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Synthesis of chiral 1-ferrocenylaldols and 1-ferrocenyl-1,3-diols via asymmetric reductions

Angela Patti* and Sonia Pedotti

Istituto di Chimica Biomolecolare del CNR, Via del Santuario 110, I-95028 Valverde, CT, Italy

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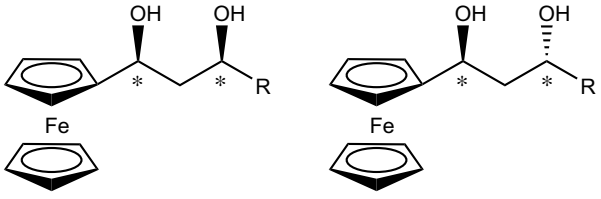
Abstract—The asymmetric transfer hydrogenation promoted by the (*R*,*R*)-(Ts-DPEN)–Ru complex of some 1-ferrocenyl-1,3-diketones was investigated and in all the cases only the carbonyl group distant to the metallocene moiety was reduced with variable selectivity depending on the C-3 substituent. The CBS-catalyzed reduction of 1-ferrocenyl-β-hydroxy-1-ketones, previously protected as acetates, was also found effective, giving both the corresponding *syn*- and *anti*-1,3-diols in satisfactory enantiomeric purity.

1. Introduction

The enantioselective reduction of a carbonyl group is a powerful tool for preparing optically active secondary alcohols and different methodologies have been developed. Among these, hydrogenation in the presence of diphosphine–Ru (or –Rh) complexes[1] and hydride reduction promoted by chiral organoboranes,[2] oxazaborolidine–borane[3] or Co-complex/$NaBH_4$[4] systems have been shown to be very effective on a broad range of ketones. The transfer hydrogenation catalyzed by Ru– (or Rh– and Ir–) complexes[5] also appears as an interesting procedure, due to its operational simplicity and the use of nonhazardous hydrogen donors such as 2-PrOH or a formic acid/triethylamine (HCOOH/TEA) mixture. Although all these methodologies have been successfully applied to simple and functionalized ketones[1–6] and ketoesters,[7] a limited number of examples have been reported for the enantio- and diastereoselective reduction of diketones,[8] which for the most part are C_2-symmetrically substituted.

As a part of our research focused on the preparation and application of new chiral ferrocenyl derivatives,[9] we have recently reported the kinetic resolution of 1-ferrocenyl-3-hydroxybutan-1-one (±)-**1a** via enantioselective lipase catalyzed esterification, which proceeded with high efficiency. Subsequent chemical reduction of each enantiomer of **1a** gave access to all four stereoisomers of 1-ferrocenyl-1,3-dihydroxybutane **2a** in enantiopure form, which were then converted into 1-ferrocenyl-1,3-aminoalcohols.[10]

In order to overcome the intrinsic limit in the yield of optically active **1a** or **2a** available from this resolution process, the asymmetric reduction of prochiral 1-ferrocenylbutane-1,3-dione **3a** or (±)-**1a** could be a useful alternative approach; herein we report the results obtained using two different methodologies. Our investigation was also extended to 1-ferrocenyl-1,3-diketones **3b–d** and the preparation of new enantiopure 1-ferrocenyl-1,3-diols is described.



R = CH_3	*syn*-**2a**	R = CH_3	*anti*-**2a**
R = *i*-Pr	*syn*-**2c**	R = *i*-Pr	*anti*-**2c**
R = Ph	*syn*-**2d**	R = Ph	*anti*-**2d**

2. Results and discussion

2.1. Transfer hydrogenation

A literature search revealed that the asymmetric reduction of unsymmetrical 1,3-diketones to the corresponding diols

* Corresponding author. Tel.: +39 0957212136; fax: +39 0957212141; e-mail: angela.patti@icb.cnr.it

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has been little investigated,[11] although some attention has been paid to 2-alkyl-1,3-diketones, whose rapid racemization can be exploited for a dynamic kinetic resolution affording the product of monoreduction with high enantio- and diastereoselectivity. In this context, protocols based on the use of premodified borohydride in the presence of a chiral Co(II)-catalyst[12] or transfer hydrogenation in the presence of (*R*,*R*)- or (*S*,*S*)-RuCl[*N*-(tosyl)-1,2-diphenylethylendiamine](*p*-cymene) (Noyori's catalyst,[13] **4**), have been shown effective.[14]

Since the amine ligand [*N*-(tosyl)-1,2-diphenylethylendiamine] (TsDPEN) is commercially available as both enantiomers, and the asymmetric transfer hydrogenation has not been previously applied to ferrocenyl substrates, we decided to investigate this methodology in the reduction of different ferrocenyl diketones **3a**–**e**, easily obtained by the reported Claisen condensation of acetylferrocene with a suitable carboxylic acid methyl or ethyl ester in the presence of lithium diisopropylamide as base.[15] For all of the ferrocenyl diketones **3a**–**e**, the only enolic form detected was that with the enolic hydroxyl distant to the cyclopentadienyl ring which was largely predominant, giving rise to keto/enol ratios in $CDCl_3$ solution ranging from 1:12 for **3d** to 1:3.5 for **3b**.[15,16]

For the transfer hydrogenation reaction, (*R*,*R*)-(TsDPEN) was complexed in situ with Ru(*p*-cymene)chloride dimer to give the active catalyst (*R*,*R*)-**4** and different conditions were tested using **3a** as a substrate (see Table 1). In all the experiments, the reduction proceeded on the sterically less congested carbonyl group affording (*S*)-**1a** as almost the exclusive product (Scheme 1). Using 2-PrOH/KOH as hydrogen source the reaction rate was low and the enantiomeric excess of (*S*)-**1a** slowly decreased during the time without a substantial improvement in its chemical yield, due to the reversibility of the reaction (entry 1).[13a] The use of the azeotropic mixture of HCOOH/TEA (5:2) allowed us to obtain complete conversion of the diketone with moderate stereoselectivity (entry 2). Carrying out the reaction at 50 °C had a beneficial effect on the reaction rate but not the stereoselectivity; however an improvement in the enantiomeric excess of (*S*)-**1a** was obtained by performing the reaction in a HCOOH/TEA (5:2) mixture without an additional solvent (entries 3 and 4); optimal conditions were found employing 5% catalyst loading (entry 5). In a preparative run, (*S*)-**1a** was obtained in 85% ee and its enantiomeric excess increased to 92% after one crystallization step.

Although the formation of enantiopure *anti*-diol (1*R*,3*S*)-**2a** was also observed, its yield was too low for practical purposes and did not increase when prolonging the reaction time. Compared with the reported data for the transfer hydrogenation of 1-phenyl-1,3-butanedione,[11d] which affords a 58:42 mixture of *anti*- and *syn*-diols, it seems evident that the reduction of a carbonyl group adjacent to the ferrocene is more difficult than a carbonyl group near to the phenyl system, possibly for steric reason. For comparison, under the same reaction conditions, acetylferrocene gave 35% of 1-ferrocenyl-1-ethanol with 92% ee whereas acetophenone was quantitatively reduced.

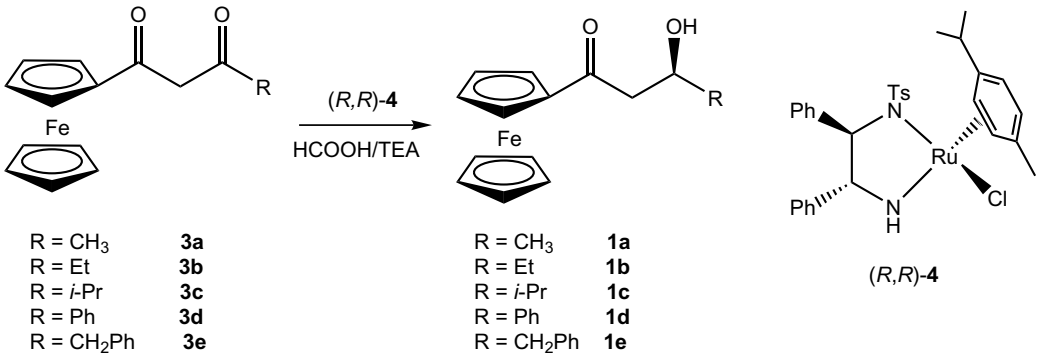
The reaction was then applied to the ferrocenyl diketones **3b** (R = Et) and **3c** (R = *i*-Pr), but the corresponding aldols **1b** and **1c** were obtained in quite low chemical yield and enantiomeric excess with respect to the analogous **1a** (entries 6 and 7). The dramatic decrease in the reaction rate observed with **3c** supported a clear influence of the steric hindrance of the alkyl substituent on the reaction course. The benzyl derivative **3e** represented an intermediate case since it was reduced with high reaction rate, but unsatisfactory selectivity.

Conversely, the reduction of **3d** (R = Ph) proceeded with complete stereoselectivity, giving after 3 h, aldol (*R*)-**1d** in >99% ee and 90% yield together with 10% of the enantiopure *anti*-diol (1*R*,3*R*)-**2d** (entry 8). This finding is in agreement with the general assumption that a phenyl substituent on the ketone substrate is essential for achieving a high level of enantioselectivity, which originates from the chiral geometry of the ruthenium five-membered chelate ring and,

Table 1. Transfer hydrogenation of ferrocenyldiketones in the presence of (*R*,*R*)-**4**[a]

Entry	Substrate	Catalyst (%)	Solvent	Temperature (°C)	Time (h)	Diketone[b] (%)	Product[b] (%)	% ee[c]	Conf.
1	**3a**	2.5	2-PrOH[d]	rt	24	**3a** (64)	**1a** (36)	77	*S*
2	**3a**	2.5	CH_2Cl_2	rt	96	—	**1a** (98)	57	*S*
3	**3a**	2.5	CH_2Cl_2	50	3	**3a** (5)	**1a** (95)	49	*S*
4	**3a**	2.5	None	50	3	—	**1a** (95)[e]	70	*S*
					72	—	**1a** (85)[e]	70	
5	**3a**	5	None	50	1	—	**1a** (90)[e]	85	*S*
6	**3b**	5	None	50	24	**3b** (62)	**1b** (38)	29	*S*
7	**3c**	5	None	50	24	**3c** (95)	**1c** (5)	55[f]	*S*
8	**3e**	5	None	50	5	—	**1e** (90)	22	*R*
9	**3d**	5	None	50	3	—	**1d** (90)[e]	>99	*R*
10	**3d**	1	None	50	24	**3d** (25)	**1d** (75)	>99	*R*

[a] All the reactions were performed using HCOOH/TEA azeotrope (5:2) as hydrogen source unless otherwise specified.
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Determined by chiral HPLC.
[d] 2-PrOH/KOH as hydrogen source.
[e] *anti*-Diol was present in the reaction mixture.
[f] Determined by chiral HPLC after chemical reduction to the corresponding diols.



Scheme 1. Asymmetric transfer hydrogenation of 1-ferrocenyl-1,3-diketones promoted by (*R*,*R*)-**4**.

additionally, from the CH/π attractive interaction between the η-[6]-arene ligand and the carbonyl aryl substituent.[17]

When the catalyst loading was decreased to 1%, the reaction rate diminished but the stereoselectivity remained unaffected, so that (*R*)-**1d** was recovered in 75% yield and >99% ee together with unreacted **3d** after 24 h (entry 10).

The absolute configuration of the aldols formed was determined by Mosher's method[18] except in the case of **3d** that lacks protons on one substituent flanking the chiral carbon bearing the hydroxyl group. We resorted to derivatization of the related *anti*-diol **2d** to the corresponding bis-MTPA ester since, according to a recently developed procedure,[19] is possible to assign the absolute configuration of an *anti*-1,3-diol by evaluating the differences in the chemical shifts of both the carbinolic and methylenic protons in its bis-(*S*)-MTPA and bis-(*R*)-MTPA esters. A positive $\Delta\delta^{SR}$ was observed for all the above protons supporting the (1*R*,3*R*) configuration of **2d**, directly derived from (*R*)-**1d**.

Optically enriched ferrocenyl-1,3-diols could be obtained by the reduction of (*S*)-**1a**, as previously reported,[10] or (*R*)-**1d**; the treatment of enantiopure (*R*)-**1d** with $LiAlH_4$ or $NaBH_4$ afforded *syn*-(1*S*,3*R*)- and *anti*-(1*R*,3*R*)-**2d** in a 2:1 ratio, as a mixture inseparable by silica gel column chromatography. The whole diols were then treated with acetone in the presence of montmorillonite K-10 to give the corresponding acetonides; the selective formation of the *syn*-acetonide was evidenced, allowing us to easily separate it from the unreacted *anti*-**2d** and recover *syn*-**2d** after deprotection.

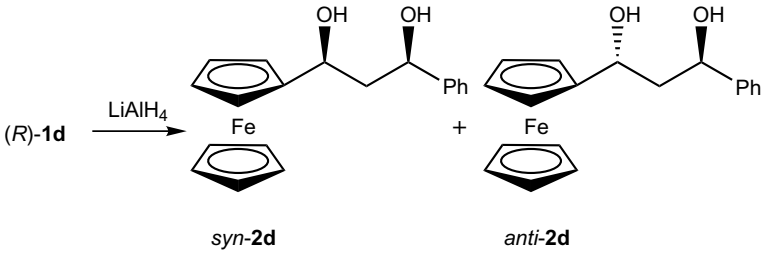
The relative configuration of the diols was established on the basis of the observed coupling constants of H-2 protons in their ^1H NMR spectra as previously discussed.[10]

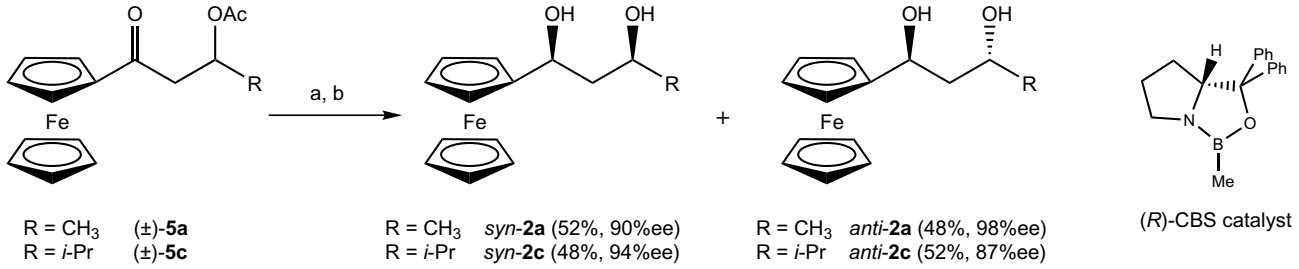
From the above data it seems evident that the (*R*,*R*)-**4**-promoted transfer hydrogenation could be applied to the preparation of optically active ferrocenyl aldols, but not the corresponding diols since reduction of the carbonyl group adjacent to the ferrocene system does not occur. The reaction course appeared highly substrate-dependent and satisfactory selectivity was obtained for the methyl or phenyl derivative.

2.2. CBS-catalyzed reduction

In the search for a system capable of catalyzing the stereoselective reduction of both the carbonyl groups of **3a**, the Corey–Bakshi–Shibata (CBS)-oxazaborolidine/borane[20] appeared to be a good choice since it has been reported as being effective in the reduction of several ferrocenyl-1,1′-diketones[21] and 1,4-diferrocenyldiketone,[22] which have been converted into the corresponding diols with high diastereo- and enantioselectivity. However, only a few examples of the reduction of 1,3-diketones or *O*-protected β-hydroxyketones in the presence of CBS-catalyst and borane as hydride donor to afford optically active 1,3-diols have been described.[23]

When **3a** was reacted with 1.2 equiv borane in the presence of 30% equiv of (*R*)-CBS at room temperature in THF, after 24 h the hydroxyketone **1a** was recovered as the main product in a nearly racemic form (9% ee) without formation of the desired diols. An attempt to obtain the target diols by increasing the reaction temperature failed since an extensive deoxygenation process,[9c,24] occurred and 1-ferrocenyl-3-hydroxybutane, 1-hydroxy-1-ferrocenylbutane and 1-ferrocenylbutane were isolated from the complex reaction mixture. No substantial differences were observed in toluene or by using other borane reagents.





Scheme 2. CBS-catalyzed asymmetric reduction of 1-ferrocenyl-β-acetoxy-1-ketones. Reagents and conditions: (a) (*R*)-CBS (30 mol %), $BH_3{\cdot}Me_2S$, THF, rt, 1 h; (b) K_2CO_3, MeOH.

This discouraging result prompted us to use (±)-**1a** as a substrate after the protection of its hydroxyl group to avoid the possible formation of a boron alcoholate, which could promote intramolecular reduction.[25] As a result we converted (±)-**1a** into the corresponding (±)-**5a**, whose reduction in the presence of 30 mol % of (*R*)-CBS clearly proceeded under the stereochemical control of the catalyst to afford in 1 h, a 52:48 mixture of 3-*O*-acetylated diols, wherefrom *syn*-(1*S*,3*S*)-**2a** and *anti*-(1*S*,3*R*)-**2a** in high enantiomeric purity (90% and 98% ee, respectively) were obtained after alkaline hydrolysis (Scheme 2).

When the same procedure was applied to (±)-**5c**, having the bulkier *iso*-propyl substituent, the *syn*-(1*S*,3*R*)-**2c** in 48% yield and 94% ee and the *anti*-(1*S*,3*S*)-**2c** in 52% yield and 87% ee are obtained.

The (*S*)-configuration of the newly created stereocentres is in agreement with the accepted model for the transition state for oxazaborolidine-promoted hydride attack,[3b,20] while the facial stereoselectivities[26] seem to be influenced by the chirality of the pre-existing centre and the size of the 3-substituent since different diastereo- and enantioselectivities were obtained in the two extreme cases considered above. The CBS-catalyzed reduction seems to have a broader substrate tolerance with respect to the Ru(II)-promoted transfer hydrogenation and could be generally applied to the preparation of chiral 1,3-diols starting from the easily accessible β-hydroxyketones.

3. Conclusions

Two different methodologies for the asymmetric carbonyl reduction were investigated for the preparation of optically active *syn*- and *anti*-1-ferrocenyl-1,3-diols and complementary results were obtained. As a result the chemical reduction of the enantiopure 1-ferrocenyl-β-hydroxy-1-ketones, available via the Ru(II)-promoted transfer hydrogenation of 1-ferrocenyl-1,3-diketones, affords the two diols with the same C-3 stereogenic centre. Conversely, the CBS-catalyzed reduction of racemic 1-ferrocenyl-β-hydroxy-1-ketones, previously protected as acetates, gave the two diols with the same C-1 stereogenic centre. The chiral ferrocenes reported herein can be also subjected to stereoselective reactions to afford 1,3-difunctionalized derivatives, whose application as chiral ligand for asymmetric synthesis are currently under investigation.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded at 400.13 and 100.62 MHz, respectively, in $CDCl_3$, unless otherwise stated. Chemical shifts (δ) are given as ppm relative to the residual solvent peak and coupling constants (J) are in hertz. In the ^1H NMR assignment, Cp and Cp′ refers to protons on the substituted and unsubstituted cyclopentadienyl rings, respectively. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument. The synthesis of ferrocenyldiketones and ferrocenylaldols was carried out under argon using standard Schlenk apparatus and THF was distilled over sodium/benzophenone ketyl. Column chromatography was performed on silica gel 60 (230–400 mesh) using the specified eluants. Chiral HPLC analyses were carried out on a thermostatted (30 °C) Chiralcel® OD column (Daicel Chemical Industries) using *n*-hexane/2-PrOH mixtures as a mobile phase and detection by UV–vis detector at 250 nm. (1*R*,2*R*)-*N*-Tosyl-1,2 diphenylethylenediamine (TsDPEN), $[RuCl_2(p\text{-cymene})]_2$ and (*R*)-CBS (1 M solution in toluene) were purchased from Aldrich.

4.2. Synthesis of 1-ferrocenyl-1,3-diketones

A representative procedure is described for the synthesis of 1-ferrocenyl-4-methylpentane-1,3-dione **3c**. To a solution of di-*iso*-propylamine (1.6 mL, 11.4 mmol) in THF (5 mL), *n*-BuLi (6.4 mL of 1.6 M solution in hexane) was added at −30 °C and the mixture was left to react at this temperature for 30 min. Acetylferrocene (1 g, 4.4 mmol) dissolved in THF (5 mL) was then added dropwise and the mixture was stirred for 1 h at −30 °C. Methyl-*iso*-butyrate (1.2 mL, 10.2 mmol) was added and the cooling bath removed. After 2 h at room temperature, TLC analysis showed that the conversion of the substrate was almost complete and the reaction was quenched by the careful addition of water. The mixture was partitioned with AcOEt and the organic layers were collected, dried over Na_2SO_4 and taken to dryness. Purification of the residue by column chromatography (silica gel, *n*-hexane–AcOEt 4:1) gave **3c** (785 mg, 60% yield) as a red oil, R_f 0.55 (*n*-hexane–AcOEt 4:1), enol/diketone ratio 4.4:1; ^1H NMR: (enol) δ 1.22 (d, $J = 6.9$, 6H, –CH_3), 2.52 (m, 1H, H-4), 4.19 (s, 5H, Cp′), 4.50 (br t, 2H, Cp), 4.79 (br t, 2H, Cp), 5.73 (s, 1H, H-2); (diketone): δ 1.16 (d, $J = 6.9$, 6H, –CH_3), 2.58 (m,

1H, H-4), 3.89 (s, 2H, H-2), 4.25 (s, 5H, Cp′), 4.56 (br t, 2H, Cp), 4.79 (br t, 2H, Cp); ^{13}C NMR: (enol) δ 20.2, 36.0, 68.5, 70.2, 72.8, 78.0, 94.2, 192.8, 194.0; (diketone): δ 17.9, 41.2, 52.7, 69.8, 69.9, 72.8, 78.8, 197.7, 208.1. Anal. Calcd for $C_{16}H_{18}FeO_2$: C, 64.45; H, 6.09. Found: C, 64.19; H, 5.99.

According to the above procedure, the known diketones **3a**,[27] **3d** and **3e**[16a] were also prepared.

4.2.1. 1-Ferrocenylpentane-1,3-dione, 3b. The reaction of acetylferrocene with ethyl propanoate according to the above procedure gave **3b** in 45% yield, R_f 0.48 (*n*-hexane–AcOEt 4:1), enol/diketone ratio 2.5:1; ^{1}H NMR: (enol) δ 1.22 (t, $J = 7.5$, 3H, –CH_3), 2.36 (q, 2H, $J = 7.5$, H-4), 4.19 (s, 5H, Cp′), 4.50 (br t, 2H, Cp), 4.79 (br t, 2H, Cp), 5.73 (s, 1H, H-2); (diketone) δ 1.10 (t, $J = 7.2$, 3H, CH_3), 2.66 (q, 2H, $J = 7.2$, H-4), 3.82 (s, 2H, H-2), 4.23 (s, 5H, Cp′), 4.56 (br t, 2H, Cp), 4.79 (br t, 2H, Cp); ^{13}C NMR: (enol) δ 10.2, 30.8, 68.5, 70.2, 71.8, 77.8, 95.5, 190.8, 192.3; (diketone) δ 7.5, 36.5, 54.9, 69.8, 70.0, 72.9, 78.8, 197.4, 204.7. Anal. Calcd for $C_{15}H_{16}FeO_2$: C, 63.41; H, 5.68. Found: C, 63.17; H, 5.61.

4.3. General procedure for transfer hydrogenation

A representative procedure is described for the asymmetric reduction of **3a**. A mixture of $[RuCl_2(p\text{-cymene})]_2$ (9 mg, 0.015 mmol) and (1*R*,2*R*)-TsDPEN (11 mg, 0.03 mmol) in 2-propanol (0.5 mL) was heated at 80 °C for 20 min under argon, then the solvent was removed under vacuum. Triethylamine–formic acid solution (2:5 mol/mol, 1 mL) and **3a** (162 mg, 0.6 mmol) were added to the Ru-complex and the mixture stirred at 50 °C while monitoring the reaction progress by TLC. After a suitable time, the solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness under vacuum. The residue was applied on silica gel column (*n*-hexane–AcOEt 7:3) to give pure **1a** (140 mg, 86% yield, 85% ee), and *anti*-(1*R*,3*S*)-**2a** (11.5 mg, 7% yield, >99% ee) whose characterization data have been reported.[10]

4.3.1. (*S*)-1-Ferrocenyl-3-hydroxypentane-1-one, 1b. Starting from **3b**, the title compound was obtained in 35% isolated yield as an orange solid, mp 65–66 °C, R_f 0.34 (*n*-hexane–AcOEt 7:3), $[\alpha]_D = -3.2$ (*c* 0.4, $CHCl_3$, 29% ee); ^{1}H NMR: δ 1.04 (t, $J = 7.4$, 3H, –CH_3), 1.61 (m, 2H, H-4), 2.78 (dd, $J = 9.2$ and 17.2, 1H, H-2a), 2.91 (dd, $J = 2.6$ and 17.2, H-2b), 3.49 (d, $J = 3.0$, –OH), 4.12 (m, 1H, H-3), 4.20 (s, 5H, Cp′), 4.55 (br t, 2H, Cp), 4.78 (br t, 1H, Cp), 4.82 (br t, 1H, Cp); ^{13}C NMR: δ 9.9, 29.4, 45.4, 69.3, 69.4, 70.0, 72.6, 78.8, 205.4. HPLC: *n*-hexane–2-PrOH 95:5, flow 0.7 mL/min, t_R/min = 18.4 (*S*) and 25.4 (*R*). Anal. Calcd for $C_{15}H_{18}FeO_2$: C, 62.96; H, 6.34. Found: C, 62.72; H, 6.25.

4.3.2. (*S*)-1-Ferrocenyl-3-hydroxy-4-methylpentane-1-one, 1c. Transfer hydrogenation of **3c** gave **1c** in 4% isolated yield as an orange solid, mp 62–63 °C, R_f 0.26 (*n*-hexane–AcOEt 4:1), $[\alpha]_D = +2.2$ (*c* 0.3, $CHCl_3$, 55% ee); ^{1}H NMR: δ 1.00 (d, $J = 6.8$, 3H, –CH_3), 1.03 (d, $J = 6.8$, 3H, –CH_3), 1.79 (m, 1H, H-4), 2.77 (dd, $J = 9.7$ and 17.0, 1H, H-2a), 2.91 (dd, $J = 2.3$ and 17.0, 1H, H-2b), 3.44 (d, $J = 2.9$, –OH), 3.95 (m, 1H, H-3), 4.24 (s, 5H, Cp′), 4.55 (br t, 2H, Cp), 4.79 (br t, 1H, Cp), 4.82(br t, 1H, Cp); ^{13}C NMR: δ 17.9, 18.5, 33.1, 42.7, 69.3, 69.4, 70.0, 72.6, 72.7, 78.9, 205.7. Anal. Calcd for $C_{16}H_{20}FeO_2$: C, 64.02; H, 6.72. Found: C, 63.75; H, 6.68.

4.3.3. (*R*)-1-Ferrocenyl-3-phenyl-3-hydroxypropane-1-one, 1d. Starting from **3d**, the title compound was isolated in 87% yield as an orange solid, mp 96–97 °C, R_f 0.36 (*n*-hexane–AcOEt 7:3), $[\alpha]_D = +18.2$ (*c* 0.88, $CHCl_3$, >99% ee); ^{1}H NMR (C_6D_6): δ 2.80 (dd, $J = 3.1$ and 17.2, 1H, H-2a), 2.95 (dd, $J = 9.1$ and 17.2, 1H, H-2b), 3.86 (s, 5H, Cp′), 3.91 (d, $J = 2.9$, 1H, –OH), 4.04 (m, 2H, Cp), 4.41 (br s, 1H, Cp), 4.63 (br s, 1H, Cp), 5.37 (m, 1H, H-3), 7.13 (t, $J = 7.5$, 1H, Ph), 7.23 (t, $J = 7.5$, 2H, Ph), 7.46 (d, $J = 7.5$, 2H, Ph); ^{13}C NMR: δ 48.1, 69.3, 69.4, 70.0, 70.3, 78.5, 125.7, 127.6, 128.5, 143.3, 204.5. HPLC: *n*-hexane–2-PrOH 9:1, flow 0.5 mL/min, t_R/min = 26.3 (*R*) and 28.3 (*S*). Anal. Calcd for $C_{19}H_{18}FeO_2$: C, 68.29; H, 5.43. Found: C, 68.12; H, 5.36.

4.3.4. (*R*)-1-Ferrocenyl-4-phenyl-3-hydroxybutane-1-one, 1e. Starting from **3e**, title compound was obtained in 86% isolated yield as an orange solid, mp 132–133 °C, R_f 0.33 (*n*-hexane–AcOEt 7:3), $[\alpha]_D = -16.8$ (*c* 0.4, $CHCl_3$, 22% ee); ^{1}H NMR: δ 2.79 (dd, $J = 9.0$ and 17.2, 1H, H-2a), 2.82 (dd, $J = 6.7$ and 13.5, 1H, H-4a), 2.93 (dd, $J = 2.8$ and 17.2, 1H, H-2b), 3.00 (dd, $J = 6.9$ and 13.5, 1H, H-4b), 3.48 (d, $J = 3.0$, –OH), 4.15 (s, 5H, Cp′), 4.45 (m, 1H, H-3), 4.53 (t, $J = 1.8$, 2H, Cp), 4.74 (t, $J = 1.8$, 2H, Cp), 7.26–7.37 (m, 5H, –Ph); ^{13}C NMR: δ 43.0, 44.8, 69.1, 69.3, 69.5, 69.9, 72.6, 72.7, 78.7, 126.5, 128.5, 129.4, 138.2, 204.9. HPLC: *n*-hexane–2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 16.0 (*S*) and 30.2 (*R*). Anal. Calcd for $C_{20}H_{20}FeO_2$: C, 68.98; H, 5.79. Found: C, 68.77; H, 5.71.

4.4. (1*S*,3*R*)-1-Ferrocenyl-3-phenyl-1,3-dihydroxypropane, *syn*-2d and (1*R*,3*R*)-1-ferrocenyl-3-phenyl-1,3-dihydroxypropane, *anti*-2d

To a solution of **1d** (100 mg, 0.3 mmol, >99% ee) in THF (5 mL), $NaBH_4$ (25 mg, 0.7 mmol) and some drops of MeOH were added and the suspension stirred at room temperature until complete disappearance of **1d** was detected by TLC. The ratio of *syn*-**2d**:*anti*-**2d** was evaluated by HPLC analysis of the crude mixture. The reaction mixture was partitioned between water and AcOEt, the organic layer dried over Na_2SO_4 and the solvent removed under reduced pressure. The residue was dissolved in 5 mL of acetone and, after addition of montmorillonite K-10 (200 mg), the suspension was left stirring at rt until the chiral HPLC analysis showed *anti*-**2d** as the only unreacted diol. After removal of the clay by centrifugation, the solution was taken to dryness and the residue purified by column chromatography (silica gel, *n*-hexane–CH_2Cl_2 3:2) to give *anti*-**2d** acetonide (8 mg), *syn*-**2d** acetonide (72 mg) and pure *anti*-**2d** (25 mg, 25% yield). To remove the protective group, *syn*-**2d** acetonide was dissolved in THF–H_2O (9:1, 5 mL) and 400 mg of Dowex 50W (H^+) was added to the solution. After overnight stirring at rt, the resin was

removed by filtration and the solution taken to dryness to afford *syn*-**2d** (62 mg, 62% yield).

(1*S*,3*R*)-*syn*-**2d**: mp 112–113 °C, $[\alpha]_D = +29.3$ (*c* 0.15, $CHCl_3$, >99% ee); ^1H NMR: δ 2.04 (dt, $J = 3.2$ and 14.3, 1H, H-2a), 2.13 (ddd, $J = 9.2$, 9.7 and 14.3, 1H, H-2b), 2.58 (d, $J = 2.7$, 1H, –OH), 3.71 (br s, 1H, –OH), 4.19 (br s, 2H, Cp), 4.21 (s, 6H, Cp′ and Cp), 4.25 (br s, 1H, Cp), 4.67 (m, 1H, H-3), 5.03 (dd, $J = 3.2$ and 9.2, 1H, H-1), ^{13}C NMR: δ 46.9, 65.7, 66.5, 68.0, 68.1, 68.4, 70.2, 74.5, 93.3, 125.8, 127.5, 128.5, 144.4. HPLC: *n*-hexane–2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 28.6 (1*S*,3*R*) and 62.2 (1*R*,3*S*). Anal. Calcd for $C_{19}H_{20}FeO_2$: C, 67.88; H, 6.00. Found: C, 67.64; H, 5.93.

(1*R*,3*R*)-*anti*-**2d**: mp 110–111 °C, $[\alpha]_D = +15.2$ (*c* 0.21, $CHCl_3$); ^1H NMR: δ 2.06 (ddd, $J = 3.0$, 8.8 and 14.3, 1H, H-2a), 2.19 (ddd, $J = 2.9$, 8.3 and 14.3, 1H, H-2b), 2.35 (d, $J = 3.0$, 1H, –OH), 3.15 (d, $J = 4.2$, 1H, –OH), 4.19 (br s, 8H, Cp and Cp′), 4.30 (br s, 1H, Cp), 4.66 (m, 1H, H-3), 5.06 (m, 1H, H-1), 7.28–7.41 (m, 5H, Ph); ^{13}C NMR: δ 45.8, 65.8, 66.7, 67.4, 68.1, 68.4, 71.6, 93.1, 125.6, 127.3, 128.4, 144.6. HPLC: *n*-hexane–2-PrOH 9:1, flow 0.7 mL/min, t_R/min = 24.3 (1*S*,3*S*) and 26.0 (1*R*,3*R*). Anal. Calcd for $C_{19}H_{20}FeO_2$: C, 67.88; H, 6.00. Found: C, 67.69; H, 5.90.

4.5. General procedure for CBS-catalyzed reduction

A representative procedure is described for the asymmetric reduction of (±)-**5a**. Racemic (±)-**1a** was obtained by aldol condensation of acetylferrocene and acetaldehyde, as previously described,[10] and quantitatively converted into (±)-**5a** by conventional acetylation (Ac_2O/pyridine).

(*R*)-CBS (0.228 mmol, 0.228 mL of 1 M solution in toluene) was dissolved in THF (10 mL) under argon and cooled to 0 °C. From a syringe charged with $BH_3{\cdot}Me_2S$ (2 M in THF, 0.38 mL, 0.76 mmol) dissolved in 10 mL of THF, 20% of the final amount was added to the catalyst solution. After 10 min of stirring, the remaining $BH_3{\cdot}Me_2S$ and the solution of (±)-**5a** (240 mg, 0.76 mmol in 10 mL of THF) were simultaneously added by syringe pump within 20 min at 0 °C. The reaction mixture was maintained at rt for 1 h. As soon as quantitative conversion of the substrate was observed, the reaction was quenched by the careful dropwise addition of MeOH (2 mL), diluted with satd NH_4Cl and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness under vacuum to give a residue that was charged on a short silica gel column (*n*-hexane–AcOEt 1:1) to remove the catalyst. After the column eluate was taken to dryness, the residue was dissolved in MeOH/H_2O (95:5) and K_2CO_3 was added and the mixture left to react under stirring. At completion, the mixture was diluted with water and partitioned with AcOEt. The organic layers were collected, dried and taken to dryness. The final residue was purified on Si gel column (*n*-hexane–AcOEt 7:3) to give *syn*-(1*S*,3*S*)-**2a** (103 mg, 49% yield, 90% ee) and *anti*-(1*S*,3*R*)-**2a** (95 mg, 45% yield, 98% ee), whose characterization data are in agreement with those previously reported.[10]

4.6. (1*S*,3*R*)-1-Ferrocenyl-1,3-dihydroxy-4-methylpentane, *syn*-2c and (1*S*,3*S*)-1-ferrocenyl-1,3-dihydroxy-4-methylpentane, *anti*-2c

According to the above procedure, (±)-**5c** (260 mg, 0.76 mmol) was reduced in 3 h in the presence of 30 mol % of (*R*)-CBS. After the work-up of the reaction mixture and the alkaline hydrolysis, *syn*-**2c** (105 mg, 46% yield, 94% ee) and *anti*-**2c** (115 mg, 50% yield, 87% ee) were isolated by column chromatography.

(1*S*,3*R*)-*syn*-**2c** was obtained as a yellow oil, R_f 0.23 (*n*-hexane–AcOEt 7:3), $[\alpha]_D = +35.3$ (*c* 0.36, $CHCl_3$, 94% ee); ^1H NMR: δ 0.95 (d, $J = 6.8$, 3H, $–CH_3$), 0.96 (d, $J = 6.8$, 3H, $–CH_3$), 1.70–1.73 (m, 2H, H-4 and H-2a), 1.83 (dd, $J = 2.4$ and 14.3, H-2b), 2.67 (br s, 1H, –OH), 3.37 (br s, 1H, –OH), 3.70 (dt, $J = 4.9$ and 8.8, 1H, H-3), 4.21 (s, 2H, Cp), 4.23 (s, 6H, Cp′ and Cp), 4.27 (s, 1H, Cp), 4.60 (m, 1H, H-1); ^{13}C NMR: δ 17.5, 18.3, 33.9, 41.1, 65.5, 66.6, 67.9, 68.0, 68.3, 68.7, 71.0, 93.7. HPLC: *n*-hexane–2-PrOH 95:5, flow 0.7 mL/min, t_R/min = 32.1 (1*S*,3*R*) and 35.8 (1*R*,3*S*). Anal. Calcd for $C_{16}H_{22}FeO_2$: C, 63.59; H 7.34. Found: C, 63.75; H, 7.22.

(1*S*,3*S*)-*anti*-**2c** was obtained as a yellow solid, mp 95–96, R_f 0.15 (*n*-hexane–AcOEt 7:3), $[\alpha]_D = +7.8$ (*c* 0.65, $CHCl_3$, 87% ee); ^1H NMR: δ 0.92 (d, $J = 6.8$, 3H, $–CH_3$), 0.95 (d, $J = 6.8$, 3H, $–CH_3$), 1.70 (m, 1H, H-4), 1.74 (ddd, $J = 2.5$, 8.3 and 14.3, 1H, H-2a), 1.84 (ddd, $J = 3.4$, 9.3 and 14.3, 1H, H-2b), 2.37 (d, $J = 3.1$, 1H, –OH), 2.40 (d, $J = 4.0$, 1H, –OH), 3.67 (m, 1H, H-3), 4.13 (s, 3H, Cp), 4.21 (s, 5H, Cp′), 4.30 (s, 1H, Cp), 4.73 (m, 1H, Cp); ^{13}C NMR: δ 17.7, 18.6, 33.7, 41.2, 65.5, 66.7, 67.6, 67.9, 68.0, 68.3, 73.6, 93.7. HPLC: *n*-hexane–2-PrOH 95:5, flow 0.7 mL/min, t_R/min = 23.4 (1*R*,3*R*) and 28.3 (1*S*,3*S*). Anal. Calcd for $C_{16}H_{22}FeO_2$: C, 63.59; H, 7.34. Found: C, 63.38; H, 7.26.

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