2-(3-Ferrocenylpyrazol-1-yl)cyclohexanol: a new building block for ferrocenyl ligands

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Dedicated to Prof. Dr. Dr. h. c. mult. E.O. Fischer on the occasion of his 85th birthday

Abstract

2-(3-Ferrocenylpyrazol-1-yl)cyclohexanol can be obtained efficiently by heating 3(5)-ferrocenyl pyrazole with neat epoxicyclohexane. The new ferrocenyl N,O-chelate ligand was characterized by means of spectroscopy, elemental analysis, and single crystal X-ray diffraction.
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1. Introduction

During the more than 50 years since the discovery of this first sandwich complex in the early 1950s [1], ferrocene chemistry has developed into a fascinating area of organometallic research. A multitude of new compounds have been synthesized following the classical routes of organic arene chemistry [2]. Beside the application of ferrocenes in material sciences, e.g. as conducting organometallic polymers [3] or in biochemistry [4], ligands bearing ferrocene units have attracted attention [2,5], since ferrocenyl groups in the backbone of chelating ligands have been found to show pronounced effects in homogeneous catalysis. This is mainly due to the special stereochemical features of the ferrocenyl group. Bidentate systems can be obtained either by 1,1′- or 1,2-substitution of the ferrocene cyclopentadienyl rings. The 1,1′-substitution pattern locates the ferrocendiyl fragment in the backside of a metal center, which is then efficiently shielded from a rear attack. From a stereochemical point of view, the

1,2-substitution is even more interesting: In this case, chiral systems can easily be obtained when two different substituents are introduced in the 1- and 2-position. A whole series of ligands of this type has been synthesized and tested for enantioselective catalysis and at least one industrial process, the synthesis of metolachlor includes an enantioselective hydrogenation catalyzed by an iridium site coordinated to a ferrocene ligand [6].

The renaissance of ferrocene chemistry during the last decade still demands new substitution patterns. Here we present the route to a new and chiral N,O-chelate ligand with a ferrocenyl substituent, which can be used as a simply accessible precursor for the synthesis of more complex ligand systems.

For some time, we have been investigating chiral substituted cycloalkan-1-ols bearing N-, P-, or C- donor sites in the 2-position of the cyclic backbone [7–10]. They are synthesized in almost quantitative yields by reacting epoxicycloalkanes with either a nitrogen nucleophile like pyrazole or imidazole, or with an alkali phosphide like Ph$_2$PLi. Following this sequence with pyrazole as the nucleophile, resulted in a whole series of differently substituted *trans*-2-pyrazolyl cyclohexanoles, which could be obtained enantiomerically pure by kinetic resolution using the immobilized lipase B from *C. antarctica* [7]. These ligands have been applied for the

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enantioselective addition of $ZnEt_2$ to benzaldehyde but have also been used for the synthesis of more complex chelating ligands [9,10].

2. Results and discussion

A further member of this series is obtained by reacting 3(5)-ferrocenyl pyrazole [11] with neat epoxicyclohexane (Scheme 1) under microwave heating.

While lipase B accepts even bulky substituents like *t*-butyl, phenyl or cyclohexyl in the 5-position of the pyrazole ring and also 4,5-annealed cyclic systems, the ferrocenyl substituent of compound **1** seems to prevent the interaction with the active site of the enzyme [12] and thus the kinetic resolution of the product. The very slow and stereo unselective acylation observed is assigned to the high activity of the acylating agent isopropenyl acetate. It seems that the special steric requirements of the ferrocenyl unit are responsible for a mismatch of **1** and the active site of the enzyme. This may be due to an intramolecular hydrogen bond between the OH group and pyrazole, which might reduce the accessibility of the OH group by the acylating center of the enzyme. Such an intermolecular hydrogen bond has never been found before in the series of pyrazolyl cyclohexanols. It was proved by a single crystal structure analysis (see below) and by IR spectroscopic investigations: The OH absorption is shifted significantly to higher energies. While the intramolecular hydrogen bond in **1** is observed at 3371 cm^{-1}, the OH absorption of *rac-trans*-2-(3-methylpyr-azol-1-yl)cyclohexanol, which forms hydrogen bound dimers in the solid state, is found at 3245 cm^{-1} [7], indicating a stronger intermolecular H···N interaction [13].

Complex **1** crystallizes from ethyl acetate–hexane as orange colored plates in the acentric monoclinic space group $P2_1$. Fig. 1 shows the molecular structure of **1** in the solid state and a selection of characteristic bond lengths, angles, and torsion angles, and Fig. 2 presents the arrangement of the molecules in the unit cell, which have found to be oriented along a crystallographic screw axis.

From its geometric parameters (O1–H11 0.78(2), H11···N2 2.09(2), O1···N2 2.799(2) Å, O1–H11···N2 151(2)°), the hydrogen bond is weak [13]. This is due to the fact that the pyrazole plane and the C4–O1–H11 plane are not in a coplanar arrangement, which hinders an optimal interaction of the OH hydrogen atom with
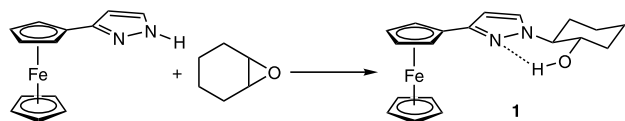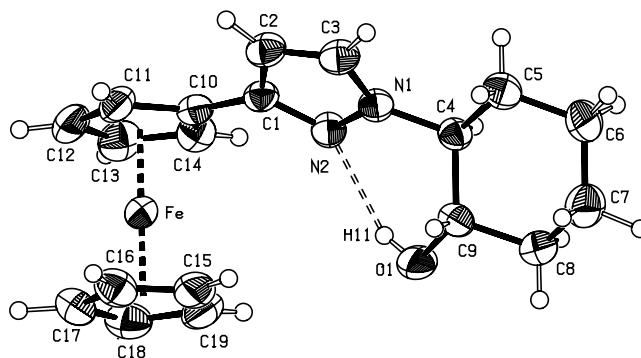

Fig. 1. ORTEP style plot of the solid state structure of **1**. Thermal ellipsoids are at the 50% probability level. Characteristic bond lengths (Å), angles (°), and torsion angles (°): Fe–C(10) 2.044(2), Fe–C(11) 2.041(2), Fe–C(12) 2.037(2), Fe–C(13) 2.035(2), Fe–C(14) 2.027(2), Fe–C(15) 2.032(3), Fe–C(16) 2.041(2), Fe–C(17) 2.034(2), Fe–C(18) 2.036(3), Fe–C(19) 2.030(3), N(1)–C(3) 1.356(2), N(2)–C(1) 1.346(2), N(1)–N(2) 1.353(2), N(1)–C(4) 1.472(2), C(1)–C(2) 1.396(3), C(2)–C(3) 1.361(3), O(1)–C(9) 1.432(2), O(1)–H(11) 0.78(2), H(11)···N(2) 2.09(2); C(9)–O(1)–H(11) 105(1), O(1)–H(11)···N(2) 151(2); N(2)–N(1)–C(4)–C(9) –64.9(2), N(2)–C(1)–C(10)–C(11) 154.0(2).

the lone pair at N2. The acentric space group $P2_1$ stringently requires the separate crystallization of the two enantiomers, which prevents an enhancement of the ee value by subsequent crystallization after an incomplete kinetic resolution of the compound. It therefore will not make very much sense to look for another enzyme for a kinetic resolution, which accepts the bulky ferrocenyl moiety. We are now going to investigate chemical routes to diastereomeric derivatives of **1**, which could be separated by crystallization or chromatography.

3. Experimental

The NMR spectra of **1** are assigned according to Fig. 1. 3(5)-Ferrocenylpyrazole was synthesized according to a published procedure.

3.1. trans-2-(3-Ferrocenylpyrazol-1-yl)cyclohexanol (1)

1.00 g (3.97 mmol) of 3-ferrocenylpyrazole [11] and 1.00 g (10.19 mmol) epoxicyclohexane are heated (6×3 min) in a pressure tube (Aldrich, Z18,108-0) under microwave irradiation (360 W). After cooling to room temperature, the liquid residue is dissolved in 5 ml of CH_2Cl_2 and 5 g of SiO_2 (for column chromatography, Aldrich, 28,862-4) are added. All volatiles are removed in vacuum and the product is extracted with Et_2O. After removing the solvent, **1** can be recrystallized from hot EtOAc–hexane (1:2). Orange-colored plates (1.15 g, 83%). M.p.: 146 °C. Anal. Calc. for $C_{19}H_{22}FeN_2O$ (350.24): C, 65.16; H, 6.33; N, 8.00. Found: C, 64.87; H, 6.10; N, 7.88%. IR (KBr, cm^{-1}): 3371 cm^{-1} ν_{O-H} s,

Scheme 1.
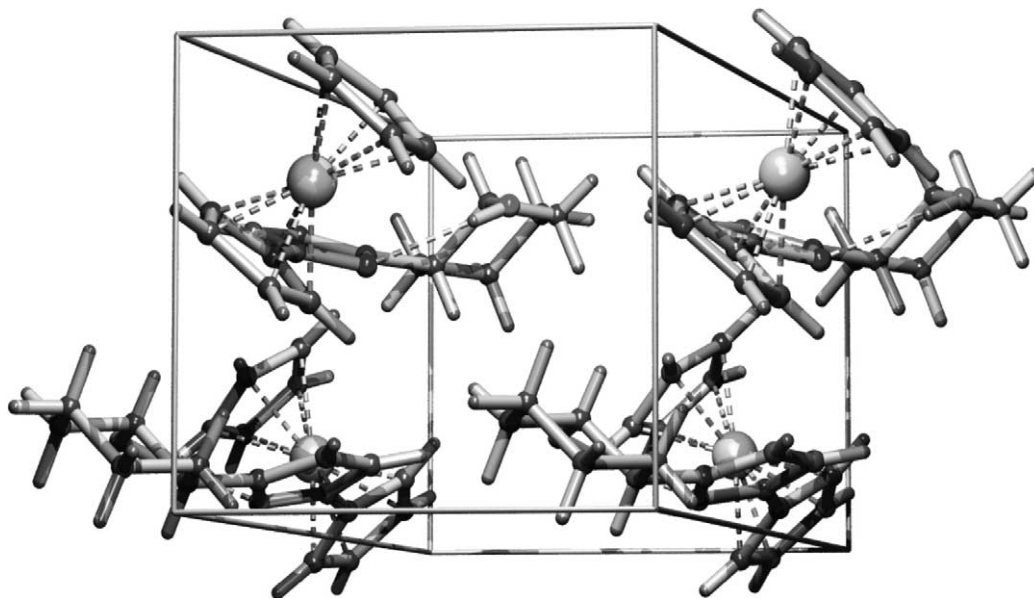
Fig. 2. PLUTON plot of the unit cell view of **1**.

3144 w, 3106 w, 3084 w, 2939 s, 2928 s, 1557 m, 1403 s, 1373 m, 1356 m, 1307 m, 1238 m, 1104 s, 1066 s, 1043 m, 1021 m, 1003 m, 870 m, 834 m, 821 vs, 808 m, 773 vs, 757 m, 548 m, 536 m, 515 vs, 500 s, 486 s. ^{1}H-NMR (400.13 MHz, 25 °C, CDCl$_3$): δ 7.38 (d, $^3J_{2,3} = 2.5$ Hz, 3-H), 6.28 (d, 2-H), 4.66 (s, 2H, 11-H), 4.55 (s, O*H*), 4.25 (s, 2H, 12-H), 4.04 (s, 5H, Cp-H), 3.90–3.74 (m, 2H, 4-H, 9-H), 2.25–2.13 (m, 2H, C*H*$_2$), 1.88–1.30 (m, 7H, C*H*$_2$). ^{13}C{^{1}H}-NMR (100.25 MHz, 25 °C, CDCl$_3$): δ 150.5 (C-1), 127.9 (C-3), 102.8 (C-2), 73.8 (C-9), 69.5 (C-Cp), 68.5, 65.8 (C-11, C-12), 66.7, 66.6 (C-4, C-10), 33.0, 30.1 (C-5, C-8), 24.7, 23.9 (C-6, C-7). MS (EI, *m/z* (%)): 350 (100) [M$^+$].

3.2. Structure determination of 1

Crystal data and details of the structure determination are presented in Table 1. Suitable single crystals for the X-ray diffraction study were grown by cooling a concentrated solution of **1** in EtOAc–hexane (1:2). A clear orange fragment ($0.18 \times 0.25 \times 0.53$ mm) was stored under perfluorinated ether, transferred in a Lindemann capillary, fixed and sealed. Preliminary examination and data collection were carried out on an imaging plate diffraction system (IPDS; Stoe&Chi) at the window of a rotating anode (Nonius; FR951) and graphite monochromated Mo–K$_\alpha$ radiation ($\lambda = 0.71073$ Å). The unit cell parameters were obtained by full-matrix least-squares refinement of 4994 reflections. Data collection were performed at 293 K (θ-range: $2.54° < \theta < 25.62°$; exposure time: 300 s per image; oscillation scan modus: $\varphi = 1°$ to 360° with $\Delta\varphi = 1.0°$). A total number of 11 212 reflections were collected. Raw data were corrected for Lorentz, polarization, decay and

Table 1
Crystal data and summary of intensity data collection and structure refinement of **1**

	1
Formula	C$_{19}$H$_{22}$FeN$_2$O
Formula weight	350.24
Color/shape	Orange fragment
Space group	$P2_1$ (No. 4)
a (Å)	8.1967(5)
b (Å)	7.6889(3)
c (Å)	13.1201(9)
β (°)	101.508(8)
V (Å^3)	810.25(8)
Z	2
ρ_{calc} (g cm^{-3})	1.436
μ (mm^{-1})	0.936
Diffractometer	Stoe IPDS
λ (Å)	Mo–K$_\alpha$ 0.71073
T (K)	293
Reflections collected	11 212
Independent reflections	2907
Observed reflections ($I > 2\sigma(I)$)	2653
Parameters refined	296
R_1 (observed/all data)	0.0192/0.0220
wR_2 (observed/all data)	0.0436/0.0442
Goodness-of-fit (observed/all data)	0.957/0.957
Flack's parameter	−0.014(11)

absorption effects. After merging ($R_{int} = 0.042$) a sum of 2907 independent reflections remained and were used for all calculations. The structure was solved by a combination of direct methods and difference Fourier syntheses. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were found in the difference Fourier maps and allowed to refine freely. Full-matrix least-squares refinements with 296 para-

meters were carried out by minimizing $\Sigma w (F_o^2 - F_c^2)^2$ with SHELXL-97 weighting scheme and stopped at shift/err < 0.001. The correct enantiomer is proved by Flack's parameter $\varepsilon = -0.014(11)$. Neutral atom scattering factors for all atoms and anomalous dispersion corrections for the non-hydrogen atoms were taken from International Tables for Crystallography. All calculations were performed on a DEC 3000 AXP workstation and an Intel Pentium II PC, with the STRUX-V system, including the programs PLATON, SIR92, and SHELXL-97 [14].

4. Supplementary material

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 206433. Copies of this information may 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 www: http://www.ccdc.cam.ac.uk).

Acknowledgements

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