

Efficient Preparation of C_2 -Symmetrical Chiral Ferrocenyl Diols by Catalytic Enantioselective Reduction of Diacylferrocenes

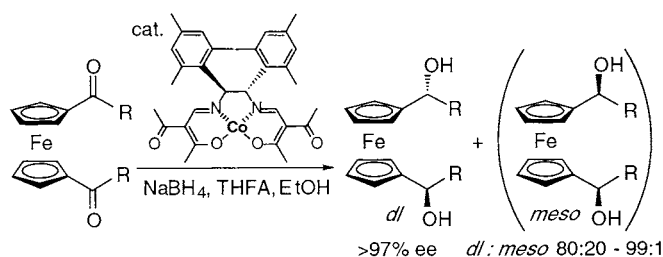
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ABSTRACT



Enantioselective borohydride reduction, catalyzed by the optically active β -ketoiminato cobalt(II) complex, was successfully applied to the 1,1'-dialkanoyl- and 1,1'-dibenzoylferrocenes to afford the corresponding C_2 -symmetrical chiral ferrocenyl diols with high diastereoselectivity and excellent enantioselectivity.

Optically active ferrocene derivatives have been widely employed as powerful chiral ligands of transition-metal complexes for various enantioselective catalyses;¹ e.g., asymmetric hydrogenation, transfer hydrogenation,² allylic substitution reactions, cross coupling, aldol reactions,³ and the Diels–Alder reaction.⁴ The C_2 -symmetrical chiral fer-

rocenyl diol is one of the most accessible precursors for the preparation of the optically active diaminodiphosphinoferrocene^{1b,5} ligands. Among several methods proposed for the optically active ferrocenyl diols,⁶ the enantioselective reduction of the corresponding 1,1'-diacylferrocenes is the most reliable since a wide variety of 1,1'-diacylferrocenes can be prepared by the conventional Friedel–Crafts reaction from ferrocene and acyl chlorides.⁷ On the basis of the results of the highly enantioselective reduction of ferrocenyl ketones⁸ with borane–THF catalyzed by the chiral oxazaborolidine

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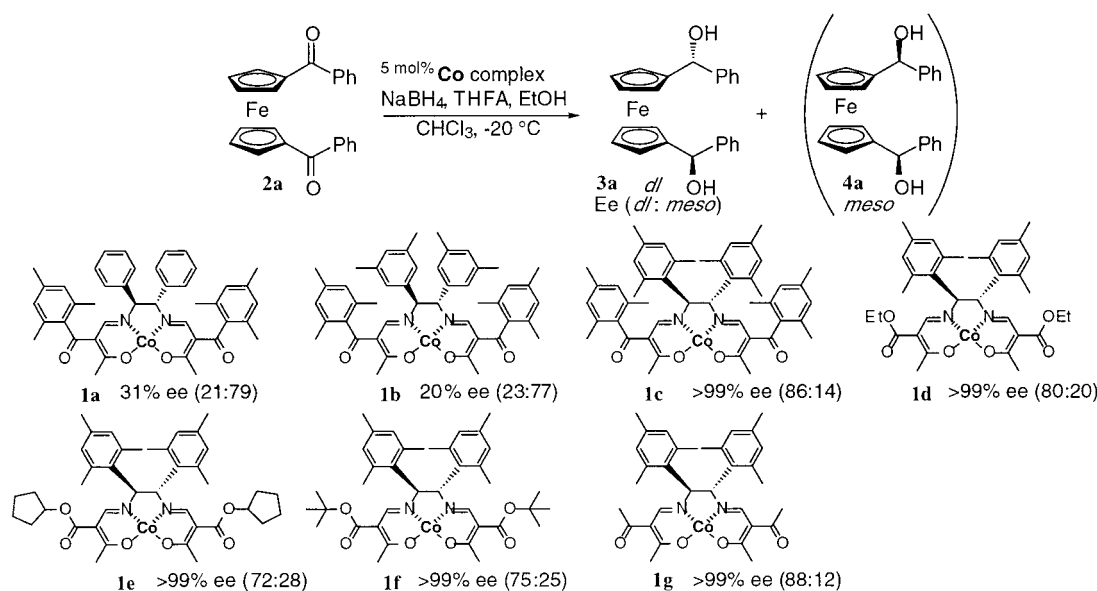


Figure 1. Various cobalt complex catalysts for enantioselective reduction of diacylferrocene **2a**.

(CBS reduction),⁹ a similar procedure was successfully applied to the reduction of the 1,1'-diacylferrocenes to afford the corresponding C₂-symmetrical chiral ferrocenyl diols with high enantioselectivity.¹⁰ Though the protocol was effective for various 1,1'-diacylferrocenes, the loading of a large amount¹¹ of the oxazaborolidine catalyst was required for the high enantioselectivity as the CBS reduction is generally sensitive to substrates and/or reaction conditions. The preparation of the antipode of the C₂-symmetrical chiral ferrocenyl diols is much more costly because the optically active oxazaborolidine catalyst was prepared from the naturally occurring (*S*)-proline.¹² Recently, the optically active β -ketoiminatocobalt(II) complex catalysts have been developed for the enantioselective borohydride reduction of a wide variety of ketones and imines to afford the corresponding chiral alcohols and amines with high catalytic efficiency and with high enantioselectivity.¹³ The enantioselective reduction system could be successfully applied to 1,3-diketones to obtain optically active 1,3-diols with high *dl/meso* and enantioselectivities.¹⁴ In this paper, we describe

the efficient and highly enantioselective synthesis of C₂-symmetrical chiral ferrocenyl diols from the corresponding 1,1'-dialkanoyl- and 1,1'-dibenzoylferrocenes achieved by enantioselective borohydride reduction catalyzed by the optically active cobalt(II) complexes.

The enantioselective borohydride reduction of 1,1'-diacylferrocenes was first examined using various optically active β -ketoiminatocobalt(II) complex catalysts adopting 1,1'-dibenzoylferrocene as the model substrate (Figure 1). It was found that the enantioselectivities in this reaction were sensitively affected by the steric demand of the chiral diamine part of the cobalt catalyst ligand. When complex **1a** or **1b**, respectively, prepared from the optically active 1,2-diphenyl-1,2-ethanediamine or 1,2-bis(3,5-dimethylphenyl)-1,2-ethanediamine, was employed as a catalyst, the enantiomeric excesses of the product were very low. However, catalysts **1c–g**, having the optically active 1,2-bis(2,4,6-trimethylphenyl)-1,2-ethanediamine unit, realized an excellent enantioselectivity (>99% ee)¹⁵ and a high *dl*-selectivity in each case. In particular, catalyst **1g**, with attached acyl groups as the side chains, indicated the highest *dl*-selectivity (88%) with excellent ee for the enantioselective reduction of 1,1'-dibenzoylferrocene.

The solvent effect was subsequently surveyed (Table 1). Each solvent achieved excellent enantiomeric excesses and high *dl*-selectivity (Table 1, entries 1–6). It is noted that the reaction time significantly depended on the reaction solvent. In chloroform (Table 1, entry 1), a suitable solvent for the enantioselective borohydride reduction and other typical solvents (Table 1, entries 2–5), the reduction was completed in 12–72 h, whereas in diethyl ether solvent, the enantioselective reduction was completed in 0.5 h at 0 °C

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Table 1. Various Solvents for Enantioselective Reduction of 1,1'-Dibenzoylferrocene **2a**

entry ^a	solvent	reaction time/h	yield ^b /%	ee ^c / % (<i>dl</i> / <i>meso</i>) ^d
1	CHCl ₃	12	99	>99 (88:12)
2	CH ₂ Cl ₂	18	86	>99 (87:13)
3	benzene	12	81	>99 (87:13)
4	CH ₃ CN	72	68	>99 (81:19)
5	THF	18	87	>99 (89:11)
6	Et ₂ O	0.5	92	>99 (89:11)

^a Reactions were carried out using 0.125 mmol of 1,1'-dibenzoylferrocene **2a**. ^b Isolated yield. ^c Determined by HPLC analysis (Chiralpak AD-H). ^d Determined by ¹³C NMR analysis.

with high enantio- and *dl*-selectivities (Table 1, entry 6).

The enantioselective borohydride reduction was successfully applied to various 1,1'-diacylferrocenes for the preparation of the corresponding C₂-symmetrical chiral diol using 5 mol % of a cobalt catalyst **1g** in diethyl ether solvent (Table 2). Various 1,1'-dibenzoylferrocene derivatives, possessing

Table 2. Enantioselective Reduction of Various Diacylferrocenes

entry ^a	1,1'-diacylferrocene	yield / % ^d	ee / % ^e (<i>dl</i> : <i>meso</i>) ^f
1		X = H 2a 92	>99 ^g (89 : 11)
2		F 2b 90	>99 ^g (87 : 13)
3		Cl 2c 89	99 ^h (87 : 13)
4		Br 2d 88	>99 ^h (89 : 11)
5		CH ₃ 2e 90	>99 ^g (88 : 12)
6		X = F 2f 94	>99 ^g (99 : 1)
7		Cl 2g 87	>99 ^g (93 : 7)
8 ^b		Br 2h 96	97 ^g (88 : 12)
9 ^c		n = 1 5a 84	>99 ⁱ (82 : 18)
10 ^c		2 5b 80	>99 ⁱ (80 : 20)
11 ^c		4 5c 90	>99 ⁱ (87 : 13)
12 ^c		6 5d 69	>99 ⁱ (85 : 15)

^a To a solution of the substrate and the cobalt catalyst **1g** was added a solution of the modified borohydride, 0.125 mmol of substrate, 0.00625 mmol (5.0 mol%) of cobalt catalyst **1g**, and 0.5 mmol of modified borohydride at 0 °C in Et₂O (10 mL), 0.5–3 h. ^b Et₂O, reflux temperature, 0.5 h. ^c 0.0125 mmol (10 mol%) of cobalt catalyst **1g**, 1.25 mmol of modified borohydride at –40 °C, 48 h. ^d Isolated yield. ^e Determined by HPLC analysis. ^f Determined by ¹H NMR analysis and/or ¹³C NMR analysis. ^g Chiralpak AD-H (2-propanol/hexane). ^h Chiralcel OD-H (2-propanol/hexane). ⁱ Chiralpak AD-H (EtOH/hexane).

p-fluorophenyl (Table 2, entry 2), *p*-chlorophenyl (Table 2, entry 3), *p*-bromophenyl (Table 2, entry 4), *p*-methylphenyl (Table 2, entry 5), *o*-fluorophenyl (Table 2, entry 6), and *o*-chlorophenyl (Table 2, entry 7) were converted to the corresponding optically active ferrocenyl diols with excellent enantiomeric excesses and high *dl*-selectivity. The reaction

of 1,1'-di(*o*-bromobenzoyl)ferrocene was very slow at 0 °C due to the steric hindrance. Therefore, the enantioselective reduction was carried out at the diethyl ether reflux temperature to afford the corresponding diols in 96% yield for 0.5 h with 87% *dl*-selectivity and 97% ee (Table 2, entry 8). The present enantioselective reduction could be applied to not only the 1,1'-dibenzoylferrocene analogues but also the 1,1'-dialkanoylferrocenes. Although the *dl*-selectivity from 1,1'-dihexanoylferrocene was not sufficient at 0 °C, the reduction was tried at –40 °C to afford the corresponding diol with 87% *dl*-selectivity and >99% enantioselectivity (Table 2, entry 11). Also, the 1,1'-dipropionyl-, dibutanoyl-, and dioctanoylferrocenes were stereoselectively reduced to the corresponding ferrocenyl diols with high *dl*-selectivity and excellent enantioselectivity (Table 2, entries 9, 10, and 12).¹⁶ Most catalytic enantioselective reductions including hydrogenation¹⁷ and hydride reduction¹⁸ are generally limited to π -system conjugated carbonyl functions, e.g., aryl ketones, vinyl ketones, and alkynyl ketones, etc. The enantioselective sense was then determined for each reduction. Comparing the optical rotation with the reported values^{10c} revealed that the enantioselective reduction of 1,1'-dibenzoylferrocene in the presence of the (*S,S*)-cobalt complex afforded the (*R,R*)-ferrocenyl diol, whereas the (*S,S*)-diol was obtained from 1,1'-dialkanoylferrocene (Figure 2). The enantioselective sense in the reduction of 1,1'-dibenzoylferrocene was in accord with that¹⁹ of acetophenone²⁰ on the condition that they both are regarded as phenyl ketones. As for the enantioselective reduction of 1,1'-dialkanoylferrocene, it is reasonable to consider that the cobalt complex catalyst should recognize the ferrocenyl group as the π -system, similar to the reduction of phenyl ketone, to achieve a high enantioselectivity. Since both enantiomers of the cobalt complex catalysts are available, both desired antipodes of the ferrocenyl diols with an aryl or alkyl substituent can be prepared

(16) **Preparation of the Modified Borohydride Solution.** To the suspension of NaBH₄ (75.7 mg, 2 mmol) in CHCl₃ (13.3 mL) were added EtOH (0.11 mL, 2 mmol) and tetrahydrofurfuryl alcohol (THFA) (2.71 mL, 28 mmol) at 0 °C under a dry nitrogen atmosphere. The mixture was stirred for 3 h at 0 °C and then cooled to –20 °C. **Enantio- and Diastereoselective Reduction of the 1,1'-Dibenzoylferrocene (2a).** 1,1'-Dibenzoylferrocene (**2a**) (0.125 mmol) and the (*S,S*)-cobalt complex catalyst **1g** (3.6 mg, 0.00625 mmol, 5.0 mol % against 1,1'-dibenzoylferrocene) were dissolved in Et₂O (10 mL) and cooled to 0 °C under a dry nitrogen atmosphere. The modified borohydride solution (4 mL, 0.5 mmol) was added to the reaction mixture and stirred for 0.5 h at 0 °C. The reaction was quenched by the dropwise addition of ice-cold water (10 mL). The reaction mixture was extracted with AcOEt. The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. After filtration and evaporation, the residue was purified by silica gel column chromatography (hexane/AcOEt) to afford the corresponding 1,1'-ferrocenyl diols **3a** and **4a**. The *dl*/*meso* selectivity was determined by ¹³C NMR analysis, and the optical purity was determined by HPLC analysis (Daicel Chiralpak AD-H, 2-propanol/hexane).

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(19) In the presence of the (*R,R*)-cobalt complex catalyst, aryl ketones were selectively converted to the corresponding (*R*)-alcohols in the previous experiments with a few exceptions. See ref 13.

(20) Since the prior order of substituents around the asymmetric carbon is hydroxyl > ferrocenyl > phenyl > alkyl > hydrogen, the descriptions for the same enantioselective sense were reversed between the reduction of 1,1'-dibenzoylferrocene and that of acetophenone.

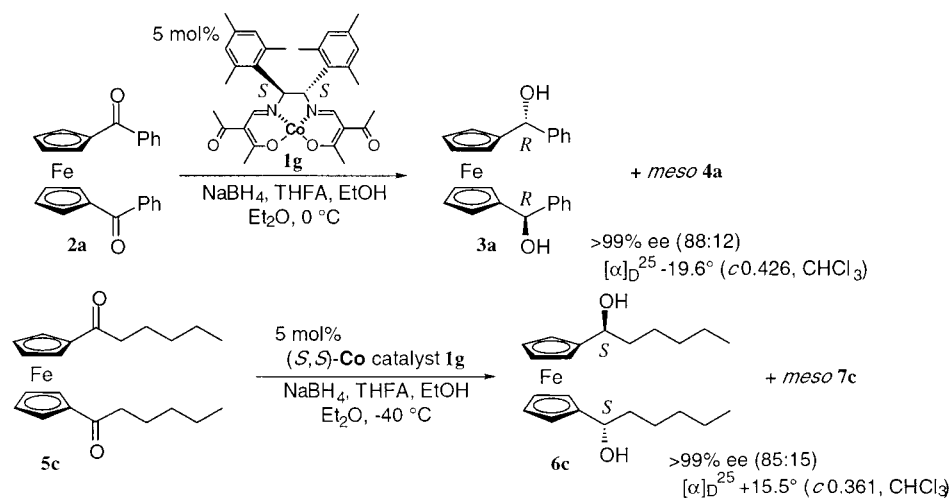


Figure 2. Enantioselective sense for dialkanoylferrocene vs dibenzoylferrocene.

with high efficiency and with high stereoselectivity.

It is noted that the efficient and highly stereoselective preparation of the C₂-symmetrical chiral ferrocenyl diols was provided by the enantioselective borohydride reduction of the 1,1'-dialkanoyl- and 1,1'-dibenzoylferrocenes catalyzed by the optically active β-ketoiminatocobalt(II) complex.

Supporting Information Available: Experimental procedures for the enantioselective reduction of the 1,1'-diacylferrocenes. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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