 H, C_6H_{10}), 1.7–1.8 (m, 3 H, C_6H_{10}), 1.9–2.1 (m, 2 H, C_6H_{10}), 2.2–2.4 (m, 1 H, C_6H_{10}), 1.92, 2.17, 2.21, 2.54 (4 s, 12 H, CH_3), 3.70 (d, ^2J(HP)=34.6 Hz, 1 H, α-CH), 4.16 (s, 5 H, Cp); 4.19 (d, ^3J(HP)=10.4 Hz, 1 H, N_2CH); ^{13}C NMR ($CDCl_3$): δ=15.1 (CH_3), 16.9 (CH_3), 24.6 (2 CH_2), 28.5 (CH_2), 29.6 (CH_2), 34.8 (NCH_3), 40.9 (NCH_3), 65.4 (NCH), 69.9 (NCH), 72.1 (Cp), 76.6 (d, ^1J(CP)=58 Hz, α-CH), 86.2 (d, ^2J(CP)=11 Hz, N_2CH), 91.4 (d, ^2J(CP)=5 Hz, β-C), 97.5 (d, ^2J(CP)=6 Hz, β-C), 101.5 (d, ^1J(CP)=57 Hz, α-C); ^{31}P-NMR ($CDCl_3$): δ=−76.9; $C_{18}H_{29}FePN_2$ (384.1): calcd. C 62.51, H 7.61, N 7.29; found: C 62.39, H 7.65, N 7.16.

(S)- and (R)-2-Formyl-3,4-dimethylphosphaferrocene (S)-1a and (R)-1b

2 N HCl (20 mL) is added to a solution of **3a** or **3b** (2.31 g, 6.0 mmol) in 30 mL of CH_2Cl_2 and the mixture is stirred vigurously at room temperature. The cleavage reaction requires 80 h for **3a** and 7 d for **3b**. The organic phase is separated, dried with Na_2SO_4 and the solvent is removed under vacuum. The crude product is purified by filtration through a 2 cm plug of alumina with hexane/ether 2:1. After removal of the solvent under vacuum pure **1a** (1.53 g, 98%) or **1b** (1.52 g, 97%) is obtained, respectively. NMR data are similar to those quoted in the literature. HPLC (Daicel CHIRALCEL OD,

7% *i*PrOH in n-heptane, 1 mL/min, 254 nm): **1a**: t_R=9.29 min; **1b**: t_R=10.43 min. $[\alpha]_D^{25}$ in CH_2Cl_2: **1a**: +163 (*c* 0.062); **1b**: −158 (*c* 0.131).

Recycling of (R),(R)-1,2-di(N-methylamino)cyclohexane 2

The acidic aqueous phase of the cleavage reaction is made alkaline by the addition of an excess of NaOH and extracted several times with CH_2Cl_2. The organic phase is separated, dried with Na_2SO_4 and the solvent is removed under vacuum. Sublimation of the residue (HV, 50°C) gave analytically pure **2** in 89% yield as white crystals.

X-Ray crystal structure determination of 1a

ENRAF-Nonius CAD4-diffractometer, $Cu_{K\alpha}$-radiation, graphite monochromator; data collection with ω-scan at 273 K, crystal size 0.30×0.20×0.15 mm; monoclinic, space group $P2_1$ (no. 4); a=6.992(2), b=10.567(2), c=8.159(1) Å, β=108.52(1)°, V=571.6(4) Å^3, Z=2, $\rho_{calcd.}$=1.511 gcm^{-3}, μ=117.3 cm^{-1}, $F(000)$=268; 1552 reflections with $5<\theta<75°$, 1045 independent reflections with $I>\sigma(I)$ in solution and refinement[12] for 135 parameters; R=5.3, R_w=5.8, $w^{-1}=\sigma^2(F_o)$, GOF=1.355, Flack-parameter:[13] −0.009(0.016); residuals for the other enantiomorph: R=7.1, R_w=7.9, GOF=1.841. Hydrogen atom positions were calculated (C–H=0.98 Å, B_H=1.3 B_C). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as "supplementary publication no. CCDC-100384". Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ (Fax: int. +1223 336033; Email: teched@chemcrys.cam.ac.uk).

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft-SFB 380: "Asymmetrische Synthesen mit chemischen und biologischen Methoden".

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(Received in UK 10 June 1997)