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Biocatalytic procedure for obtaining all four diastereoisomers of 1-(1-hydroxyethyl)-3-ethylferrocene: synthons for chiral 1,3-disubstituted ferrocenes

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Abstract—Lipase from *Candida antarctica* has been successfully used to realise the selective esterification of the four 1-(1-hydroxyethyl)-3-ethylferrocene isomers, possessing central/planar chirality. In this reaction, the lipase recognises only the two isomers possessing an (*R*)-configuration, independently from planar chirality. This allows us to split the mixture into two couples of diastereoisomers, namely the (S_p,R_c)-/(R_p,R_c)- and (R_p,S_c)-/(S_p,S_c)-isomers, conveniently separated in the single constituents by crystallisation from hexane.

1. Introduction

There is considerable interest today in ferrocene derivatives, due to their great demand as auxiliaries in homogenous catalysis,[1] intermediates in the preparation of new materials having special properties[2] and compounds for medicinal and diagnostic uses.[3] The presence of two different substituents on the same cyclopentadienyl ring makes these organometallics chiral and allows the preparation in enantiopure form molecules with attractive and valuable stereochemical features.

Chiral 1,2-disubstituted ferrocenyl derivatives can easily be obtained by resorting to well-known syntheses, exploiting diastereoselective *ortho*-lithiation of ferrocenes containing chiral directing groups.[4] In particular, ancillary groups such as acetals,[5] oxazolines[6] and imines[7] can furnish chiral 1,2-derivatives with specific planar-only chirality, while tertiary amines[8] and sulfoxides[9] give access to 1,2-disubstituted ferrocenes possessing both central and planar chirality. Conversely, the preparation of chiral 1,3-disubstituted ferrocenes is difficult and the main procedure deals with the use of asymmetric lithiation of substituted ferrocenes in the presence of (−)-sparteine.[10]

Alternatively, the resolution of ferrocene racemates may be a valid and particularly efficient way to obtain both enantiomers. In this context, kinetic resolution catalysed by lipases is efficient in preparing enantiopure 1,2-ferrocenes possessing exclusively planar chirality.[11] Unfortunately, resolution catalysed by lipases was found to be ineffective when applied to 1,3-disubstituted ferrocenes, resulting in very poor enantioselectivity.[12] However, we deemed possible that the enzymatic procedure could be advantageously applied to 1,3-disubstituted ferrocenes bearing a stereogenic centre in one of the substituents, since central recognition could have a pivotal role for the resolution.

Herein we report the case of *C. antarctica* lipase successfully exploited in an esterification process to obtain the four stereoforms of 1-(1-hydroxyethyl)-3-ethylferrocene, a compound that appears to be a promising chiral synthon due to the easy transformation at the α-position of both the substituents.

2. Results and discussion

Treatment of ketone *rac*-**1**, obtained by acylation of ethylferrocene, with $LiAlH_4$ gave an oil, whose HPLC analysis on a chiral column showed the presence of four peaks with comparable areas, indicating it to be a

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mixture of two racemates (±)-**2** (A) and (±)-**3** (B) (Scheme 1). The strong structural similitude of the two components A and B was highlighted by an almost total coincidence of signals in the NMR spectra, probably due to the feeble influence between the planar and central chirality, responsible for the diastereoisomeric diversity. Consequently, all attempts to separate the racemates by conventional chromatographic methods or preferential crystallisation were ineffective.

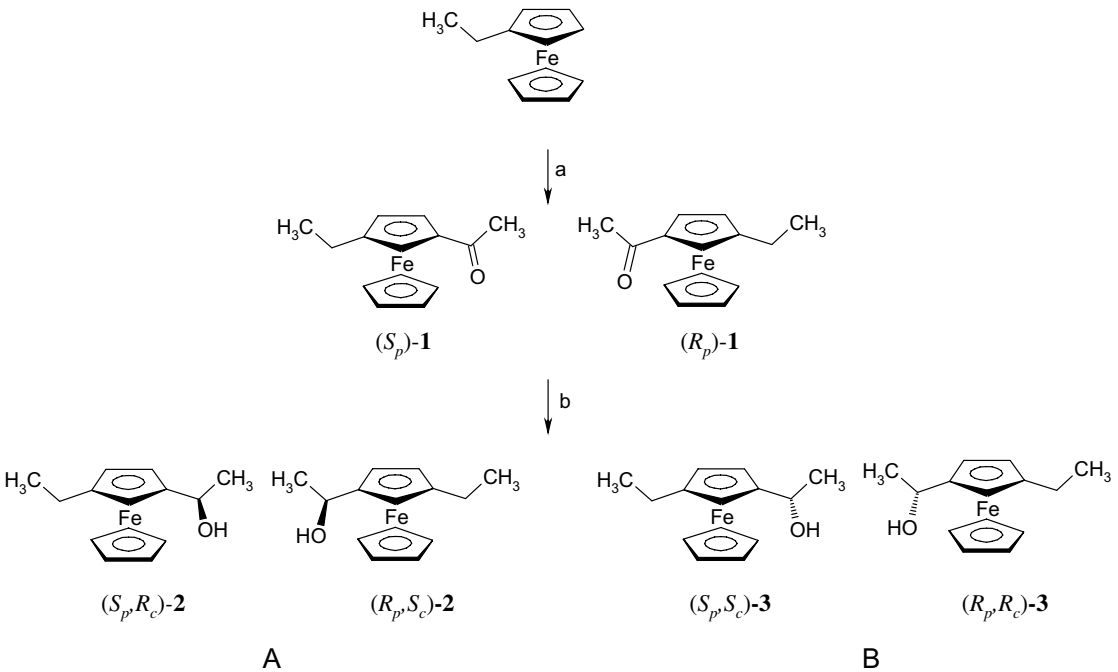
Therefore, we decided to subject the mixture of A and B, to selective esterification catalysed by lipase from *C. antarctica*, an enzyme possessing an *R*-preference for the secondary alcohols. We hoped that esterification would involve only two of the four stereoforms, regardless of the planar chirality, leading to two diastereoisomeric esters, with the consequent advantage of realising the first step of the separation of the mixture's constituents.

However, before proceeding in this direction, we considered it necessary to have at our disposal reference samples of two diastereomeric forms of the alcohol with known stereochemistry. For this purpose, samples of (S_p,R_c)-**2** and (S_p,S_c)-**3** were prepared from the commercially available enantiopure aminoferrocene (*R*)-**4**, through the stereocontrolled multistep transformation reported in Scheme 2. Thanks to the *ortho*-orienting properties of its *N*,*N*-dimetylaminomethyl group[8] (*R*)-**4** was transformed into *t*-butylsulfide (R_p,R_c)-**5**, which easily undergoes oxidation to give only (R_p,R_c,R_c)-**6**.[13] The presence of a sulfoxide group of an appropriate configuration drives the *ortho*-metallation in a diastereoselective manner, allowing the formation of the single trisubstituted ferrocene (R_p,R_c,R_c)-**7**. This derivative was desulfurated to give the 1,3-disubstituted ferrocene (S_p,R_c)-**8**, subsequently transformed into homochiral (S_p,R_c)-**2** by treatment with Ac_2O followed by hydrolysis. MnO_2 oxidation of (S_p,R_c)-**2**, followed by $LiAlH_4$ reduction, permitted access also to the diastereoisomer (S_p,S_c)-**3**.

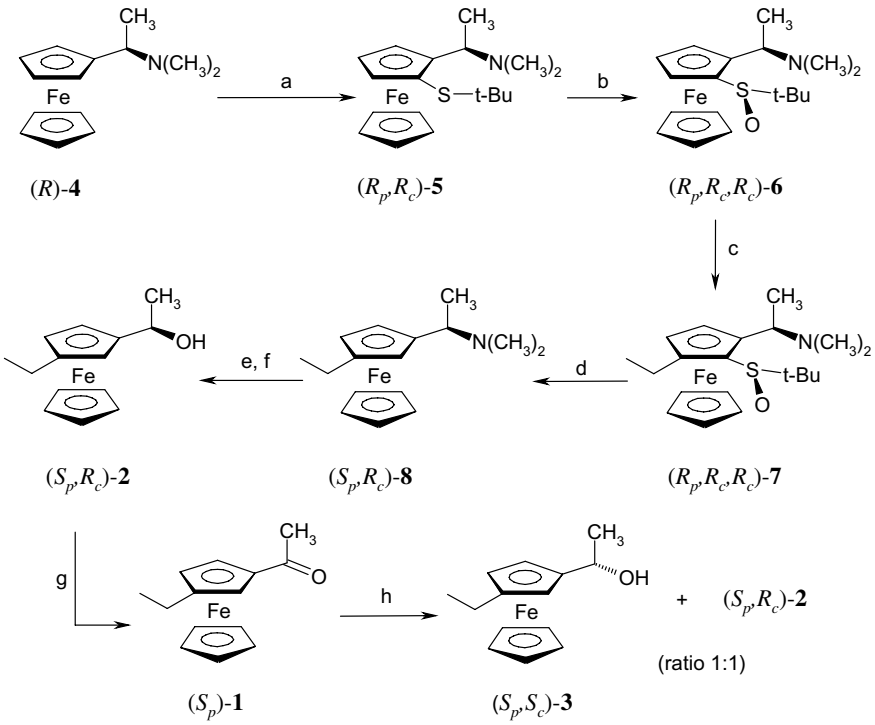
At this point the mixture (±)-**2**/(±)-**3** was submitted to esterification in TBME, with vinyl acetate as the acyl donor, in the presence of lipase from *C. antarctica* (Scheme 3).

The investigation by chiral HPLC of the reaction course showed the progressive decrease of alcohols (S_p,R_c)-**2** and (R_p,R_c)-**3**, transformed with different rates (Fig. 1) into esters (S_p,R_c)-**9** and (R_p,R_c)-**10**. After 4 h, the total conversion of the alcohols bearing an (*R*)-central configuration was observed, while the (*S*)-isomers remained unconverted even when prolonging the reaction time for 24 h. Unfortunately, the subsequent chromatographic separation of the esters from the unreacted alcohols proved unsuccessful, even when resorting to different supports. Moreover, due to the easy hydrolysis of the former, purification leads to a heavy fall in terms of chemical yield and consequential loss of enantiomeric purity of all the constituents of the reaction mixture.

This drawback was overcome by resorting to a chemical conversion of these sensitive esters into the corresponding homochiral amines. Thus in a preparative experiment, the final reaction pool was treated with dimethylamine transforming quantitatively the obtained esters (S_p,R_c)-**9** and (R_p,R_c)-**10** into amino compounds (S_p,R_c)-**8** and (R_p,R_c)-**11**, respectively. Partition between TMBE and water resulted in the easy separation of compounds possessing S_p,R_c and R_p,R_c configuration from those having R_p,S_c and S_p,S_c.



Scheme 1. Preparation of racemates (±)-**2** (A) and (±)-**3** (B). (a) CH_3COCl, $AlCl_3$, CH_2Cl_2, rt, 43%, Ref. 16b; (b) $LiAlH_4$, Et_2O, rt, 96%.



Scheme 2. Synthesis of enantiopure (S_pR_c)-**2** and (S_pS_c)-**3**. (a) BuLi, (t-BuS)$_2$, Et_2O, rt; (b) $NaIO_4$, H_2O/dioxane, rt, 39% overall Ref. 13; (c) BuLi, Et_2O, EtI, rt → reflux, 18%; (d) MeOH, Ni-Raney, reflux, 75%; (e) Ac_2O, TBME, reflux, 74%, Ref. 14; (f) K_2CO_3, EtOH, 90%; (g) MnO_2, Et_2O, rt, 95%; (h) $LiAlH_4$, Et_2O, rt, 95%.

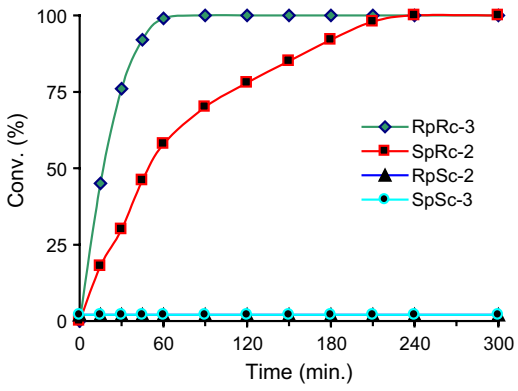


Figure 1. Conversion rate of mixture A and B constituents in the esterification catalysed by *C. antarctica* lipase.

The mixture of alcohols was then dissolved in hexane and left overnight at 0 °C to give (S_p,S_c)-**3** as a low-melting solid with 94% de. From the mother liquor, (R_p,S_c)-**2** was isolated with 90% de. Conversely, attempts at separating amines (S_p,R_c)-**8** and (R_p,R_c)-**11** by crystallisation were unsuccessful. Therefore, they were easily and quantitatively transformed into the corresponding homochiral alcohols which were separated as above, to furnish (R_p,R_c)-**3** and (S_p,R_c)-**2** with de >90%.

From an enzymatic point of view, it is noteworthy that in this separation process, lipase from *C. antarctica* possesses a high stereopreference in central chirality recognition. Furthermore, the different esterification rates observed between (S_p,R_c)-**2** and (R_p,R_c)-**3** indicate that lipase from *C. antarctica* has preferential recognition for isomers with an *R*-planar chirality, contrary to our previous observation for the resolution of 1,2-disubstituted hydroxymethylferrocenes.[11c]

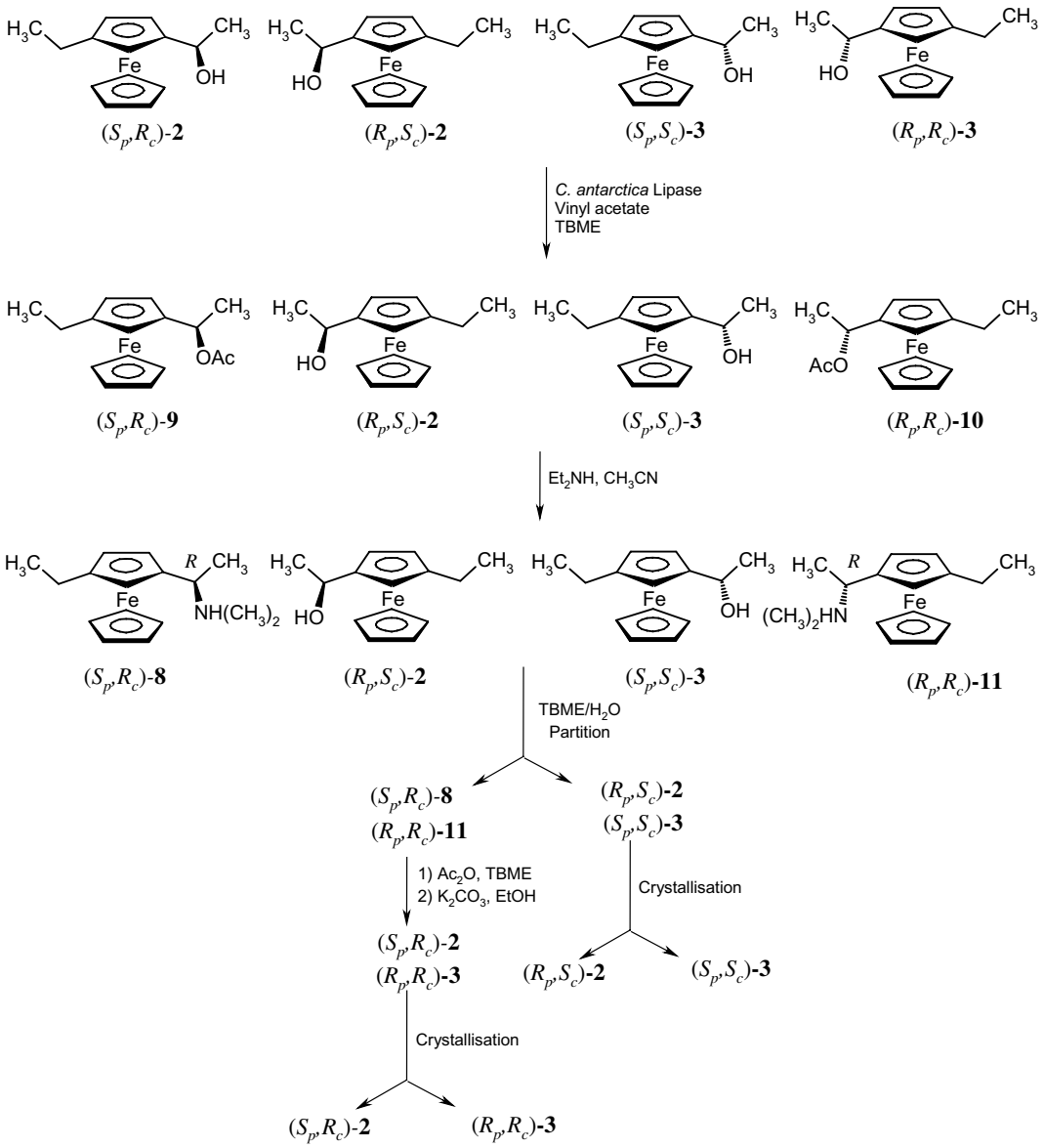
3. Conclusions

We have developed a suitable biocatalysed procedure to obtain the four stereoisomers of 1-(1-hydroxyethyl)-3-ethylferrocene in enantiopure form. Esterification catalysed by *C. antarctica* lipase allows a preliminary separation into two couples of diastereoisomeric alcohols, each separable by preferential crystallisation. Since 1-(1-hydroxyethyl)-3-ethylferrocene is able to undergo various transformations at the α-positions, the enantiomers obtained are the starting materials for the preparation of a variety of chiral 1,3-difunctionalysed ferrocenes.

4. Experimental

4.1. General

t-Butyl methyl ether (TBME) and all other solvents were purified or dried prior to use according to standard literature procedure. TLC analysis was performed with Merck 60 F_{254} silica gel plates. Column chromatography was conducted on Merck 60 silica gel (230–400 mesh). NMR spectra were recorded on a Bruker Avance 400 spectrometer operating at 400 MHz for hydrogen and at 100.62 MHz for carbon. Optical rotations were measured at 25 °C on a Jasco DIP 370 digital polarimeter. All biocatalysed reactions were monitored (conversion and



Scheme 3. Enantiomeric separation of (±)-**2**/(±)-**3**.

de values) by a Dionex HPLC apparatus (Dionex P580 pump, Dionex UV170S) equipped with Chiralcel-OD column (250 × 4.6 mm) using 0.5% of 2-propanol in hexane as eluent. Lipase from *C. antarctica* (Novozym 435®) was a gift from Novo Nordisk.

4.2. 1-Acetyl-3-ethylferrocene (±)-1

Ketone (±)-**1** was prepared according to the literature.[15] ^{13}C NMR ($CDCl_3$): δ = 14.41, 22.27, 27.29, 29.69, 68.82, 70.34, 71.96, 78.23, 95.82, 202.51.

4.3. 1-(1-Hydroxyethyl)-3-ethylferrocene (±)-2/(±)-3

To a solution of (±)-**1** (1.0 g, 3.9 mmol) in dry diethyl ether, aliquots of $LiAlH_4$ under stirring were added and the reaction monitored by TLC until total conversion of the substrate. The mixture was then partitioned three times with diethyl ether and 0.05 M H_2SO_4, the organic phases pooled and dried over Na_2SO_4. Evaporation of the solvent gave a equimolecular mixture of the two alcohols, (±)-**2** and (±)-**3** (990 mg). ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, J = 7.5 Hz, CH_2CH_3), 1.42 (d, J = 6.4 Hz, $CHCH_3$), 2.29 (q, J = 7.5 Hz, CH_2CH_3), 4.09 (m, *H*cp), 4.13 (m, *H*cp), 4.14 (s, cp'system), 4.16 (m, *H*cp), 4.47 (q, J = 6.4 Hz, $CHCH_3$). ^{13}C NMR ($CDCl_3$): δ = 14.38, 22.11, 23.48, 23.51, 65.13, 65.56, 65.87, 67.30, 67.36, 69.03, 91.37, 91.43, 94.04.

4.4. Preparation of reference samples, (S_p,R_c)-2 and (S_p,S_c)-3

Commercially available (*R*)-**4** was transformed into sulfoxide ($R_pR_cR_c$)-**6** (39% overall yield) following a multistep procedure reported by Ugi and co-workers[13] ($R_pR_cR_c$)-**6** (520 mg) was dissolved in dry ethyl ether (10 mL), at which point *t*-BuLi (1.8 mL, 1.7 M in pentane) was added and the mixture stirred at rt for 1 h. Ethyl iodide (900 μL) was then added and the solution refluxed for 5 h. Work-up of the reaction mixture, fol-

lowed by purification on SiGel column (acetone as the eluent) furnished 102 mg of ($R_pR_cR_c$)-**7** (18% yield). ^{1}H NMR ($CDCl_3$): δ = 1.11 (t, 8 Hz, 3H), 1.24 (d, 2 Hz, 3H), 1.25 (s, 9H), 2.04 (s, 6H), 2.34 (q, 7.4 Hz, 2H), 4.25–4.29 (m, 3H), 4.28 (s, cp'system). $[\alpha]_D = -140.0$ (*c* 0.2, $CHCl_3$). Sulfoxide **7** (80 mg) was dissolved in MeOH (4 mL), mixed with moist Ni-Raney (200 mg) and the suspension refluxed for 2 h. After cooling, the supernatant was decanted and the catalyst repeatedly washed with methanol. Evaporation of the solvent afforded 45 mg (75% yield) of (S_p,R_c)-**8**. ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 7.5 Hz, 3H), 1.41 (d, 10.1 Hz, 3H), 2.08 (s, 6H), 2.32 (q, 7.5 Hz, 2H), 3.53 (q, 1H), 4.00 (m, 1H), 4.03–4.06 (m, 2H), 4.05 (s, 5H). Amino derivative **8** (45 mg) dissolved in TBME (0.5 mL) and Ac_2O (0.5 mL), was refluxed for 1 h. Work-up of the reaction mixture furnished a residue that was treated with K_2CO_3/EtOH to give 30 mg (74% yield) of (S_p,R_c)-**2**. ^{1}H and ^{13}C NMR was in agreement with the structure. To (S_pR_c)-**2** dissolved in Et_2O was added 60 mg of MnO_2, and the suspension stirred at rt for 3 h to give 25 mg of (S_p)-**1**. ^{1}H and ^{13}C NMR data were in agreement with the structure. $[\alpha]_D = +43.9$ (*c* 0.4, $CHCl_3$). Reduction of (S_p)-**1** with $LiAlH_4$ in dry Et_2O furnished 20 mg of equimolecular (S_p,R_c)-**2** and (S_p,S_c)-**3**. ^{1}H NMR spectrum was in agreement with the structures.

4.5. Enantiomeric separation of (±)-2/(±)-3

To a solution of (±)-**2**/(±)-**3** (600 mg, 2.31 mmol) in TBME (60 mL) were added *C. antarctica* lipase (1.0 g) and vinyl acetate (855 μL, 11.4 mmol) and the mixture incubated at 45 °C under shaking (300 rpm). The reaction was monitored by chiral HPLC until complete disappearance of two constituents of the mixture (4 h). The reaction was then quenched, filtering off the enzyme and the solvent gently evaporated under vacuum to give 630 mg of a residue, which was then dissolved in 9 mL of CH_3CN and treated with 9 mL of dimethylamine (40 wt% solution in water) at 45 °C under stirring. After 12 h, a 10% solution of citric acid (30 mL) was added and the solution extracted three times with TBME. The organic phase was dried over Na_2SO_4 and the solvent removed to give 280 mg of a equimolecular mixture of alcohols (R_p,S_c)-**2** and (S_p,S_c)-**3**. The mixture was dissolved in hexane and left overnight at 0 °C, to give 115 mg of (S_p,S_c)-**3** as a yellow low-melting solid (de 94%). After concentration the mother liquor was left for 12 h as above to give a small amount of less de pure (S_p,S_c)-**3**. The filtrate was then taken to dryness to furnish 120 mg of (R_p,S_c)-**2** in 90% de. The aqueous phase was treated with a solution of NaOH until basic pH and extracted three times with TBME. The combined organic phases were dried over Na_2SO_4 and the solvent evaporated to afford 300 mg of an equimolecular mixture of (S_p,R_c)-**8** and (R_p,R_c)-**11**. ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, 7.5 Hz, $CH_2CH_3 \times 2$), 1.41 (d, 6.8 Hz, $CHCH_3$), 1.43 (d, 6.8 Hz, $CHCH_3$), 2.08 (s, $N(CH_3)_2$), 2.09 (s, $N(CH_3)_2$), 2.32 (dq, $CH_2CH_3 \times 2$), 3.54 (m, $CHCH_3 \times 2$), 4.00 (m, *H*cp), 4.03–4.04 (br s, *H*cp × 4), 4.06 (s, cp'system × 2), 4.09 (br s, *H*cp). ^{13}C NMR ($CDCl_3$): δ = 14.11, 14.25, 15.25, 16.01, 21.96, 22.05, 40.41, 40.61, 58.57, 58.61, 65.45, 66.30, 66.34, 68.09, 68.70, 68.89, 86.14, 86.34, 90.24, 90.42. The whole mixture was dissolved in 15 mL of TBME, to which was added 15 mL of Ac_2O, and refluxed for 1 h. The reaction was washed with $NaHCO_3$ solution, followed by partition between water and TBME, to furnish 284 mg of an equimolecular mixture of (S_p,R_c)-**9** and (R_p,R_c)-**10**. ^{1}H NMR ($CDCl_3$): δ = 1.18 (t, J = 2.7 Hz, $CH_2CH_3 \times 2$), 1.57 (d, J = 6.5 Hz, $CHCH_3$), 2.05 (s, $COCH_3 \times 2$), 2.35 (m, $CH_2CH_3 \times 2$), 4.11 (s, cp'system × 2), 4.14–4.23 (m, *H*cp × 6), 5.83 (q, J = 6.5 Hz, $CHCH_3$). ^{13}C NMR ($CDCl_3$): δ = 14.29, 14.38, 19.81, 21.44, 22.11, 64.79, 65.57, 67.31, 67.40, 67.69, 68.05, 69.22, 86.80, 90.50, 91.50, 170.51. Treatment of the mixture with K_2CO_3/EtOH gave the corresponding alcohols which were treated in hexane as above to furnish 105 mg of (R_p,R_c)-**3** in 94% de and 110 mg of (S_p,R_c)-**2** in 90% de.

4.5.1. 1-(1-Hydroxyethyl)-3-ethylferrocene, (R_p,S_c)-2. Yield, 80%; low-melting solid; $[\alpha]_D$ = +25.5 (*c* 1, $CHCl_3$); de 90%; ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, J = 7.5 Hz, CH_2CH_3), 1.43 (d, J = 6.4 Hz, $CHCH_3$), 2.34 (q, J = 7.5 Hz, CH_2CH_3), 4.10 (m, *H*cp), 4.13 (m, *H*cp, 1H), 4.14 (s, cp'system), 4.15(m, *H*cp), 4.51 (q, J = 6.4 Hz, $CHCH_3$). ^{13}C NMR ($CDCl_3$): δ = 14.26, 21.99, 23.40, 65.01, 65.44, 65.75, 67.24, 68.91, 91.31, 93.92. Anal. Calcd for $C_{14}H_{18}FeO$: C, 65.14; H, 7.03. Found: C, 65.01; H, 6.95.

4.5.2. 1-(1-Hydroxyethyl)-3-ethylferrocene, (S_p,S_c)-3. Yield, 76%; low-melting solid; $[\alpha]_D$ = +24.2 (*c* 0.6, $CHCl_3$); de 94%; ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, J = 7.5 Hz, CH_2CH_3), 1.43 (d, J = 6.4 Hz, $CHCH_3$), 2.34 (q, J = 7.5 Hz, CH_2CH_3), 4.10 (m, *H*cp), 4.13 (m, *H*cp), 4.14 (s, cp'system), 4.16 (m, *H*cp), 4.51 (q, J = 6.4 Hz, $CHCH_3$). ^{13}C NMR ($CDCl_3$): δ = 14.30, 21.99, 23.44, 64.77, 65.46, 65.54, 67.05, 68.62, 90.99, 93.71. Anal. Calcd for $C_{14}H_{18}FeO$: C, 65.14; H, 7.03. Found: C, 64.90; H, 6.94.

4.5.3. 1-(1-Hydroxyethyl)-3-ethylferrocene, (S_p,R_c)-2. Yield 73%, low-melting solid, $[\alpha]_D = -25.8$ (*c* 1, $CHCl_3$); de 90%.

4.5.4. 1-(1-Hydroxyethyl)-3-ethylferrocene, (R_p,R_c)-3. Yield 70%, low-melting solid; $[\alpha]_D = -24.6$ (*c* 0.6, $CHCl_3$); de 94%.

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