Pergamon

Tetrahedron Letters, Vol. 37, No. 1, pp. 25-28, 1996

0040-4039/96 $15.00 + 0.00

0040-4039(95)02098-5

A New Practical Asymmetric Synthesis of C_2-Symmetrical 1,1'-Ferrocenyl Diols via CBS-Reduction

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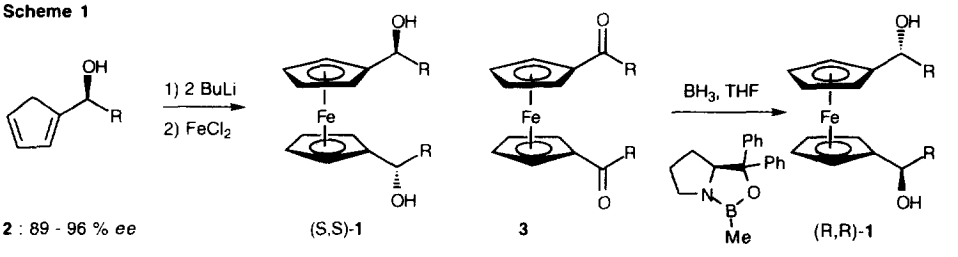
Abstract: CBS-reduction of ferrocenyl diketones **3** provides C_2-symmetrical ferrocenyl diols (R,R)-**1** in > 98 % *ee* accompanied by small amounts of the *meso*-diols (R,S)-**1**. The utility of **1** for the preparation of various potential ligands for asymmetric catalysis such as **9**, **12**, **13** and **14** is demonstrated.

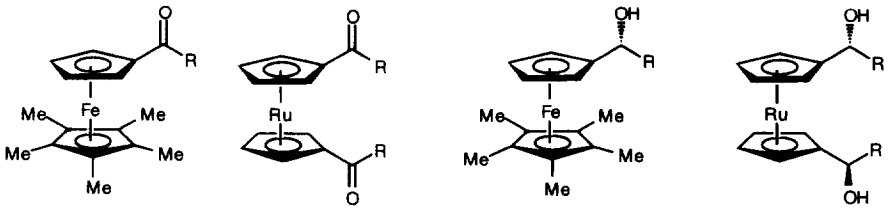
A range of chiral phosphines or amines bearing a ferrocene unit have been used as ligands for transition metal catalyzed asymmetric transformations.[1] These complexes have been prepared by resolution methods or by using precursors from the chiral pool.[2] Recently, we have reported a new synthesis of chiral C_2-symmetrical ferrocenyl diols of type **1** using chiral cyclopentadienyl alcohols **2** obtained by asymmetric synthesis.[3] Although this method provides a general access to the ferrocenes **1** with high enantioselectivity and allows the preparation of other chiral iron and

Scheme 1



2 : 89 - 96 % *ee* (S,S)-**1** **3** **4**: 60 mol% (R,R)-**1**

ruthenium complexes, the synthesis of the chiral cyclopentadienyl alcohols **2** requires 4 steps and is not well suited for large scale preparations. Herein, we wish to report a practical approach to the chiral diols **1** starting from the readily available ferrocenyl diketones[4] **3** using a borane reduction in the presence of an oxazaborolidine catalyst[5] (**4**). Although the CBS-reduction has already been applied successfully in the synthesis of ferrocenes bearing one alcohol function,[6] we were pleased to find that the reduction can be extended to the diketones **3** without difficulty[7] (Scheme 1 and Table 1). Thus the simultaneous slow addition of a THF solution of BH_3·Me_2S (ca. 2.0 equiv) and a THF solution of the diketone **3** to the CBS-catalyst **4** (0.6 equiv) at 0 °C provides the desired diols (R,R)-**1** in high yields and over 98 % *ee*.



5a : R = Me
5b : R = Pent

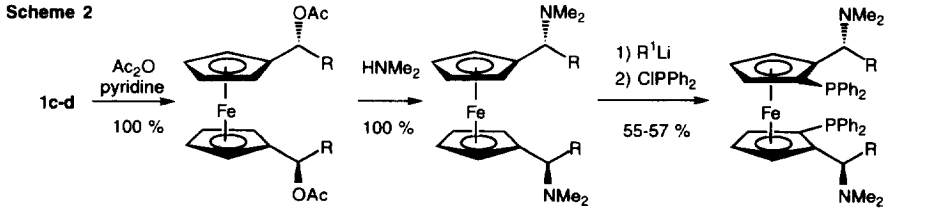
6a : R = Me
6b : R = Pent

7a : R = Me
7b : R = Pent

8a : R = Me
8b : R = Pent

They are accompanied by small amounts of the *meso*-diols (R,S)-**1** (3-13 %) (entries 1-6 of Table 1).[8] This reduction can be further extended to the heteroleptic ferrocenyl ketones **5a-b** (entries 7-8) and to the corresponding ruthenocenyl diketones **6a-b** (entries 9-10) leading to the alcohols **7a-b** and ruthenocenyl diols **8a-b** respectively.

Scheme 2



10a : R = Pent
10b : R = Ph

11a : R = Pent
11b : R = Ph

9a : R = Pent; R^1 = *t*-Bu
α_D = -357 (c=0.78, $CHCl_3$)
9b : R = Ph; R^1 = *n*-Bu
α_D = -331 (c=1.99, $CHCl_3$)

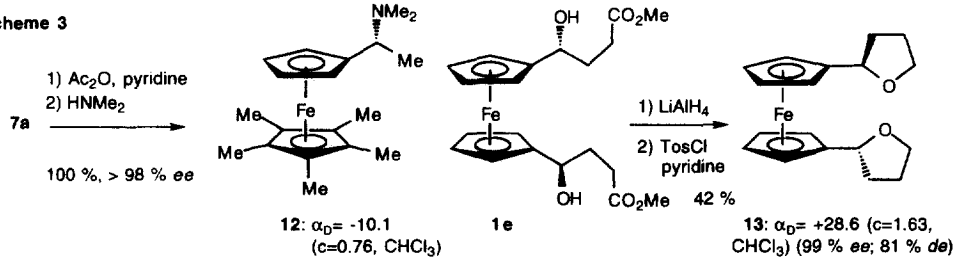
The new chiral diols (R,R)-**1** are important starting materials for the further elaboration of useful ligands of interest for asymmetric synthesis. The *bis*-(dimethylamino)ferrocenyl diphosphines **9a-b** are obtained using standard methods in 55-57 % overall yield (3 steps) starting from the diols **1c-d**. Thus the acylation of **1c-d** (Ac_2O, pyridine, rt, 12 h) affords the acetates **10a-b** in quantitative yield. Their treatment with dimethylamine furnishes the *bis*-(dimethylamino)ferrocenes **11a-b** in quantitative yields with retention of configuration (>96 % retention).[9] Directed metallation[10] of the compounds **11** with *n*-BuLi for **11b** (4 equiv, rt, 4 h)[11] or *t*-BuLi for **11a** (3 equiv, 0 °C, 4 h) and addition of $ClPPh_2$ affords the chelating *bis*-aminophosphines[12] **9a-b** (Scheme 2). The same method has been used to prepare efficiently the heteroleptic ferrocenyl amine **12** (98-99 % *ee*) which had been previously obtained via a diastereoselective multi-step procedure requiring stoichiometric amounts of a chiral auxiliary[13] (Scheme 3). New structural entities can be readily synthesized by $LiAlH_4$ reduction of the functionalized ferrocenyl diol **1e** with $LiAlH_4$ in THF (99 % yield) followed by a cyclization of the intermediate tetraol using *p*-TosCl (2 equiv) in pyridine (0 °C to 40 °C, 2 h) which furnishes the new C_2-symmetrical ferrocenyl tetrahydrofuran **13** in 42 % yield (Scheme 3). The reaction of the diacetate **10b** with potassium thioacetate provides the ferrocenyl *bis*-thioacetate **14** in quantitative yield (Scheme 4).[14]

Table 1. Ferrocenyl diols **1a-f**, ferrocenyl alcohols **7a-b** and ruthenocenyl diols **8a-b** obtained by CBS-reduction of the corresponding diketones **3a-f**, **6a-b** and ketones **5a-b**.

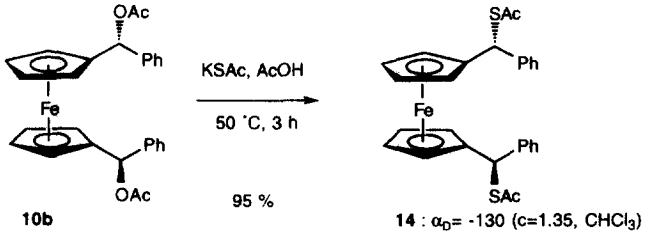
entry	ketone	R	product	yield[a] (%)	% *ee*[b]	*meso-dl*[c] ratio	α_D[d]
1	**3a**	Me	**1a**	98	>99	97:3	-97.7 (2.34)[e]
2	**3b**	i-Pr	**1b**	98	>99	91:9	-46.7 (1.62)
3	**3c**	Pent	**1c**	98	>98	87:13	-28.5 (2.79)
4	**3d**	Ph	**1d**	89	>99	96:4[f]	-75.1 (0.05)
5	**3e**	$(CH_2)_3CO_2Me$	**1e**	86	>99	95:5	-23.0 (1.64)
6	**3f**	Me, Pent[g]	**1f**	94	>99	95:5[h]	-47.1 (2.79)
7	**5a**	Me	**7a**	74	>96[i]	-	-45.5 (2.36)
8	**5b**	Pent	**7b**	87	94[i]	-	-53.0 (2.37)
9	**6a**	Me	**8a**	85	>99	98:11	-52.2 (1.09)
10	**6b**	Pent	**8b**	91	>98	84:16	-38.9 (3.74)

[a] Yield of analytically pure product. [b] Determined by HPLC measurement using a chiral column (Chiralcel-OD) and when available by comparison with literature specific rotation. [c] Ratio determined by ^{13}C-NMR. [d] α_D was measured in $CHCl_3$. [e] Measured in benzene. [f] A ratio >99 : <1 can be obtained by recrystallization. [g] An asymmetrical diketone having a COMe-group attached to one Cp-ring and a COPent-group to the other was used. [h] Diastereomeric ratio. [i] Determined by ^{1}H-NMR in the presence of $Eu(hfc)_3$.

Scheme 3



Scheme 4



In summary, we have developed a short and efficient preparation of C_2-symmetrical ferrocenyl diols of type **1** in high enantiomeric purity and have demonstrated the utility of these compounds for the

synthesis of potential ligands for asymmetric synthesis like **9a-b**, **12**, **13** and **14**. Further developments are currently underway in our laboratories.

Acknowledgments: We thank the DFG (SFB 260) and the Fonds der Chemischen Industrie, BASF AG, Witco AG, Chemetall, Sipsy, Bayer AG and Chiroscience for generous financial support and gift of chemicals.

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8. **Typical procedure:** Preparation of the (R,R)-ferrocenyl diol **1e**. A 100 mL three-necked flask with an argon inlet was equipped with rubber septa and was charged with the oxazaborolidine **4** (82.5 mg, 0.30 mmol) in THF (4 mL) and a small fraction of a THF solution of BH_3 (0.2 mmol) and was cooled to 0 °C. A 1M THF solution of $BH_3{\cdot}Me_2S$ (0.8 mmol) and the diketone **3e** (207 mg, 0.5 mmol) in THF (8 mL) were added simultaneously within 15 min via syringe. After 20 min of stirring, the reaction mixture was quenched with MeOH (2 mL) and was worked up as usual affording a crude product which after evaporation of the solvent, was purified by a short chromatography (ether) affording the desired diol **1e** (180 mg, 0.43 mmol, 86 % yield). α_D = -23.7 (c = 1.77 in $CHCl_3$). The diastereomeric ratio *meso:dl* was 5:95 (determined by ^{13}C-NMR spectroscopy).
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11. NMR-spectroscopy of the crude reaction mixture of **9b** indicates ca. 95 % selectivity for the directed metallation. Recrystallization from *t*-BuOMe affords the pure enantiomer **9b**.
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(*Received in Germany* 25 *October* 1995; *accepted* 31 *October* 1995)