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Chiral ferrocenes derived from (+)-longifolene—determination of the configuration by NMR spectroscopy and X-ray crystallography

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Abstract—The addition of monolithium ferrocene to *exo*-longifolyl aldehyde and *endo*-longifolyl aldehyde, respectively, prepared from (+)-longifolene, leads to four diastereoisomeric α-hydroxyalkyl ferrocenes, which were isolated in pure form. The configurations of the newly formed stereogenic centers were determined by means of NMR spectroscopy and X-ray crystallography.

1. Introduction

In recent years, the design of new ferrocene derivatives has been of considerable interest as a result of their utility in organic synthesis and materials science.[1,2] Interest in the preparation of 1,2-disubstituted ferrocenes with planar chirality has increased owing to the ability of such compounds to serve as ligands in asymmetric synthesis.[1,3] For the preparation of planar chiral ferrocene derivatives, chiral *N*,*N*-dialkylferrocenylalkylamines play a crucial role because of the possibility of highly diastereoselective *ortho*-lithiation with simple organolithium reagents (e.g. *n*-BuLi). Further transformation of the lithiated chiral ferrocenes leads to useful functionalized 1,2-disubstituted derivatives (aminoalcohols, aminophosphanes etc.).[1–3] Chiral non-racemic α-hydroxyalkyl ferrocenes are attracting increased interest as key compounds that can be converted into *N*,*N*-dialkylferrocenylalkylamines with complete retention of configuration.[4] There are several routes for the synthesis of α-hydroxyalkyl ferrocenes,[1–3] e.g. the enantioselective addition of dialkylzinc compounds to ferrocene carbaldehyde,[5] the enantioselective reduction of acyl ferrocenes,[6] or the addition of monolithium ferrocene to chiral carbonyl compounds.[7] We were interested in the latter synthetic pathway.

(+)-Longifolene is a naturally occurring sesquiterpene whose role in a number of oxidation and rearrangement reactions has been intensively investigated[8] due to its significance to the fragrance industry.[9] To our knowledge, the preparation of bis-longifolyl borane and its use as a chiral reducing agent[10] is the only example of the application of (+)-longifolene as a source of chirality in the synthesis of a chiral modified reagent for asymmetric synthesis. We have recently developed a highly efficient procedure for the synthesis of *exo*- and *endo*-longifolyl aldehydes on a multigram scale by ozonolysis of longifolene followed by rearrangement.[11] In this paper we present results on the preparation of ferrocene derivatives bearing the longifolane skeleton. We were mainly interested in proving that it is possible to determine the configuration of the newly formed stereogenic center by using NMR spectroscopic methods in analogy to recent investigations.[12]

2. Results and discussion

The diastereoisomeric aldehydes **1** and **2** were prepared by ozonolysis of the exocyclic double bond of (+)-longifolene, which leads to the formation of an epoxide as a result of the so-called 'abnormal ozonolysis'. The detailed procedure for the isomerization of longifolene epoxide into aldehydes **1** and **2**, which is possible in multigram quantities, will be published elsewhere.[11]

The in situ generation of monolithium ferrocene **3** was a crucial step for the planned syntheses, because it is difficult to obtain this compound free of 1,1′-dilithium ferrocene in a reproducible manner. Several procedures

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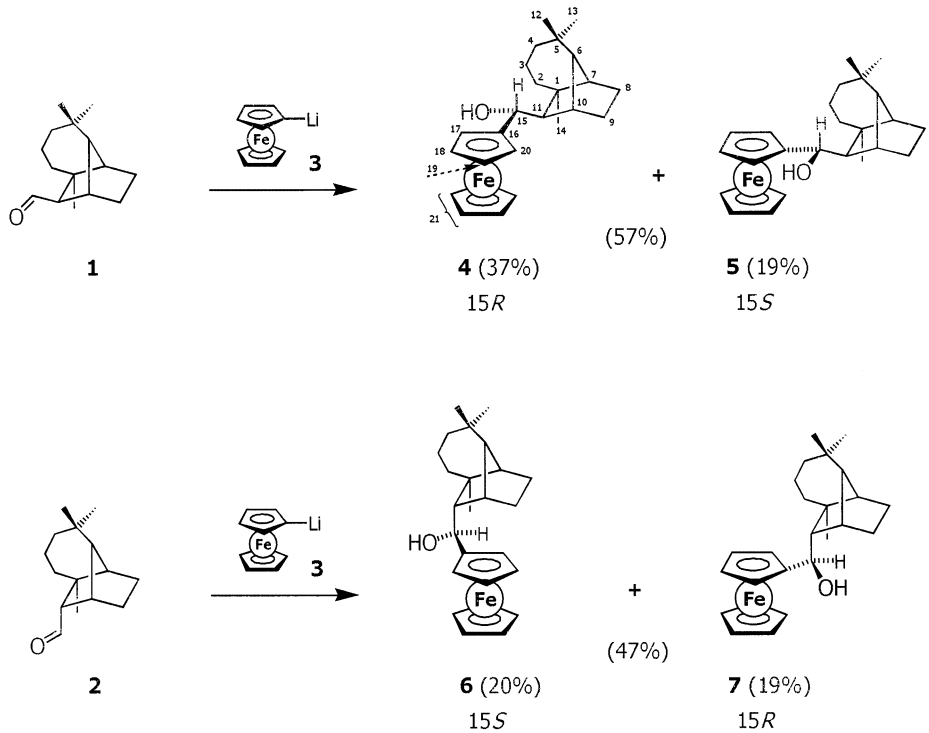
for the preparation of **3** have been described, but our experience showed that the simplest one was that of Kagan et al.[13] Thus, a solution of ferrocene in THF was cooled to 0°C and an equimolar quantity of *tert*-BuLi was added dropwise. After stirring for 30–40 minutes at 0°C the mixture was allowed to warm to room temperature within 10 minutes and stirred for no more than a further 10 minutes at this temperature. Aldehyde **1** or **2** (Scheme 1) was added at room temperature, which resulted in a rapid exothermic reaction. After acidic work-up, the diastereoisomers **4** and **5** and **6** and **7**, respectively, were isolated in pure form by column chromatography in the given yields (Scheme 1). The presence of 1,1′-disubstituted ferrocene derivatives as undesirable by-products, which indicated the formation of dilithium ferrocene, was also observed. The formation of these products obviously lowered the yields of **4**–**7**. It was not possible to determine the ratio of the reaction products in the crude reaction mixture by NMR spectroscopy, due to overlapping of the signals. The disubstituted species were not isolated and, therefore, their nature was not determined. At this stage we were only interested in the isolation of the monosubstituted ferrocenes.

The diastereoselectivity of the addition reactions could not be determined exactly; however, qualitative conclusions are possible based on the isolated pure diastereoisomers. We expected high steric hindrance of the carbonyl carbon atom and were surprised by the poor selectivity. In the case of aldehyde **1**, it is possible to conclude that the attack of reagent **3** occurs preferentially from the *Re*-side of the carbonyl group.

Unambiguous assignment of the ^{1}H and ^{13}C NMR spectra of **4**–**7** was achieved by HSQC, HMBC,



Scheme 1.

Table 1. ^{13}C NMR chemical shifts of compounds **4**–**7** ($CDCl_3$, 300 K, δ in ppm from TMS)

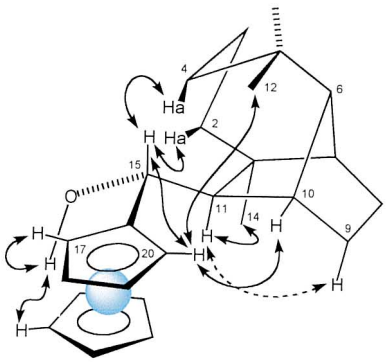
	C no.										
	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)
4	46.08	36.24	21.42	39.09	33.12	64.15	45.77	24.87	34.77	41.07	64.70
5	45.12	36.78	21.45	39.30	33.18	63.76	46.49	24.99	34.52	41.75	64.15
6	41.12	44.58	21.69	40.08	33.19	61.46	46.45	22.20	29.14	42.34	55.38
7	40.25	43.68	21.52	39.97	33.29	60.78	46.56	21.27	25.99	42.48	54.29
	C(12)	C(13)	C(14)	C(15)	C(16)	C(17)	C(18)	C(19)	C(20)	C(21)	
4	31.45	31.65	32.76	70.14	97.36	64.34	67.02	68.33	68.88	68.09	
5	32.25	31.12	32.01	68.25	98.36	65.19	68.10	66.70	70.06	68.14	
6	29.34	32.91	23.57	69.10	96.55	63.87	67.11	68.13	68.35	68.04	
7	29.40	32.97	24.71	66.24	97.84	70.84	66.52	68.12	65.43	68.12	

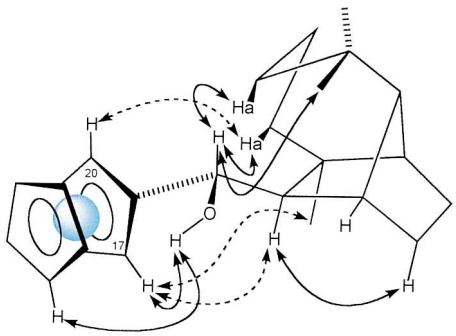
NOESY and DQF-COSY experiments (Table 1 and Experimental). The rigidity of the longifolane skeleton allowed the relative configuration to be established through NOESY experiments. Therefore, the absolute configuration of the newly formed stereogenic centers could be derived by using the known configuration of the longifolane moiety. The most significant NOEs observed are illustrated with arrows in Scheme 2. The *exo*-position of the (ferrocenyl)hydroxymethyl moiety of **4** and **5** could be deduced from the close proximity of C(15)H to C(2)H_a and C(4)H_a, as well as from the NOEs of C(11)H with the C(9)H_{endo} and C(14)H methyl protons. For the *endo*-substituted compounds **6** and **7**, the C(15) proton is situated, as the smallest substituent, near the C(9)H_{endo} and C(14) methyl protons. The observed high vicinal constants $J_{11\text{-H},15\text{-H}}$ of ca. 10–11 Hz for **4**–**7** and the distance constraints obtained by NOESY allowed us to verify the corresponding preferred conformation along the C(11)–C(15) bond, as shown in Scheme 2. The observed NOEs of the hydroxy group with C(17)H of the substituted Cp-ring (C(20)H in the case of **7**) and with the protons of the unsubstituted Cp-ring for **4**–**7** led to the conclusion that the proton of the hydroxy group is situated between the two Cp-rings near the Fe-atom and that there is hydrogen bond formation with the d-electrons from the metal. The most significant arguments for the determined configuration at C(15) are summarized as follows.

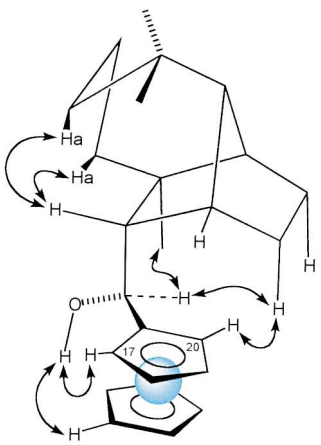
For (15*R*)-**4**: Close proximity of C(20)H to the C(10)H and C(12)H methyl protons was observed.
For (15*S*)-**5**: The C(17) proton is situated near the C(11) proton and the C(14) methyl protons.
For (15*S*)-**6**: The C(20) proton is near the C(9)H_{endo} proton.
For (15*R*)-**7**: The C(17) proton is in close proximity to the C(14)H methyl protons, whereas C(20)H is situated near C(11)H.

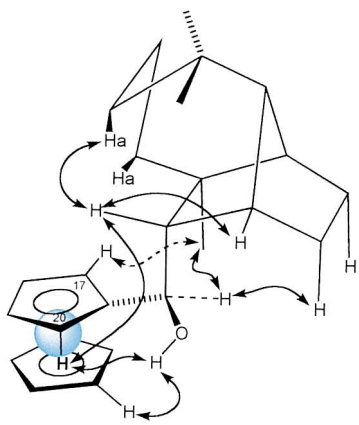
The information obtained from the NOESY experiments allowed the assumption to be made that the conformations deduced for compounds **4**–**7**, given in Scheme 2, are the preferred ones. Further, the observed Cp-ring current-induced proton chemical shift is in agreement with the determined configurations.

The absolute configuration of compound **5** was obtained independently by X-ray crystal structure anal-









Scheme 2.

ysis, which confirmed unambiguously that the assignments based on the NMR spectroscopic results were correct. In addition, the crystal structure of **5** shows that the hydroxy proton does indeed lie between the Cp-rings and is directed towards the Fe-atom with an Fe···H distance of 2.88(1) Å. This distance is approximately 0.46 Å less then the sum of the van der Waals radii of the Fe and H atoms and is therefore clearly indicative of an Fe···H hydrogen bonding interaction (Fig. 1).

In conclusion, we have prepared new diastereomerically pure α-hydroxyalkyl ferrocenes bearing the sterically crowded longifolane skeleton, thus showing the potential of (+)-longifolene as a chiral auxiliary for asymmetric synthesis. The high utility of NMR spectroscopy for configuration determination has also been demonstrated and the validity of the deductions was confirmed by X-ray crystallography.

3. Experimental

3.1. General methods

The reactions were carried out in flame dried Schlenk flasks under an argon atmosphere. The solvents were dried (sodium/benzophenone for THF) and distilled. Thin layer chromatography (TLC): aluminum sheets pre-coated with silica gel 60 F_{254} (Merck). Column chromatography: at normal pressure, silica gel 60 (0.063–0.200 mm, Merck).

Melting points were recorded on a Mettler FP-5/FP-52. $[\alpha]_D^{20}$ measurements were obtained using a Perkin–Elmer 241 polarimeter. Mass spectra (MS) were recorded on a Finnigan MAT 90 or Finnigan SSQ 700 and are reported as fragmentation in m/z with relative intensities (%) in parentheses. NMR spectra were obtained using a Bruker DRX-500 and DRX-600.

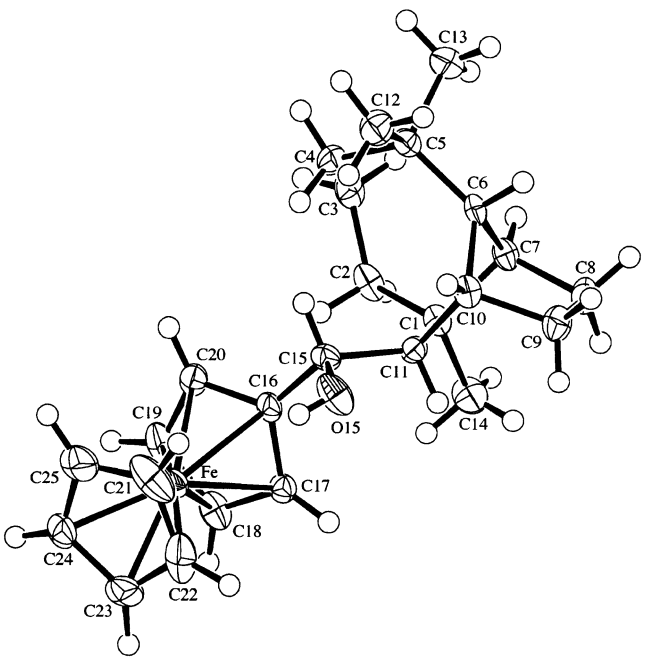


Figure 1. ORTEP[14] plot of the molecular structure of **5** with 50% probability ellipsoids.

3.2. (*R*)-[1-Ferrocenyl]-[(1*S*,6*S*,7*R*,10*S*,11*R*)-1,5,5-trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-yl]methanol 4 and (*S*)-[1-Ferrocenyl]-[(1*S*,6*S*,7*R*,10*S*,11*R*)-1,5,5-trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-yl]methanol 5

A solution of *tert*-BuLi/pentane (1.5 M, 9.30 mL, 13.95 mmol) was added to a solution of ferrocene (2.53 g, 13.60 mmol) in THF (35 mL), cooled to 0°C and the mixture was stirred for 30 min at 0°C. After allowing the mixture to warm to rt, a solution of **1** (1.90 g, 8.62 mmol) in Et_2O (15 mL) was added at this temperature, and the mixture was stirred for 1 h, then hydrolyzed (2N HCl), washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed ($\varnothing = 40$ mm, $h =$ 500 mm, 400 g silica gel; the crude product was adsorbed on the silica gel from a concentrated CH_2Cl_2 solution, eluted with hexane and then hexane/$Et_2O =$ 15:1–10:1) to give fractions containing ferrocene, **4** (1.30 g, 37%), mixed fractions (0.05 g) and **5** (0.66 g, 19%). The total yield was 57%. Anal. calcd for $C_{25}H_{34}FeO$ (406.39): C, 73.89; H, 8.43. Found: C, 73.97; H, 8.56%. MS (EI) m/z (rel. int.): 406 ($M^{+\bullet}$, 100), 388 ($[M-H_2O]^{+\bullet}$, 50).

Data for **4**. Mp 103–104°C. $[\alpha]_D^{20} = -62.1$ ($c = 1.00$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 K): $\delta = 5.56$ (d, 1H, 15-H, $J = 10.9$ Hz), 4.25 (s, 5H, 21-H), 4.26–4.24 (m, 1H, 20-H), 4.24–4.22 (m, 1H, 17-H), 4.22–4.20 m, 2H, 18-H, 19-H), 2.29–2.21 (m, 1H, 2-H_a), 2.20 (s, 1H, OH), 2.10–1.97 (m, 1H, 7-H), 1.72–1.62 (m, 2H, 3-H_b, 8-H_{endo}), 1.61–1.51 (m, 2H, 3-H_a, 4-H_a), 1.51–1.41 (m, 2H, 2-H_b, 10-H), 1.41–1.31 (m, 3H, 4-H_b, 8-H_{exo}, 9-H_{exo}), 1.22 (s, 1H, 6-H), 1.19 (d, 1H, 11-H, $J = 10.9$ Hz), 1.13 (s, 3H, 14-H), 1.00–0.92 (m, 1H, 9-H_{endo}), 0.98 (s, 3H, 13-H), 0.88 (s, 3H, 12-H).

Data for **5**. Mp 102–105°C. $[\alpha]_D^{20} = +106.0$ ($c = 1.02$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 K): $\delta = 4.45$ (d, 1H, 15-H, $J = 10.7$ Hz), 4.33–4.30 (m, 1H, 20-H), 4.30–4.27 (m, 1H, 17-H), 4.25 (s, 5H, 21-H), 4.23–4.20 (m, 1H, 18-H), 4.19–4.16 (m, 1H, 19-H), 2.53–2.48 (m, 1H, 10-H), 2.25 (d, 1H, OH, $J = 0.9$ Hz), 1.92–1.87 (m, 1H, 7-H), 1.77–1.69 (m, 1H, 2-H_a), 1.66–1.53 (m, 4H, 3-H_b, 4-H_a, 8-H_{endo}, 9-H_{exo}), 1.48–1.33 (m, 3H, 3-H_a, 4-H_b, 8-H_{exo}), 1.40 (s, 1H, 6-H), 1.34 (d, 1H, 11-H, $J = 10.7$ Hz), 1.23–1.15 (m, 1H, 9-H_{endo}), 1.11–1.04 (m, 1H, 2-H_b), 1.07 (s, 3H, 13-H), 1.01 (s, 3H, 12-H), 0.65 (s, 3H, 14-H).

3.3. (*S*)-[1-Ferrocenyl]-[(1*S*,6*S*,7*R*,10*S*,11*S*)-1,5,5-trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-yl]methanol 6 and (*R*)-[1-Ferrocenyl]-[(1*S*,6*S*,7*R*,10*S*,11*S*)-1,5,5-trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-yl]methanol 7

A solution of *tert*-BuLi (1.5 M in pentane, 3.80 mL, 5.70 mmol) was added to a solution of ferrocene (1.10 g, 5.91 mmol) in THF (20 mL), at 0°C, and the mixture

stirred for 30 min at 0°C. After allowing the mixture to warm to rt, a solution of **2** (0.70 g, 3.18 mmol) in Et_2O (10 mL) was added at this temperature, and the mixture was stirred for 1 h, then hydrolyzed (2N HCl), washed with 5% aq. $NaHCO_3$, H_2O and dried (Na_2SO_4). After evaporation of the solvent, the crude product was chromatographed ($\varnothing = 25$ mm, $h = 600$ mm, 200 g silica gel; the crude product was adsorbed on the silica gel from a concentrated CH_2Cl_2 solution, eluted with hexane and then hexane/Et_2O = 15:1–10:1) to give fractions containing ferrocene, **6** (0.26 g, 20%), mixed fractions (0.10 g) and **7** (0.25 g, 19%). The total yield was 47%. Anal. calcd for $C_{25}H_{34}FeO$ (406.39): C, 73.89; H, 8.43. Found: C, 74.00; H, 8.58%. MS (EI) m/z (rel. int.): 406 ($M^{+\bullet}$, 100), 388 ($[M-H_2O]^{+\bullet}$, 35).

Data for **6**. Mp 90–93°C. $[\alpha]_D^{20} = +75.1$ ($c = 1.00$, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 K): $\delta = 4.40$ (d, 1H, 15-H, $J = 9.9$ Hz), 4.24–4.22 (m, 1H, 17-H), 4.22 (s, 5H, 21-H), 4.18–4.16 (m, 1H, 19-H), 4.16–4.14 (m, 1H, 18-H), 4.14–4.12 (m, 1H, 20-H), 2.03 (s, 1H, OH), 1.96–1.90 (m, 2H, 7-H, 11-H), 1.73–1.61 (m, 4H, 2-H_a, 3-H_b, 4-H_a, 9-H_{endo}), 1.59–1.51 (m, 1H, 3-H_a), 1.50–1.43 (m, 2H, 2-H_b, 10-H), 1.32–1.21 (m, 3H, 4-H_b, 8-H_{endo}, 9-H_{exo}), 1.19 (s, 1H, 6-H), 1.20–1.11 (m, 1H, 8-H_{exo}), 1.13 (s, 3H, 14-H), 0.93 (s, 3H, 13-H), 0.75 (s, 3H, 12-H).

Data for **7**. Mp 85–86°C. $[\alpha]_D^{20} = -183.3$ ($c = 1.00$, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 K): $\delta = 4.33$–4.28 (m, 2H, 17-H, 20-H), 4.25 (d, 1H, 15-H, $J = 10.2$ Hz), 4.24 (s, 5H, 21-H), 4.23–4.19 (m, 1H, 19-H), 4.17–4.14 (m, 1H, 18-H), 2.46–2.42 (m, 1H, 10-H), 2.19 (s, 1H, OH), 2.05 (dd, 1H, 11-H, $J = 10.2$, 2.4 Hz), 1.84–1.80 (m, 1H, 7-H), 1.64–1.49 (m, 4H, 3-H_b, 4-H_a, 8-H_{endo}, 9-H_{endo}), 1.45–1.33 (m, 2H, 3-H_a, 8-H_{exo}), 1.35 (s, 1H, 6-H), 1.33–1.24 (m, 2H, 4-H_b, 9-H_{exo}), 1.07–0.99 (m, 1H, 2-H_b), 1.01 (s, 3H, 12-H), 0.97 (s, 3H, 13-H), 0.92–0.84 (m, 1H, 2-H_a), 0.75 (s, 3H, 14-H).

3.4. X-Ray crystallographic details for compound 5

$C_{25}H_{34}FeO$, $M_r = 406.38$, orthorhombic, space group $P2_12_12_1$, $a = 10.8832(1)$, $b = 12.4374(1)$, $c = 15.0587(1)$ Å, $V = 2038.33(3)$ Å^3, $Z = 4$, $D_c = 1.324$ Mg m^{-3}, μ(Mo Kα) = 0.751 mm^{-1}, $F(000) = 872$, $T = 160(1)$ K, yellow prism, dimensions: 0.20×0.25×0.25 mm, Nonius Kappa CCD diffractometer, Mo Kα radiation, $\lambda = 0.71073$ Å, $2\theta_{max} = 60°$, 62766 measured reflections of which 5945 were unique. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method[15] was applied ($T_{min} = 0.760$, $T_{max} = 0.875$). The structure was solved by direct methods using SHELXS-97[16] and refined on F by full-matrix least-squares methods using teXsan,[17] non-H atoms were refined anisotropically, hydroxy H-atoms were refined isotropically, all other H-atoms fixed in calculated positions. The refinement of 249 parameters using 5414 observed reflections with $I > 2\sigma(I)$ gave $R = 0.032$, $wR = 0.030$, $S = 2.237$; weights: $[\sigma^2(F_o) + (0.005F_o)^2]^{-1}$, max. and min. $\Delta\rho = 0.27$; –0.39 e Å^{-3}, absolute structure parameter = –0.003(6). Crystallographic data (excluding structure factors) for the structures of **5** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-162250. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

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References

1. (a) *Ferrocenes—Homogeneous Catalysis, Organic Synthesis, Materials Science*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995; (b) *Metallocenes—Synthesis, Reactivity, Application*; Togni, A.; Halterman, R. L., Eds.; Wiley-VCH, 1998; Vol. 2.
2. Long, N. J. *Angew. Chem.* **1995**, *107*, 37–56.
3. (a) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407; (b) Togni, A. *Angew. Chem.* **1996**, *108*, 1581–1583.
4. (a) Gokel, G. W.; Marquarding, D.; Ugi, I. *J. Org. Chem.* **1972**, *37*, 3052–3058; (b) Siglmüller, F.; Herrmann, R.; Ugi, I. *Liebigs Ann. Chem.* **1989**, 623–635.
5. Watanabe, M. *Synlett* **1995**, 1050–1052.
6. Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 25–28.
7. Dimitrov, V.; Genov, M.; Simova, S.; Linden, A. *J. Organomet. Chem.* **1996**, *525*, 213–224.
8. (a) Dev, S. *Prog. Chem. Org. Nat. Prod.* **1981**, *40*, 49–104; (b) Dev, S. *Acc. Chem. Res.* **1981**, *14*, 82–88.
9. Kraft, P.; Bajgrowicz, J. A.; Denis, C.; Fràter, G. *Angew. Chem.* **2000**, *112*, 3106–3138.
10. Jadhav, P. K.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 2988–2990.
11. Dimitrov, V.; Hopp, G.; Linden, A.; Hesse, M. *Helv. Chim. Acta*, in preparation.
12. (a) Dimitrov, V.; Philipova, I.; Simova, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1493–1500; (b) Philipova, I.; Dimitrov, V.; Simova, S. *Tetrahedron: Asymmetry* **1999**, *10*, 913–921; (c) Philipova, I.; Dimitrov, V.; Simova, S. *Tetrahedron: Asymmetry* **1999**, *10*, 1381–1391.
13. Rebiere, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, *31*, 3121–3124.
14. Johnson, C. K. ORTEP II. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.
15. Blessing, R. H. *Acta Crystallogr., Sect. A* **1995**, *51*, 33–38.
16. Sheldrick, G. M. SHELXS-97. Program for the Solution of Crystal Structures. University of Göttingen, Germany, 1997.
17. teXsan. Single Crystal Structure Analysis Software, Version 1.10. Molecular Structure Corporation, The Woodlands, TX, USA, 1999.