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TETRAHEDRON: *ASYMMETRY*

Chemoenzymatic synthesis of enantiopure 1,1′-disubstituted ferrocenyl aminoalcohols

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Abstract

1,1′-Disubstituted ferrocenyl aminoalcohols were synthesized in high enantio- and diastereomeric purities from the ketoalcohol obtained by microbial reduction of 1,1′-diacetylferrocene.

Recently, chiral cyclopentadienyl complexes of transition metals have found widespread applications as catalysts or ligands in enantioselective reactions as exemplified by the use of ferrocenyl diphosphines.[1] More recently, much effort has been devoted to the design of 1,2-disubstituted bidentate ferrocene ligands because of their inherent planar chirality.[2] However the design and use of 1,1′-disubstituted bidentate ferrocenyl compounds was less common and restricted to diphosphines or diamines.[3] We have been interested in synthesising optically active 1,1′-ferrocenyl aminoalcohols in order to use them as ligands for ruthenium-catalysed hydrogen transfer and related reactions. To the best of our knowledge, only one example of such aminoalcohols has been described as a by-product in the course of the synthesis of 1,1′-disubstituted ferrocenyl diamines and successfully used as a chiral ligand in asymmetric synthesis.[4] Suspecting that such syntheses were probably difficult enough to achieve by chemical reactions, we decided to investigate a chemoenzymatic approach.

Our strategy consisted of using the initial microbial reduction of 1,1′-ferrocenyl prochiral diacyl derivatives. It was therefore necessary to be able to discriminate between two identical substituents.[5]

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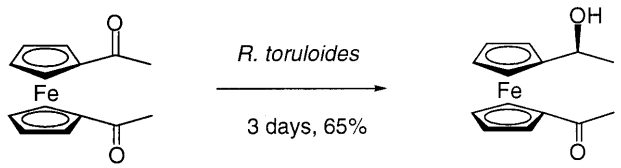
The use of microorganisms to reduce prochiral ketones to the corresponding enantiopure alcohols is now a well documented technique. Baker's yeast is commonly used for this purpose[6] but other strains may allow the best results or different stereoisomers to be obtained. An inherent advantage of the microbial reduction of diketones is that it can provide the corresponding ketoalcohols by transformation of only one keto group.[7]

Metallocenyl ketones have already been reduced by microorganisms.[8] For example, acetylferrocene was reduced to (*S*)-hydroxyethylferrocene[9] whereas both enantiomers of the alcohol deriving from the reduction of trifluoroacetylferrocene have been obtained using different strains.[10]

We have tested some twenty strains (yeasts and fungi) currently used for the reduction of β-ketoesters or ketones to reduce diacetylferrocene **1**. About ten were active and, in most cases, the ketoalcohol **2** was obtained in moderate yields. Only four yeast strains (*R. glutinis* NRRL Y1091, *Pichia anomalis* NRRL Y40, *Rhodosporium toruloides* MUCL 30010 and *Saccharomyces montanus* CBS 6772) were able to produce the ketoalcohol in significant amounts. Preparative-scale reductions were performed in the culture broth[11] in the dark, to avoid degradation of substrate and product. The enantiomeric excesses were determined on compound **3** by chiral HPLC (column: Chiralcel OD). Enantiomerically pure (*S*)-**2** was obtained in good yield (Scheme 1) using *R. toruloides* MUCL 30010,[12] whereas (*R*)-**2** was produced in a lower enantiomeric excess by *S. montanus* CBS 6772.[13]



1 2

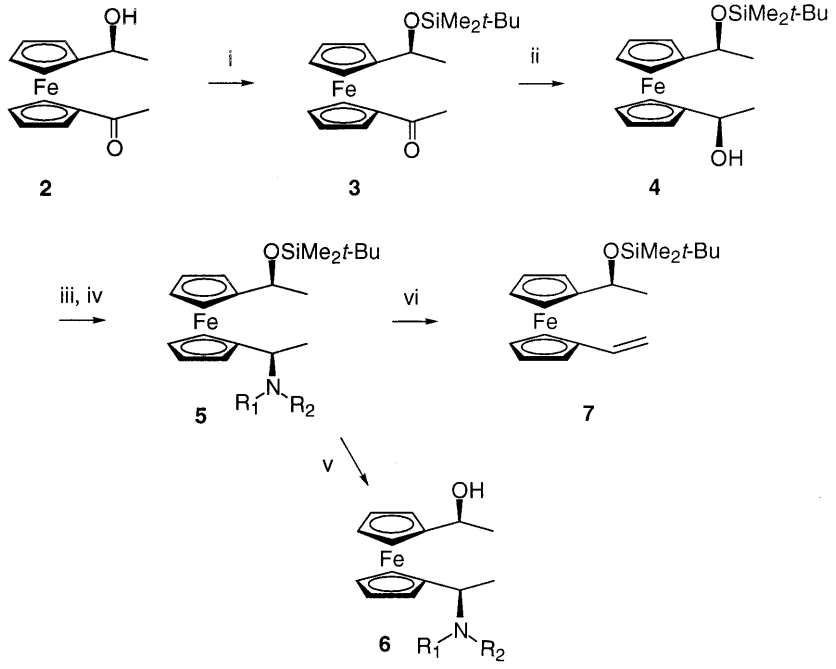
Scheme 1.

The absolute configuration of (*S*)-**2** was established after $NaBH_4$ reduction into a 1:1 mixture of inseparable diastereomeric diols (*meso* and optically active) and measurement of optical activity. The rotation of the mixture[14] compared to the value given in the literature[15] indicated an (*S*,*S*)-configuration for the diol obtained from the ketoalcohol and consequently an (*S*)-configuration for the latter.

With this ketol (*S*)-**2** in hand, a first approach was to stereospecifically transform the keto group into an amino group. However, the reductive amination[16] with methylamine in the presence of sodium cyanoborohydride afforded a 1:1 mixture of two diastereomers. Another approach, the reduction with various reducing agents ($NaBH_4$, $Zn(BH_4)_2$, Lithium Selectride®) of the aminoketone obtained after substitution of a mesylate[17] derived from the ketol **2**, gave very poor diastereomeric excesses.

We thus decided to reduce the keto group with an enantioselective reducing agent (Scheme 2). In order to differentiate the two potential alcohols, the hydroxyl group was preliminarily protected as a silyl ether. Using the oxazaborolidine-catalysed borane reduction (CBS reduction)[18] which was previously shown to be efficient in the reduction of some ferrocenyl ketones,[3b,19] we were pleased to isolate the monoprotected diol **4** as the 1*S*,1′*R* isomer with a diastereomeric excess higher than 99%. The relative configuration was determined by desilylation of this compound, affording the optically inactive *meso* diol. The monosilylated diol was

then activated as an acetate to react with various primary or secondary amines (neat or in methanol), affording the *O*-silylated ferrocenyl amines **5** stereospecifically. By contrast, the activation as a mesylate[17] afforded the corresponding protected aminoalcohols in 40% de only. After tetrabutylammonium fluoride desilylation, the aminoalcohols **6** were isolated in high diastereomerical purities (Table 1). In order to confirm their relative configuration, crystallised **6e** was submitted to X-ray analysis.[20] Together with the previously determined stereochemistry of the hydroxyl group, the X-ray data (Fig. 1) demonstrate the relative configuration of the two stereogenic centres and thus the (1*S*,1′*R*) absolute configuration of the aminoalcohol **6e**. This result verifies that the substitution of the acetate proceeds with total retention of configuration, as previously reported.[21] The enantiomeric purities were measured by HPLC of the vinylic



Scheme 2. (i) *t*-BuMe$_2$SiCl, DMF, rt, 10 h, 95%; (ii) (*S*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo-[1,2-*c*]-[1,3,2]-oxazaborole 0.2 equiv., BH_3–Me_2S 3 equiv., 0°C, 0.3 h, 93%, de >97%; (iii) Ac_2O, pyridine, rt, 16 h, 86%; (iv) amine, MeOH, rt, 15 h; (v) Bu_4NF 2 equiv., THF, rt, 16 h; (vi) MeI 4 equiv., THF, rt, 6 h

Table 1
1,1′-Ferrocenyl aminoalcohols from monoprotected diol **4**

	R_1	R_2	**5**	**6**		
			Yield %	Yield %	$[\alpha]_D^{20}$	*c* ($CHCl_3$)
a	H	H	62	–	–	–
b	CH_3	H	74	64	+23	0.20
c	Bn	H	50	95	−10	0.40
d	C_2H_5	C_2H_5	50	95	+8	0.30
e	$(CH_2)_5$		80	95	+20	0.34

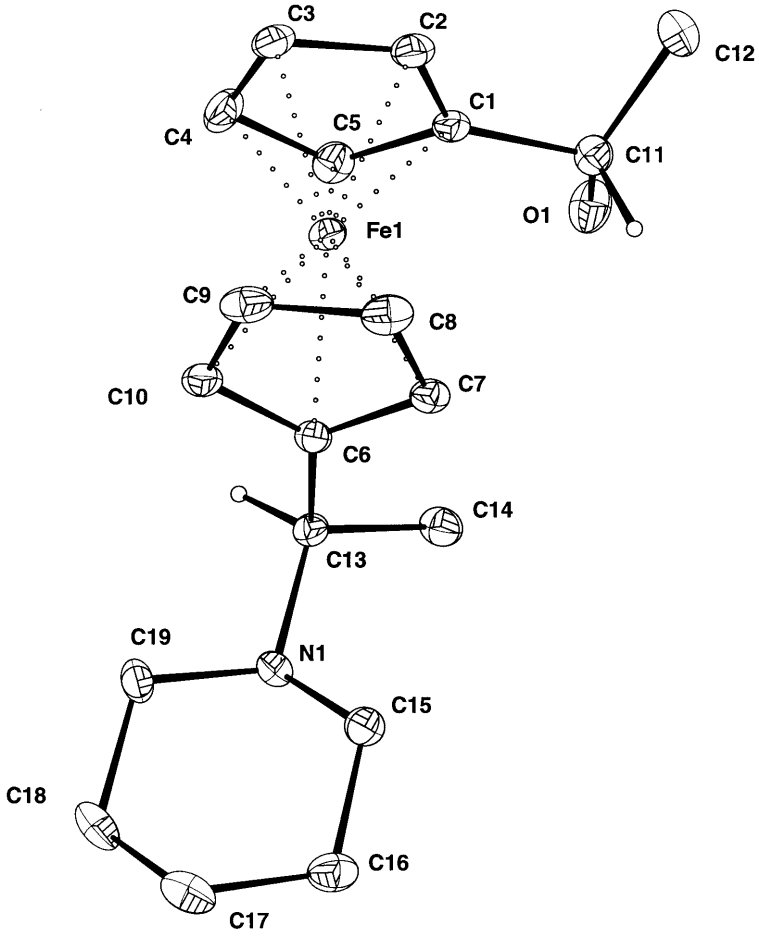


Figure 1. ORTEP drawing of aminoalcohol **6e**

ferrocene **7** (ee>99%) obtained after reaction with iodomethane and spontaneous elimination of the quaternary ammonium group.

Further application of these aminoalcohols to asymmetric synthesis reactions is in progress.

Acknowledgements

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11. The culture medium (3 L, containing glucose, 20 g; pancreatic peptone, 5 g; yeast extract, 5 g and malt extract, 10 g per litre) was inoculated and incubated in a rotatory shaker (200 rpm) at 30°C for 60 hours before adding the substrate (3 g) solubilized in acetone–ethanol (9+15 mL).
12. 65% isolated yield, $[\alpha]_D^{20}$ +68 (*c* 1, $CHCl_3$) and 15–20% remaining substrate.
13. 45% ee, 52% yield, $[\alpha]_D^{20}$ −28 (*c* 0.8, $CHCl_3$).
14. $[\alpha]_D^{20}$ +35 (*c* 1, C_6H_6). Lit[15]: $[\alpha]_D^{20}$ +74 (*c* 0.43, C_6H_6) for the (*S*,*S*) diol.
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20. The X-ray data were collected on an Enraf–Nonius CAD-4 diffractometer (Mo–Kα $\lambda = 0.71069$ Å) at room temperature. Crystal data: $C_{19}H_{27}FeNO$, M = 341.28, orthorhombic, $a = 6.174$ (2), $b = 12.299$ (3), $c = 21.708$ (6) Å, $U = 1648.5$ (8), $T = 293$ K, Space group $P2_12_12_1$, $Z = 4$, $\mu = 9.14$ cm^{-1}, 2316 reflections measured, 2291 unique ($R_{int} = 0.046$), $wR = 0.055$
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