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Synthesis of chiral alcohols containing the 1,3-diferrocenylpropane structural motif

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ABSTRACT

The Claisen–Schmidt condensation of ferrocenecarboxaldehyde with acetylferrocene under microwave irradiation was applied as a simple route to gain access to 1,3-diferrocenyl-1-oxo-prop-2-ene **2**, whereas the analogous reaction with 1,1′-diacetylferrocene afforded the 1,1′-disubstituted α,β-enone **13** with three ferrocene units and/or 1,5-dioxo-3-ferrocenyl[5]ferrocenophane **14**, depending on the experimental conditions. Michael addition of acetylferrocene enolate to **2** afforded 1,3,5-triferrocenyl-1,5-dioxopentane **7**, whose formation was also evidenced during the double bond hydrogenation of **2** on Pd/C as a result of an unusual reaction.

The study of the asymmetric reduction of **2** in the presence of CBS/borane system revealed that this enone was not a suitable substrate for the reaction, with it mainly being converted into the corresponding alkene. On the other hand, the reduction of the saturated ketones proceeded with high stereoselectivity affording novel chiral ferrocenylalcohols possessing multiple ferrocene units.

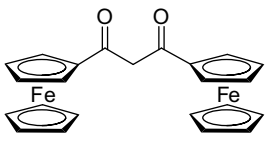
1. Introduction

Chiral ferrocenylalcohols are important starting materials for the synthesis of ferrocene-based ligands active in asymmetric catalysis,[1] since they undergo a peculiar nucleophilic substitution with retention of configuration giving rise to several related derivatives.[2] A large number of alcohols with different patterns of substitution on the ferrocene scaffold have been prepared in enantiopure form via asymmetric synthesis,[3] or biocatalysed kinetic resolution of their racemates.[4]

Derivatives possessing more than one ferrocene unit in their structure have attracted some interest as multielectron redox systems useful as selective receptors and sensors,[5] molecular electronic devices and material with specific magnetic, conductive or optical properties.[6]

Among the compounds in which two ferrocene units are linked by an aliphatic chain, the 1,2-diferrocenylethane derivatives have been prepared via the samarium-promoted coupling of α-substituted ferrocenecarboxaldehydes;[3c,7] the synthesis of 1,4-diferrocenyl-1,4-dioxobutane and 1,5-diferrocenyl-1,5-dioxopentane has also been reported, and some related enantiopure diols and/or amines have been evaluated as catalysts.[8]

The 1,3-diferrocenylpropane unit is accessible from the reaction of acetylferrocene enolate with ferrocene carboxylate or ferrocenecarboxaldehyde;[9] using this method, diketone **1** and its metal complexes, as well as diferrocenylenone **2**, have been prepared and their biological activities evaluated;[10] the corresponding chiral derivatives have, however, not been reported. The Claisen–Schmidt condensation of 1,1′-diacetylferrocene and aldehydes has been also described,[11] and we have recently seen that under microwave



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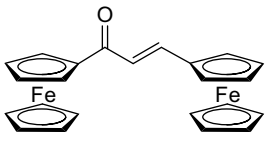

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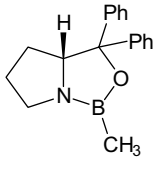

(*R*)-CBS, **3**

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irradiation, the reaction can be driven towards the selective formation of [5]ferrocenophanes.[12]

As part of our research project on the asymmetric reduction of ferrocenylketones for the preparation of novel optically active ferrocenylalcohols,[13] we prepared some ketones containing the 1,3-diferrocenylpropane structural motif with the aim of investigating their reduction in the presence of the oxazaborolidine/borane system; herein, we report the results obtained.

2. Results and discussion

2.1. Synthesis of 1,3-diferrocenylpropane derivatives

The reduction of ketones in the presence of Corey–Bakshi–Shibata oxazaborolidine **3** (CBS)[14] has been successfully applied to the synthesis of several enantiopure ferrocenylalcohols[3b,13a] and diols;[3d,8b,c,13b,c] we have recently reported that the reaction is effective for the preparation of 1-ferrocenyl-1,3-diols providing that the starting substrate is the 1,3-O-protected aldol rather than the 1,3-diketone.[13c] On this basis, at the onset of our work, we focused our attention on aldol **4** as a useful substrate from which to access chiral difunctionalised 1,3-diferrocenylpropanes. Unfortunately, this compound showed a strong tendency to dehydrate giving the corresponding enone **2**; hence, all attempts to perform the O-protection step failed. This behaviour, which had not been observed in the series of 1-ferrocenyl-1,3-diketones, could be explained by the stabilisation within the highly conjugated chalcone **2**. The direct synthesis of **2** was achieved by Claisen–Schmidt condensation between acetylferrocene and ferrocenecarboxaldehyde; the optimal conditions for a nearly quantitative yield were found by carrying out the reaction without solvent under microwave irradiation for 10 min (Scheme 1).

When **2** was subjected to CBS-mediated reduction, the substrate was readily consumed to give a mixture of *trans*-1,3-diferrocenylprop-1-ene **5** and 1,3-diferrocenyl-1-oxopropane **6**; although this reaction course was in contrast with the reported CBS-reduction of acyclic enones to give the corresponding allylic alcohols,[15] the borane-promoted deoxygenation of ferrocenylketones had been observed in some instances.[13b,16]

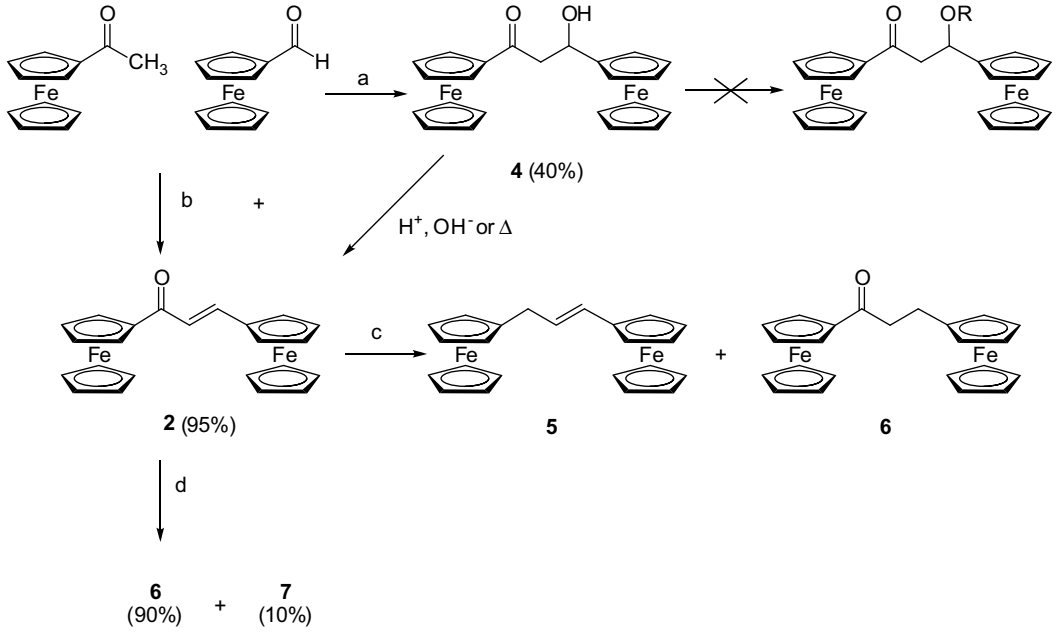
In the search for a more suitable ketone as a substrate for the CBS-promoted reduction, the functionalisation of **2** via Michael addition of nucleophiles ($BzNH_2$, BzOH, NaN_3) was attempted in the presence of different catalysts ($CeCl_3$, TBAI, Amberlyst-15, β-cyclodextrin,)[17] as well as in the catalyst-free conditions specifically reported for ferrocenylenones;[18] however, all the reactions did not proceed significatively.

Hydrogenation of **2** with Pd/C gave **6**, which was found to be a good substrate for the asymmetric reduction with (*R*)-**3**/BH_3 system; using our standard conditions (30% catalyst, THF, 0 °C) the reaction proceeded stereoselectively to give alcohol (+)-**8** in 85% isolated yield and 97% ee, whose (*S*)-absolute configuration was assigned on the basis of the known stereochemical course of the reaction.[14] Alcohol (+)-**8** can be easily converted into enantiopure derivatives via nucleophilic substitution on the intermediate acetate; by this route, dimethylaminoferrocene (+)-**9** and azidoferrocene (+)-**10** were prepared in high yield and enantiomeric purity (Scheme 2).

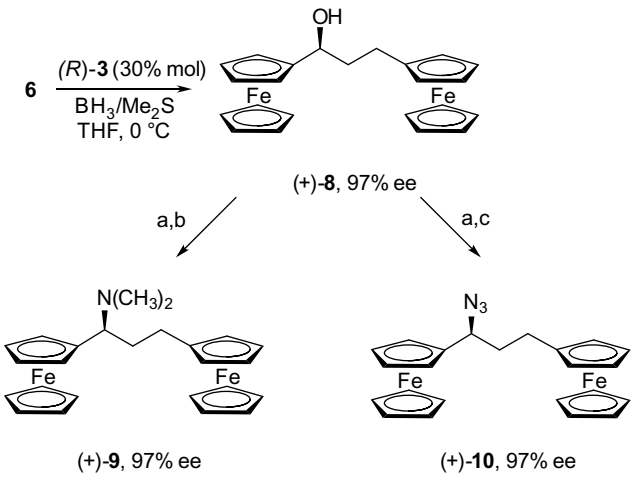
In an attempt to confirm this absolute configuration by NMR, alcohol (+)-**8** was converted into two diastereoisomeric esters by reaction with (*R*)- and (*S*)-methoxyphenylacetic acid (MPA),[19] respectively; however, the differences in the chemical shifts of the two substituents (cyclopentadienyl ring and methylenic units) linked to the stereogenic carbon of (+)-**8** could not be evaluated due to overlapping with other resonances. However, assuming that a ferrocene system should exert a shielding effect similar to the phenyl group, the observed $\Delta\delta_{RS}$ for the resonances of methoxyacetic moiety appeared consistent with an (*S*)-configuration of (+)-**8** (Fig. 1).

2.2. Synthesis of 1,3,5-triferrocenylpentane derivatives

The hydrogenation of **2** with H_2 on Pd/C afforded the expected saturated ketone **6** together with 1,3,5-triferrocenyl-1,5-dioxopentane **7** in a 9:1 ratio independent of the substrate/catalyst ratio or hydrogen pressure, and the same unusual reaction course was also observed when ammonium formate was used as a hydrogen source. The spectrum of **7** showed two sets of resonances for cyclopentadienyl protons in a 2:1 ratio, an AB system, each part being a



Scheme 1. Condensation of ferrocenecarboxaldehyde and acetylferrocene. Reagents and conditions: (a) LDA, THF, −50 °C; (b) NaOH (5 equiv), 80 °C, 50 W Mw, 10 min; (c) (*R*)-**3** (30 mol %) BH_3Me_2S (1.0 mol), THF, 0 °C; (d) H_2 (1.2 atm), C/Pd, CH_2Cl_2.



Scheme 2. Synthesis of chiral 1,3-diferrocenylpropanes. Reagents: (a) Ac_2O, Py; (b) aq $NH(CH_3)_2$ in CH_3CN; (c) NaN_3, CH_3CN/H_2O.

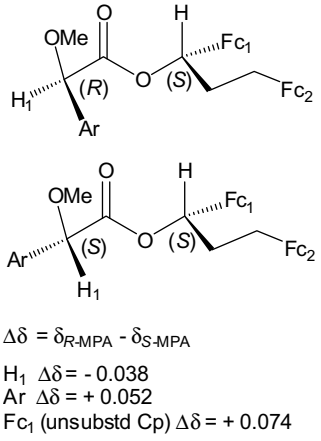


Figure 1. Chemical shift differences in diastereomeric (+)-**8** esters with (*R*)- and (*S*)-methoxyphenylacetic acid (MPA).

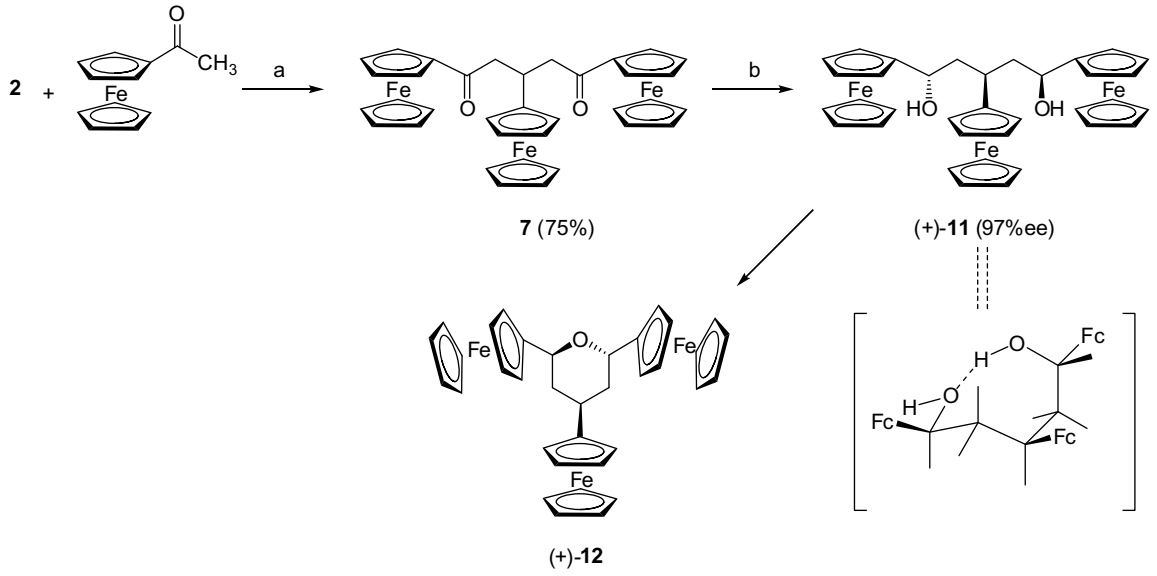
double doublet, accounting for the four methylenic protons and a multiplet for the methinic proton.

The direct synthesis of diketone **7**, which had been previously obtained by Liu et al.[20] as a side-product in only 5% yield, was attempted via the addition of acetylferrocene enolate to **2** under different conditions; the maximum isolated yield (75%) of the target diketone was achieved by carrying out the reaction with a moderate excess of acetylferrocene under microwave irradiation without any solvent (Scheme 3).

Preliminary chemical reduction of **7** with $NaBH_4$ or $LiAlH_4$ and chiral HPLC analysis of the reaction mixture allowed us to identify all three possible diols deriving from the diketone; two of them are *meso*-forms possessing the C-3 ferrocene in a *trans* or *cis*-relationship with both the adjacent hydroxyl groups, whereas the third diol, **11**, exists as racemate and it was eluted as baseline separated enantiomers. The asymmetric reduction of **7** with borane in the presence of (*R*)-**3** proceeded with complete diastereoselectivity and high stereoselectivity to give (+)-**11** as the sole diol in 97% ee whose (*S*,*S*)-configuration was assigned by analogy with (+)-**8** and the reported 1,4- and 1,5-diferrocenylderivatives.[8b,c]

The NMR spectra of **11** displayed single resonances for all the protons and carbons in the molecule as proof of its unsymmetrical nature; the two methinic protons bearing the hydroxyl groups gave two double doublets with the same coupling constants (J = 3.5 and 9.9 Hz) with the vicinal methylenic protons, which were observed as four separated resonances with a double double doublet pattern. The chemical shifts of the hydroxyl protons resonances were found to be independent of the sample concentration so that an intramolecular hydrogen bond, giving rise to a distorted cyclooctane conformation, could be reasonable. In this cyclic conformation, the observed J-values of the C-3 methinic proton are in agreement with its *trans*-diaxial relationship with two adjacent protons so that the equatorial disposition of the ferrocenyl unit on C-3 can be deduced.

The observed tendency of diol **11** to spontaneously undergo cyclisation into ether **12** on standing in solution of aprotic organic solvents (complete conversion in $CDCl_3$ after 4 h was detected) could be related to its strong intramolecular hydrogen bond that promotes the correct orientation for nucleophilic attack of an alcoholic group on the other. Dissolving **11** in EtOH, where



Scheme 3. Synthesis of 1,3,5-triferrocenylpentane derivatives. In brackets, proposed conformation for (+)-**11**. Reagents and conditions: (a) NaOH (5 equiv), 80 °C, 50 W Mw, 90 min; (b) (*R*)-**3** (60 mol %) BH_3Me_2S (2.0 mol), THF, 0 °C.

intermolecular hydrogen bonds could be more effective than the intramolecular ones, the diol was indeed stable and recovered unchanged after 24 h.

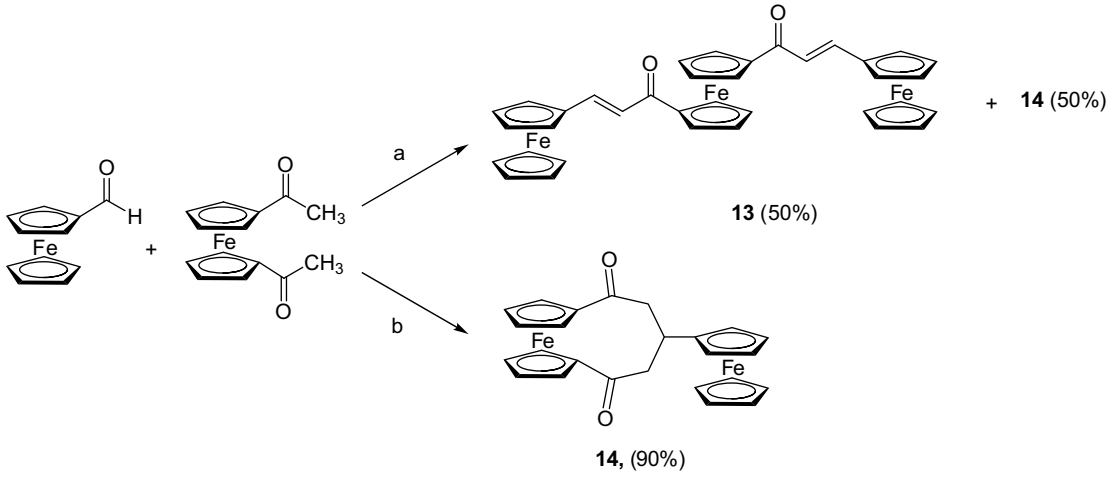
The above cyclisation occurred with retention of configuration, as deduced by the retained optical activity of (+)-**12**, that also displayed the NMR spectral features of the parent diol, whereas an inversion of configuration should give a symmetrical *meso*-compound.

2.3. Claisen–Schmidt condensation of 1,1′-diacetylferrocene with ferrocenecarboxyaldehyde

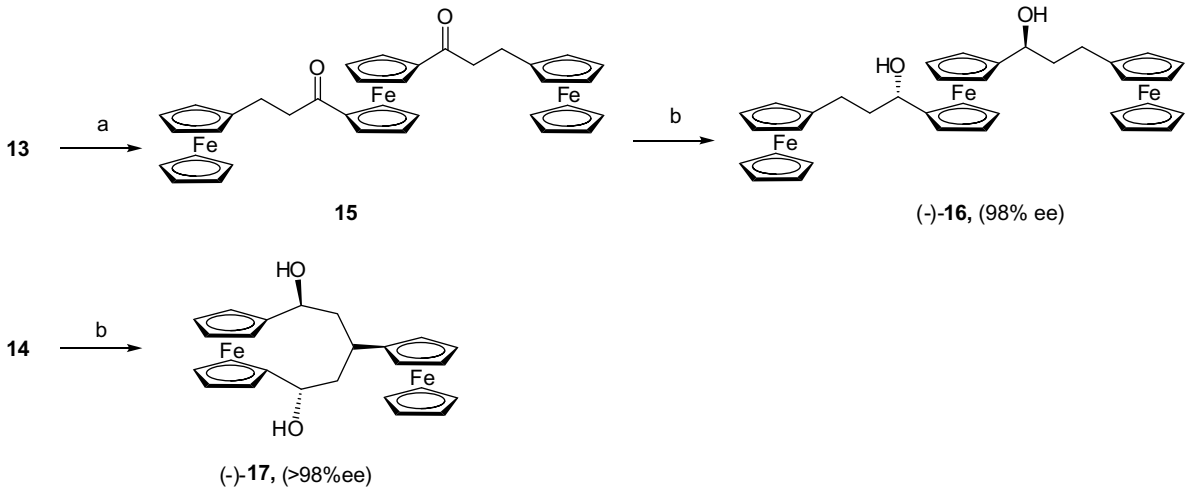
The reaction of 1,1′-diacetylferrocene enolate with aldehydes has been reported for the synthesis of 1,1′-dienoyl derivatives, which were prepared in high yield using 4–6 equiv excess of aldehyde in dry conditions.[11] However, these conditions were not effective, with ferrocenecarboxaldehyde giving low substrate conversion (43% at 24 h time reaction) and a mixture of mono- and dienoyl derivatives together with [5]ferrocenophane **14**. Under microwave irradiation at 80 °C without solvent, the reaction rate was consistently increased and complete conversion of 1,1′-diacetylferrocene was achieved in 30 min; however, the formation of **14** could not be suppressed and under optimal conditions, **13** and **14** were obtained in a 1:1 ratio.

Conversely, in EtOH–water 4:1 solution the reaction is driven towards the exclusive formation of the [5]ferrocenophane system, and an equimolar ratio of 1,1′-diacetylferrocene and ferrocenylcarboxaldehyde is sufficient to obtain **14** in 90% yield, easily isolated in pure form exploiting its low solubility in common organic solvents other than CH_2Cl_2 (Scheme 4).[12]

In analogy with enone **2**, dienoyl derivative **13** was converted into **15** as a more suitable substrate for the asymmetric reduction, which was carried out in CH_2Cl_2/THF mixture in order to have good solubility of the diketone. The expected diol (−)-**16** was obtained in 98% enantiomeric excess and a 96:4 diastereoisomeric ratio, as determined by chiral HPLC after conversion into the corresponding dimethoxy derivative (Scheme 5). The (*S*,*S*)-configuration was assigned to diol (−)-**16** in analogy with (+)-**8** and, on the basis of the observation that the CBS-catalysed asymmetric reduction of monosubstituted ferrocenylketones as well as the related 1,1′-disubstituted diketones, proceeded with the same stereochemical outcome.[3b,d] Compounds **13**, **15** and **16** showed a noteworthy similarity in their NMR spectra with the corresponding monosubstituted ferrocenes **2**, **6** and **8**, and it seems reasonable to assume that the two 1,1′-substituents did not exert any mutual influence.



Scheme 4. Claisen–Schmidt condensation of ferrocenecarboxaldehyde and 1,1′-diacetylferrocene. Reagents and conditions: (a) NaOH (5 equiv), 80 °C, 50 W Mw, 30 min; (b) NaOH (5 equiv), EtOH/H_2O (4:1), 80 °C, 50 W Mw, 30 min.



Scheme 5. Asymmetric reduction of ferrocenyldiketones. Reagents and conditions: (a) H_2 (1.2 atm), C/Pd, CH_2Cl_2; (b) (*R*)-**3** (60 mol %) BH_3Me_2S (2.0 mol), CH_2Cl_2/THF, 0 °C.

In the same way, the CBS-promoted reduction of **14** was performed in CH_2Cl_2/THF mixture and proceeded with excellent stereoselectivity affording, among three possible diols, only [5]ferrocenophane (−)-**17** in 70% yield and >98% ee. This diol displayed the NMR spectral features expected for an asymmetric compound and was eluted as a resolved couple of enantiomers on chiral stationary phase so that it was easily distinguished from the other two possible *meso*-forms, each of them revealed its symmetry by NMR and was detected as a single peak by chiral HPLC analysis.

Also in this case, the *S*,*S* absolute configuration was ascribed to (−)-**17** as an extension of the assignment reported for the CBS-promoted reduction of a related monoketone.[21]

3. Conclusions

The condensation reactions of ferrocenylenolates with ferrocenecarboxaldehyde or enone **2** were carried out efficiently under microwave irradiation under dry conditions or in solution; compared with the same reactions with conventional heating, we evidenced a higher reaction rate and selectivity resulting in good to excellent yields of the desired products. The CBS/borane-promoted reduction of the saturated ketones **6**, **7**, **13** and **15** was found to be an efficient way to prepare new ferrocenylalcohols with high enantio- and diastereomeric purity that can be considered as the starting material for the synthesis of related derivatives with different functional groups. The presence of multiple ferrocene units and a cyclic cavity in the case of [5]ferrocenophane system make these compounds attractive in the development of novel ligands, sensors or materials with peculiar electronic properties, and the investigation of their properties is currently in progress.

4. Experimental

4.1. General methods

Reactions under microwave irradiation were performed in a CEM Discover Benchmate equipped with a pressure control device. Microprills sodium hydroxide was purchased from Riedel-de-Haën. Synthesis of **4** and **14** was performed according to reported procedures.[4f,12] The asymmetric reductions were carried out under argon using standard Schlenk apparatus; THF and CH_2Cl_2 were distilled over sodium/benzophenone ketyl and CaH_2, respectively. Oxazaborolidine (*R*)-**3** (1 M solution in toluene) and $BH_3{\cdot}Me_2S$ (2 M solution in THF) were purchased from Aldrich. Column chromatography was performed on silica gel 60 (230–400 mesh) using the specified eluants. Chiral HPLC analyses were carried out on a thermostatted Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane–EtOH mixtures as mobile phase and UV- detection at 250 nm. ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.62 MHz, respectively, in $CDCl_3$. Chemical shifts (δ) are given as ppm relative to the residual solvent peak and coupling constants (J) are in hertz. In the ^{1}H NMR assignment Cp and Cp′ refers to protons on the substituted and unsubstituted cyclopentadienyl ring, respectively. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument.

4.2. General procedure for microwave-assisted synthesis

The solid reactants (0.5 mmol scale) were mixed in a closed vessel and maintained at 80 °C under vigorous stirring and microwave irradiation (50 W power) until TLC analysis showed the disappearance of the substrate. The reaction mixture was then suspended in saturated NH_4Cl and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4 and taken to dryness to give a residue that was purified on Si gel column using the specified eluents.

4.2.1. 1,3-Diferrocenyl-1-oxo-prop-2-ene, 2

Ferrocenecarboxaldehyde, acetylferrocene and NaOH were mixed in a 1:1:5 mol ratio for 10 min and after work-up, enone **2** was isolated (SiO_2, *n*-hexane–AcOEt 8:2, R_f 0.30) in 95% yield and identified by comparison with its reported spectroscopic data.[9c]

4.2.2. 1,3,5-Triferrocenyl-1,5-dioxopentane, 7

Enone **2**, acetylferrocene and NaOH were mixed in 1:4:5 mol ratio and left to react for 90 min (3 × 30 min). After purification (SiO_2, *n*-hexane–AcOEt 8:2, R_f 0.25), the diketone was obtained in 75% yield, mp 184–185 °C, ^{1}H NMR δ: 3.11 (dd, 2H, J = 5.7 and 16.4, $-CH_{2a}$), 3.23 (dd, 2H, J = 7.2 and 16.4, $-CH_{2b}$), 3.75 (m, 1H, –CH), 4.10 (s, 2H, Cp), 4.15 (s, 5H, Cp′), 4.16 (s, 10H, 2 × Cp′), 4.19 (s, 2H, Cp), 4.50 (s, 4H, Cp), 4.81 (s, 2H, Cp), 4.85 (s, 2H, Cp). ^{13}C NMR δ: 30.74, 45.49, 67.36, 67.48, 68.52, 69.26, 69.42, 69.78, 72.12, 79.44, 93.21, 203.13.

4.2.3. 1,1′-Bis(β-ferrocenylacryloyl)ferrocene 13

1,1′-Diacetylferrocene, ferrocenecarboxaldehyde and NaOH in a 1:4:10 mol ratio were subjected to three cycles of 10 min each of microwave irradiation. After partitioning the reaction mixture between saturated NH_4Cl and CH_2Cl_2, the organic phase was taken to dryness. The residue was suspended in *n*-hexane and the solution containing the excess of ferrocenecarboxaldehyde was discarded. The insoluble solid was separated, dissolved in CH_2Cl_2 and purified by Si gel chromatography (*n*-hexane–AcOEt:CH_2Cl_2 3:1:1, R_f 0.35) to afford pure **13** as a deep red solid in 45% yield, mp 238–239 °C (dec), ^{1}H NMR δ: 4.21 (s, 10H, Cp′), 4.49 (t, 4H, J = 1.7, Cp), 4.55 (t, 4H, J = 1.9, Cp), 4.63 (t, 4H, J = 1.7, Cp), 4.87 (t, 4H, J = 1.9, Cp), 6.72 (d, 2H, J = 15.3, –CH), 7.74 (d, 2H, J = 15.3, –CH). ^{13}C NMR δ: 69.01, 69.81, 71.16, 71.22, 74.17, 79.28, 82.17, 119.91, 143.40, 191.45. Anal. Calcd for $C_{36}H_{30}Fe_3O_2$: C, 65.30; H, 4.57. Found: C, 65.98; H, 4.63.

4.3. General procedure for the hydrogenation of enones

To a solution of enone (0.25 mmol) in CH_2Cl_2 (5 mL), 10% palladium on charcoal (50 mg) was added and the suspension was stirred and maintained at room temperature under a H_2 atmosphere (1.2 atm) until the red solution turned to orange and TLC analysis showed complete conversion of the substrate. The suspension was then filtered on a short plug of Celite, and the solution concentrated in vacuo to give a residue that was purified by chromatography.

4.3.1. 1,3-Diferrocenyl-1-oxopropane, 6

Hydrogenation of **2** as above afforded **6** and **7** in a 9:1 ratio, as determined by ^{1}H NMR analysis of the reaction mixture. Pure **6** was recovered from Si gel chromatography (*n*-hexane–Et_2O 9:1, R_f 0.22) in 85% yield, mp 123–124 °C, ^{1}H NMR δ: 2.77 (br t, 2H, $-CH_2$), 2.92 (br t, 2H, $-CH_2$), 4.08 (m, 2H, Cp), 4.15 (s, 12H, Cp′ and Cp), 4.49 (t, 2H, J = 1.9, Cp), 4.77 (t, 2H, J = 1.9, Cp). ^{13}C NMR δ: 24.25, 41.52, 67.41, 68.33, 68.57, 69.29, 69.72, 72.17, 79.08, 88.27, 203.39. Anal. Calcd for $C_{23}H_{22}Fe_2O$: C, 64.83; H, 5.20. Found: C, 65.32; H, 5.28.

Further elution with *n*-hexane–AcOEt 8:2 gave **7** in 9% yield.

4.3.2. 1,1′-Bis(3-ferrocenylpropanoyl)ferrocene 15

Hydrogenation of **13** and subsequent purification of the reaction mixture (SiO_2, *n*-hexane–AcOEt 8:2, R_f 0.26) gave **15** in 80% isolated yield, mp 170–171 °C, ^{1}H NMR δ: 2.76 (m, 4H, $-CH_2$), 2.83 (m, 4H, $-CH_2$), 4.08 (m, 4H, Cp), 4.16 (s, 10H, Cp′), 4.18 (m, 4H, Cp), 4.40 (t, 4H, J = 1.9, Cp), 4.69 (t, 4H, J = 1.9, Cp). ^{13}C NMR

δ: 23.91, 41.71, 67.43, 68.44, 68.58, 70.48, 73.37, 80.31, 88.04, 202.41. Anal. Calcd for $C_{36}H_{34}Fe_3O_2$: C, 64.90; H, 5.14. Found: C, 65.45; H, 5.21.

4.4. General procedure for CBS-catalysed reduction of ketones

A representative procedure is described for the asymmetric reduction of **6**. (*R*)-CBS (0.14 mmol, 0.14 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, 0.24 mL, 0.47 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 **6** (200 mg, 0.47 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 the quantitative conversion of the substrate was observed, the reaction was quenched by the careful dropwise addition of MeOH (2 mL), diluted with saturated 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 purified on Si gel column (*n*-hexane–Et_2O 7:3, R_f 0.28) to give (*S*)-1,3-diferrocenyl-1-hydroxypropane, (+)-**8** (170 mg, 85% yield, 97% ee) as a yellow solid, mp 126–127 °C, $[\alpha]_D$ = +18.2 (*c* 0.7, $CHCl_3$), ^{1}H NMR δ: 1.90 (m, 2H, $-CH_2$), 1.97 (d, 1H, *J* = 3.5, –OH), 2.39 (ddd, 1H, *J* = 6.3, 10.0 and 14.4, $-CH_{2a}$), 2.52 (ddd, 1H, *J* = 5.3, 10.2 and 14.4, $-CH_{2b}$), 4.07 (m, 3H, Cp), 4.10 (s, 5H, Cp′), 4.21 (br s, 9H, Cp′ and Cp), 4.27 (s, 1H, Cp), 4.35 (m, 1H, –CH); ^{13}C NMR δ: 25.82, 39.23, 67.10, 67.17, 67.78, 67.86, 67.96, 68.11, 68.24, 68.46, 69.16, 88.70, 94.21. HPLC: *n*-hexane–EtOH 98:2, 30 °C, flow 0.5 mL/min, t_R/min = 27.9 (*S*) and 30.5 (*R*). Anal. Calcd for $C_{23}H_{24}Fe_2O$: C, 64.52; H, 5.65. Found: C, 64.72; H, 5.68.

4.5. (*S,S*)-1,3,5-Triferrocenyl-1,5-dihydroxypentane (+)-11

Diketone **7** (150 mg, 0.23 mmol) was dissolved in THF and reacted with (*R*)-**3** (0.14 mmol) and $BH_3{\cdot}Me_2S$ (0.46 mmol) as above described. After 1 h at room temperature, the reaction was quenched with MeOH and subjected to the usual work-up. Purification on Si gel column (*n*-hexane–AcOEt 8:2, R_f 0.17) gave (+)-**11** (105 mg, 70% yield, 97% ee), mp 76–77 °C, $[\alpha]_D$ = +2.6 (*c* 0.6, $CHCl_3$), ^{1}H NMR δ: 1.72 (ddd, 1H, *J* = 3.5, 7.9 and 13.6, $-CH_{2a}$), 1.81 (ddd, 1H, *J* = 3.5, 9.6 and 13.7, $-CH_{4a}$), 2.08 (ddd, 1H, *J* = 4.1, 9.9 and 13.6, $-CH_{2b}$), 2.24 (br s, 1H, –OH), 2.29 (ddd, 1H, *J* = 3.5, 9.9 and 13.7, $-CH_{4b}$), 2.43 (br s, 1H, –OH), 2.90 (m, 1H, –C(3)H), 3.97 (s, 1H, Cp), 4.09 (s, 1H, Cp), 4.12 (m, 2H, Cp), 4.15 (br s, 12H, Cp and Cp′), 4.21 (m, 3H, Cp), 4.22 (br s, 6H, Cp and Cp′), 4.26 (s, 1H, Cp), 4.32 (s, 1H, Cp). ^{13}C NMR δ: 31.73, 44.09, 44.53, 65.46, 65.61, 66.00, 66.92, 67.20,67.76, 67.82, 67.90, 67.97, 68.28, 68.33, 68.54, 94.28, 94.62, 94.77. HPLC: *n*-hexane–EtOH 9:1, 25 °C, flow 1.0 mL/min, t_R/min = 9.4 (*S,S*), 10.6 (*R,R*), 11.9 (*meso*-diol) and 14.4 (*meso*-diol). Anal. Calcd for $C_{35}H_{36}Fe_3O_2$: C, 64.06; H, 5.53. Found: C, 64.34; H, 5.55.

On standing in a solution, (+)-**11** in CH_2Cl_2 was slowly converted into (*S,S*)-2,4,6-triferrocenyltetrahydropyrane, (+)-**12** and the process was accelerated in the presence of acidic or basic agents and suppressed in EtOH. A pure sample of (+)-**12** was obtained by column chromatography (Si gel, *n*-hexane–Et_2O 9:1, R_f 0.40), mp 194–195 °C, $[\alpha]_D$ = +7.6 (*c* 0.4, $CHCl_3$), ^{1}H NMR δ: 1.55 (m, 1H, $-CH_{2a}$), 1.95 (ddd, 1H, *J* = 6.0, 12.4 and 13.5, $-CH_{4a}$), 2.08 (m, 1H, $-CH_{2b}$), 2.35 (m, 1H, $-CH_{4b}$), 2.86 (dt, 1H, *J* = 3.6 and 12.4, –C(3)H), 4.10 (br s, 6H, Cp and Cp′), 4.15 (m, 6H, Cp and CHO), 4.16 (s, 5H, Cp′), 4.21 (br s, 6H, Cp and Cp′), 4.24 (m, 1H, Cp), 4.27 (m, 1H, Cp), 4.32 (m, 1H, Cp), 4.59 (m, 1H, Cp), 5.70 (m, 1H, –CHO) ^{13}C NMR δ: 31.56, 34.78, 40.48, 65.79, 65.82, 66.11, 67.08, 67.19, 67.24, 67.47, 67.63, 67.70, 68.12, 68.33, 68.57, 68.94, 69.81, 72.67, 87.60, 90.18, 94.40. Anal. Calcd for $C_{35}H_{34}Fe_3O$: C, 65.87; H, 5.37. Found: C, 66.23; H, 5.47.

4.6. (*S,S*)-1,1′-Bis(3-ferrocenyl-1-hydroxypropyl)ferrocene (−)-16

Compound **15** (100 mg, 0.15 mmol) was dissolved in CH_2Cl_2 (10 mL) and reacted with (*R*)-**3** (0.09 mmol) and $BH_3{\cdot}Me_2S$ (0.30 mmol) in THF (10 mL) according to the general procedure for 1 h at 0 °C. After the work-up, the residue was purified on Si gel (*n*-hexane–Et_2O 7:3, R_f 0.17) to afford (−)-**16** as a viscous oil (80 mg, 80% yield, 98% ee, 96:4 diastereomeric ratio), $[\alpha]_D$ = −2.7 (*c* 0.3, $CHCl_3$), ^{1}H NMR δ: 1.85 (m, 4H, $-CH_2$), 2.42 (m, 4H, $-CH_2$), 3.68 (br s, 2H, –OH), 4.05 (s, 6H, Cp), 4.08 (s, 12H, Cp and Cp′), 4.17 (br s, 4H, Cp), 4.20 (m, 2H, Cp), 4.25 (m, 2H, Cp), 4.52 (dd, *J* = 5.4 and 6.9, –CH); ^{13}C NMR δ: 25.53, 40.82, 66.10, 66.55, 67.14, 67.68, 67.87, 68.02, 68.47, 69.79, 88.57, 93.77. HPLC of the corresponding methoxyderivative: *n*-hexane–EtOH 9:1, 25 °C, flow 1.0 ml/min, t_R/min = 15.4 (*S,S*), 16.8 (*R,S*), 20.7 (*R,R*). Anal. Calcd for $C_{36}H_{38}Fe_3O_2$: C, 64.51; H, 5.71. Found: C, 64.78; H, 5.74.

4.7. (*S,S*)-1,5-Dihydroxy-3-ferrocenyl[5]ferrocenophane (−)-17

Diketone **14** (150 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (20 mL) and reacted with (*R*)-**3** (0.19 mmol) and $BH_3{\cdot}Me_2S$ (0.64 mmol) in THF (20 mL) according to the general procedure for 2 h at room temperature. After work-up, the reaction mixture was applied on Si gel column (*n*-hexane–AcOEt 3:2, R_f 0.18) and fractions containing pure diol were pooled and taken to dryness affording (−)-**17** (115 mg, 76% yield, >98% ee), mp 169–170 °C, $[\alpha]_D$ = −11.6 (*c* 0.6, $CHCl_3$), ^{1}H NMR δ: 1.44 (d, 1H, *J* = 4.5, –OH), 1.54 (d, 1H, *J* = 3.0, OH), 2.13 (ddd, 1H, *J* = 2.6, 6.9 and 13.3, $-CH_{2a}$), 2.30 (m, 2H, CH_{2a} and CH_{4a}), 2.37 (ddd, 1H, *J* = 4.8, 9.1 and 13.6, $-CH_{4b}$), 3.36 (m, 1H, –C(3)H), 4.11 (m, 1H, Cp), 4.17 (br t, 2H, Cp), 4.20 (m, 2H, Cp), 4.22 (s, 5H, Cp′), 4.24 (m, 4H, Cp), 4.28 (m, 1H, Cp), 4.31 (m, 1H, Cp), 4.38 (ddd, 1H, *J* = 2.6, 3.0 and 9.7, C(1)H), 4.46 (m, 1H, Cp), 4.77 (ddd, 1H, *J* = 4.5, 4.5 and 9.1). ^{13}C NMR δ: 33.87, 39.76, 41.69, 65.85, 66.16, 66.30, 66.71, 67.11, 67.40, 67.69, 67.91, 68.05, 68.45, 68.52, 68.96, 69.02, 70.29, 70.48, 90.21, 94.43, 94.76. HPLC: *n*-hexane–EtOH 9:1, 23 °C, flow 0.5 ml/min, t_R/min = 39.21 (*meso*-diol), 50.22 (*R,R*), 54.74 (*S,S*) and 64.4 (*meso*-diol). Anal. Calcd for $C_{25}H_{26}Fe_2O_2$: C, 63.86; H, 5.57. Found: C, 64.32; H, 5.65.

4.8. General procedure for nucleophilic substitution on ferrocenylalcohol (+)-8

A solution of (+)-**8** (75 mg, 0.17 mmol) in CH_2Cl_2 was treated with Ac_2O and pyridine at room temperature overnight, and then the solvent and reagents were removed under vacuum. The acetoxyderivative, which was used without further purification, was dissolved in CH_3CN (5 mL) and to the solution 10 mol excess of aq $NH(CH_3)_2$ or NaN_3 was added. When TLC analysis showed satisfactory conversion of the substrate, the reaction mixture was diluted with H_2O and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, taken to dryness and the residue was purified by column chromatography using the specified eluent.

4.8.1. (*S*)-1,3-Diferrocenyl-1-dimethylaminopropane, (+)-9

According to the general procedure, starting from (+)-**8**, compound (+)-**9** was obtained in 90% yield (SiO_2, *n*-hexane–AcOEt 3:2 containing 1% triethylamine, R_f 0.33); mp 78–80 °C, $[\alpha]_D$ = +2.3 (*c* 0.6, $CHCl_3$), ^{1}H NMR δ: 1.96 (m, 1H, $-CH_{2a}$), 2.03 (s, 6H, $-N(CH_3)_2$), 2.12 (m, 1H, $-CH_{2b}$), 2.50 (ddd, 1H, *J* = 6.4, 7.5 and 14.0, $-CH_{2a}$), 2.69 (ddd, 1H, *J* = 4.6, 9.5 and 14.0, $-CH_{2b}$), 3.36 (dd,

1H, J = 2.3 and 11.0, –CH), 4.00 (s, 1H, Cp), 4.05 (s, 5H, Cp′), 4.10 (m, 5H, Cp), 4.15 (br s, 6H, Cp′ and Cp), 4.18 (s, 1H, Cp). ^{13}C NMR δ: 27.28, 33.23, 40.54, 62.37, 66.91, 67.12, 67.17, 67.26, 67.40, 67.90, 68.48, 68.65, 69.24, 85.21, 89.40. Anal. Calcd for $C_{25}H_{29}Fe_2N$: C, 65.96; H, 6.42; N, 3.08. Found: C, 66.18; H, 6.45; N, 3.11.

4.8.2. (*S*)-1,3-Diferrocenyl-1-azidopropane, (+)-10

According to the general procedure, starting from (+)-**8** compound (+)-**10** was obtained as an oil in 82% yield (SiO_2, *n*-hexane–CH_2Cl_2 7:3, R_f 0.25); $[\alpha]_D$ = +27.0 (*c* 0.4, $CHCl_3$), ^{1}H NMR δ: 1.95 (m, 1H, $-CH_{2a}$), 2.05 (m, 1H, $-CH_{2b}$), 2.46 (ddd, 1H, J = 6.4, 7.5 and 14.0, $-CH_{2a}$), 2.61 (ddd, 1H, J = 4.6, 9.5 and 14.0, $-CH_{2b}$), 4.11 (s, 3H, Cp), 4.14 (s, 6H, Cp′ and Cp), 4.15 (s, 5H, Cp′), 4.19 (m, 4H, –CH and Cp), 4.24 (s, 1H, Cp). ^{13}C NMR δ: 26.48, 36.66, 61.58, 66.20, 67.06, 67.31, 67.49, 67.79, 68.02, 68.12, 68.56, 68.84, 87.77, 88.42. Anal. Calcd for $C_{23}H_{23}Fe_2N_3$: C, 60.96; H, 5.12; N, 9.27. Found: C, 61.31; H, 5.15; N, 9.30.

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