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Screening of chiral ferrocenyl amino alcohols as ligands for ruthenium-catalysed transfer hydrogenation of ketones

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Abstract—A variety of ferrocenyl amino alcohols possessing central chirality have been screened as ligands for ruthenium(II)-catalysed transfer hydrogenation of acetophenone using 2-propanol in the presence of KOH as the hydrogen source. Enantiomerically enriched 1-phenylethanol was obtained in high yield and 70% e.e. using ligand **9**. This ligand was employed in the asymmetric reduction of different arylalkyl ketones and the corresponding alcohols were obtained in up to 80% e.e. A comparison of the catalytic properties of ferrocenyl amino alcohols and their phenyl analogues is discussed briefly.

1. Introduction

The asymmetric reduction of ketones is a pivotal reaction for the preparation of chiral alcohols[1] which form an extremely important class of intermediates for fine chemicals and pharmaceuticals.[2] Ruthenium(II)-catalysed asymmetric transfer hydrogenation has recently received much attention due to its operational simplicity and the use of non-hazardous hydrogen donors such as 2-propanol or formic acid.[3] Several complexes of $[(\eta^6\text{-arene})RuCl_2]_2$ with structurally different bidentate ligands have been tested and some efficient catalyst systems are available for the reduction of both simple[4] and functionalised ketones.[5] The reaction mechanism and the origin of the enantioselectivity have recently been proposed on the basis of theoretical and experimental approaches for the case when β-amino alcohol–Ru complexes are used and the presence of an NH moiety in the ligand has been shown to be crucial for efficient catalysis and asymmetric induction.[6]

Enantiopure ferrocenyl derivatives have been reported as active catalysts in several reactions[7] and are very attractive compounds for the design of new ligand–metal complexes owing to their different chirality features according to the substitution pattern on the ferrocene backbone. Using stereoselective synthesis protocols,[8] it is possible to access a large number of chiral ferrocene derivatives whose properties as catalysts can be easily modulated by the introduction of suitable functional groups and, in some cases, enhanced by cooperativity effects between central and planar chirality.[9]

Although some ferrocenyl diamines and phosphines have been employed successfully as ligands in ruthenium-(II)-promoted transfer hydrogenation of ketones,[10] a screening of catalytic activity of ferrocenyl amino alcohols in this reaction is not yet reported.

Herein, we describe the results obtained in the transfer hydrogenation of ketones using ferrocenyl amino alcohols possessing central chirality as ligands and the evidence of some structure–activity relationships.

2. Results and discussion

2.1. Simple ferrocenyl amino alcohols: comparison with phenyl analogues

The recent availability of ferrocenyl amino alcohol (*S*)-**3**,[11] which can be considered the 'three-dimensional' analogue of phenylglycinol (*R*)-**2**, allowed us to test it as a ligand for transfer hydrogenation of acetophenone using $[RuCl_2(p\text{-cymene})]_2$ as precatalyst and 2-propanol in the presence of KOH as hydrogen source.

In a standard protocol, 1% mol of ligand and 0.25% mol of $[RuCl_2(p\text{-cymene})]_2$ were dissolved in 2-propanol to give a red complex that was used in situ to

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reduce acetophenone (0.1 M) in the presence of 2.5% mol KOH at room temperature.

Compound (*S*)-**3** showed comparable activity with respect to phenylglycinol, (*R*)-**2**, but lower efficiency in the asymmetric induction (Table 1, entries 1 and 2) so that (*S*)-1-phenylethanol, (*S*)-**1**, was recovered with only 10% e.e. (Fig. 1). Increasing the catalyst loading influenced only the reaction rate without affecting the enantioselectivity (Table 1, entry 3).

Using ligand (*R*)-**4**,[12] where the stereogenic carbon is in the β-position with respect to the cyclopentadienyl ring, we observed the same reaction course and stereopreference as phenylglycinol (*R*)-**2**[13] (Table 1, compare entries 4 and 1). This finding could be rationalised on the basis of better spatial similarity of ligand **4** (cf. **3**) with phenylglycinol, as shown by molecular mechanics models (Fig. 2) and previously reported experimental data on enzymatic recognition of 1-aryl-1,2-ethandiols and 1,2-dihydroxy-3-ferrocenylpropane.[14]

For comparison, the phenyl derivative (*R*)-**5** was also tested and a marked decrease in the reaction rate together with a lower selectivity was observed with respect to both (*R*)-**2** and (*R*)-**4** (Table 1, entry 5). So, it is evident that moving the stereogenic centre from the α-position to the β-position with respect to the cyclopentadienyl ring has a positive effect on the selectivity of the hydrogen transfer, possibly a result of release of steric hindrance in the Ru–ferrocene complex. However, the same change in the position of the stereogenic centre is detrimental in the analogous phenyl ligand.

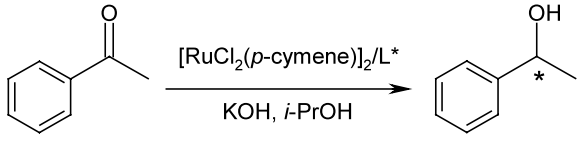
The isomeric β-ferrocenyl amino alcohol (*R*)-**6**[12] gave higher asymmetric induction, affording (*R*)-**1** with 46% e.e. (Table 1, entry 6) in agreement with data from other catalyst screenings, indicating that steregenicity of the carbon bearing the hydroxyl group is required for better selectivity.[5b,5c]

2.2. Optimisation of ligand structure

Taking amino alcohol (*R*)-**6** as a reference (Fig. 3), we tried to vary the ligand structure by *N*-alkylation. Derivatives **7**–**11** were, therefore, prepared by nucleophilic opening of the known β-ferrocenyl epoxide[12] with the appropriate primary amines and tested under the standard conditions described above.

The presence of an *N*-methyl group in ligand (*R*)-**7** provided an improvement in the reaction rate and the level of stereoinduction so that (*R*)-**1** was obtained in

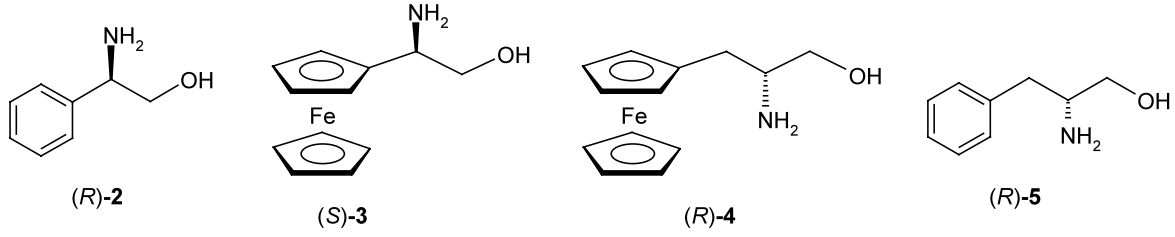
Table 1. Asymmetric transfer hydrogenation of acetophenone in the presence of ligands **2**–**6**[a]



1

Entry	Ligand	Time (h)	Conversion (%)[b]	E.e. (%)[c]	Config.[d] of **1**
1	**2**	2	94	26	*R*
2	**3**	2	84	10	*S*
3	**3**[e]	0.5	96	10	*S*
4	**4**	2	97	27	*R*
5	**5**	24	48	20	*R*
6	**6**	3	75	46	*R*

[a] The reaction was carried out at rt using acetophenone (5 mmol) in a 0.1 M solution in 2-propanol solution with [acetophenone]/[KOH]/[ligand]/[Ru] = 200:5:2:1.
[b] Determined by GC analysis.
[c] Determined by chiral GC analysis.
[d] Assigned by comparison of the specific rotation with literature values.
[e] 2% ligand was used and [acetophenone]/[KOH]/[ligand]/[Ru] = 100:5:2:1.



(*R*)-**2** (*S*)-**3** (*R*)-**4** (*R*)-**5**

Figure 1. Phenyl- and ferrocenyl-amino alcohols for use in Ru(II)-catalysed transfer hydrogenation of acetophenone.

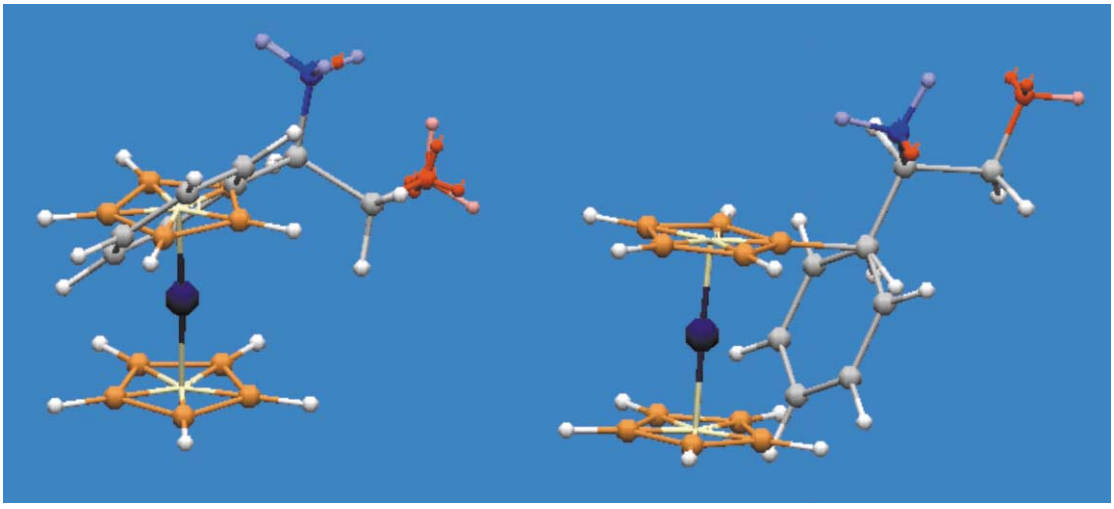


Figure 2. Superimposition of minimised (MM2) structures of (*R*)-**2** and ferrocenyl amino alcohol (*S*)-**3** (left) or (*R*)-**4** (right).

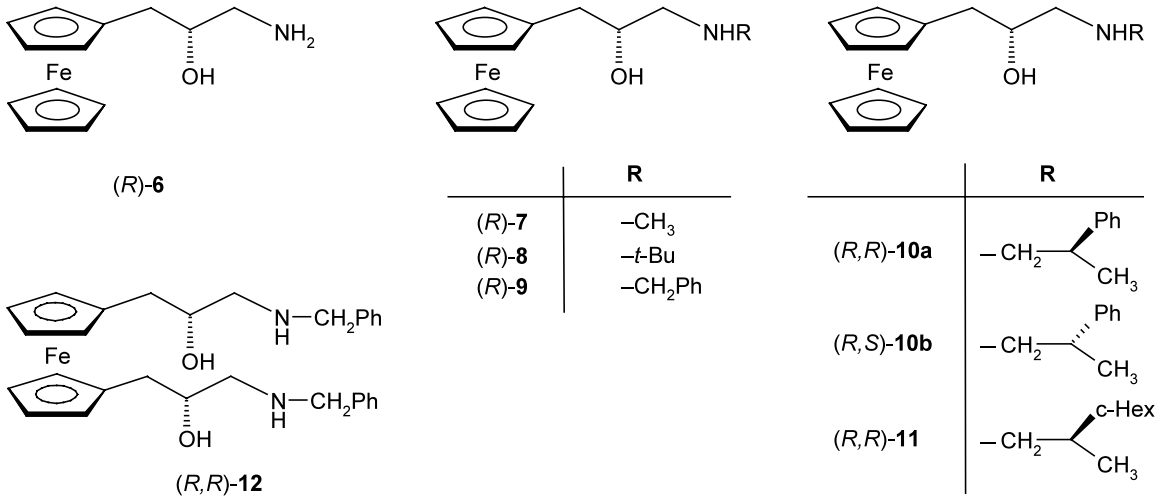


Figure 3. *N*-Alkyl ferrocenyl amino alcohols as ligand for Ru(II)-transfer hydrogenation of acetophenone.

Table 2. Asymmetric transfer hydrogenation of acetophenone in the presence of ligands **7**–**12**[a]

Entry	Ligand	Time (h)	Conversion (%)[b]	E.e. (%)[c]	Config.[d] of **1**
1	**6**	3	47	46	*R*
2	**7**	1	68	65	*R*
3	**7**	5	68	61	*R*
4	**8**	24	–	–	–
5	**9**	3	94	70	*R*
6	**9**[e]	48	24	72	*R*
7	**10a**	24	78	65	*R*
8	**10b**	24	18	33	*R*
9	**11**	24	14	61	*R*
10	**12**	1	86	68	*R*

[a] The reaction was carried out at rt using acetophenone (5 mmol) in a 0.1 M solution in 2-propanol solution with [acetophenone]/[KOH]/[ligand]/[Ru]=200:5:2:1.
[b] Determined by GC analysis.
[c] Determined by chiral GC analysis.
[d] Assigned by comparison of the specific rotation with literature values.
[e] The reaction was carried out at −15°C.

65% e.e.; however, a little erosion of the enantiomeric purity of the formed alcohol was detected during the reaction time,[15] as a consequence of the known reversibility of the hydrogen transfer when 2-propanol is used as hydride donor (Table 2, entries 2 and 3).

Amino alcohol (*R*)-**8**, containing the more sterically demanding *N*-*tert*-butyl substituent, was completely inactive (Table 2, entry 4), whereas good improvement in the catalytic activity was obtained with *N*-benzyl derivative (*R*)-**9** that catalysed fast formation of (*R*)-**1** with 70% e.e. (Table 2, entry 5). This improvement in enantioselectivity with *N*-methylation or *N*-benzylation is in agreement with reported data for the use of phenylethanolamine and norephedrine derivatives in Ru(II)-catalysed transfer hydrogenation.[5a,16] Instead, in the case of 1,1-bis-ferrocenyldiamines, complete inactivity had been reported for the *N*-benzyl derivative.[10b]

Diastereoisomeric amino alcohols **10a** and **10b**, containing an additional stereogenic centre, led to different enantioselectivities and reaction rates, the (*R*,*R*)-derivative possessing the matched configuration (Table 2, entries 7 and 8); in both cases alcohol (*R*)-**1** was produced allowing us to deduce the low influence of remote chirality on the sense of asymmetric induction. The exchange of the phenyl group of **10a** for a cyclohexyl group in ligand **11** resulted in a considerable loss of catalytic activity while the stereoselectivity was affected to a lesser degree (Table 2, entry 9).

As the Ru(II)-**9** catalytic system gave the best result so far, we tried further optimisation of the stereoselection by lowering the reaction temperature to −15°C, but only the expected decrease in the reaction rate was observed without a significant effect on the enantiomeric excess of the formed (*R*)-**1** (Table 2, entry 6).

Since C_2-symmetrical ligands often give high levels of enantioselectivity in asymmetric reactions,[17] we decided to prepare the 1,1′-disubstituted derivative (*R*,*R*)-**12**, as a C_2-symmetrical analogue of (*R*)-**9** starting from (*R*,*R*)-1,1′-bis[(2,3-epoxy)propyl]ferrocene.[18] Using (*R*,*R*)-**12** at 1 mol% loading, the reaction rate was nearly doubled with respect to ligand (*R*)-**9**, but the asymmetric induction was roughly the same and (*R*)-**1** was produced with 68% e.e. (Table 2, entry 10). This result could be explained as a consequence of the possible coordination of each β-amino alcohol moiety with a ruthenium atom, so that a single molecule of ligand **12** affords two reaction centres. The alternative coordination of the two amine groups of **12** with ruthenium should also be taken into account and at this stage cannot be ruled out.

2.3. Variation of the substrate

In order to check the application range of the Ru(II)-catalysed transfer hydrogenation, arylalkylketones other than acetophenone were subjected to asymmetric reduction using the conditions described above and amino alcohol (*R*)-**9** as ligand.

Substitution of the phenyl ring of the acetophenone substrate led to a marked decrease in the enantioselectivity: 4-bromo- and 2-bromoacetophenone were converted with quite different reaction rates into the corresponding alcohols possessing the same enantiomeric purity, whereas the lowest reactivity was observed in the reduction of 4-methoxyacetophenone (Table 3, entries 1–3),

1-Acetylnaphtalene gave comparable results with respect to acetophenone and the best result in terms of enantioselectivity was observed with α-tetralone, which was reduced in moderate yield and 80% e.e. (Table 3, entry 5).

3. Conclusion

In summary, we have shown that ferrocenyl amino alcohols bearing a stereogenic carbon at the β-position with respect to the cyclopentadienyl ring represent a promising class of ligands for ruthenium(II)-catalysed transfer hydrogenation of ketones with 2-PrOH/KOH as hydrogen source. We have also evidenced the parallels in the catalytic activity and the effects influencing the activity between β-ferrocenyl amino alcohols and α-phenylethanolamine derivatives.

Table 3. Asymmetric transfer hydrogenation of arylalkylketones in the presence of ligand **9**[a]

Entry	Ar	R	Time (h)	Conversion (%)[b]	E.e.[c] (%)	Config.[d]
1	(*p*-Br)Ph	Me	2	91	54	*R*
2	(*o*-Br)Ph	Me	24	40	54	*R*
3	(*p*-OMe)Ph	Me	24	30	61	*R*
4	1-Naphtyl	Me	3	72	68[e]	*R*
5	α-Tetralone	α-Tetralone	24	35	80	*R*

[a] The reaction was carried out at rt using acetophenone (5 mmol) in a 0.1 M solution in 2-propanol solution with [ketone]/[KOH]/[ligand]/[Ru] = 200:5:2:1.
[b] Determined by GC analysis.
[c] Determined by chiral GC analysis.
[d] Assigned by comparison of the specific rotation with literature values.
[e] Determined by chiral HPLC analysis.

Ligand **9** afforded satisfactory levels of asymmetric induction in the Ru(II)-catalysed transfer hydrogenation of ketones, considering that high enantioselectivity in this reaction has been achieved only with ligands possessing more than one stereogenic centre and/or a cyclic structure.[3] Fine-tuning of the induction properties of **9** by functionalisation of its *N*-benzyl group or by introduction of additional planar chirality (a characteristic peculiar to ferrocene stereochemistry) is currently in progress.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance™ 400 spectrometer at 400.13 and 100.62 MHz, respectively. Chemical shifts (δ) are given as ppm relative to the residual solvent peak and coupling constants (J) are in Hz. Melting points are uncorrected. Optical rotations were measured on a DIP 135 JASCO instrument at 25°C. Propan-2-ol (HPLC grade) was distilled over CaH_2. $[RuCl_2(p\text{-cymene})]_2$ was purchased from Aldrich and used as given. Reactions were carried out under argon using standard Schlenk techniques. Column chromatography was performed on silica gel 60 (70–230 mesh) using the specified eluants.

Chiral HPLC analyses were carried out on Chiracel® OD column (Daicel Chemical Industries) using *n*-hexane/*iso*-propanol mixtures as a mobile phase and detection by UV–vis detector at 225 nm. Chiral GC analyses were carried out on a MEGA® diacetyl-*tert*-butylsilyl-β-CDX (coated on OV 1701) column.

4.2. General procedure for ruthenium-catalysed transfer hydrogenation of ketones

A solution of $[RuCl_2(p\text{-cymene})]_2$ (7.7 mg, 0.0125 mmol) and ligand (0.05 mmol) in dry 2-propanol (4 ml) was heated at 80°C for 20 min under argon. The light brown solution was then cooled to rt and diluted with 45 ml of 2-propanol. Ketone (5 mmol) and KOH (1.25 ml of a 0.1 M in 2-propanol solution, 0.125 mmol) were sequentially added and the solution turned dark red. Aliquots were taken at different times, filtered through a little pad of silica gel (with CH_2Cl_2 washings) and analysed by GC or HPLC.

4.2.1. Chiral chromatography. 1-Phenylethanol: GC (80–150°C, 2°C/min), t_R/min: 20.2 (*R*), 20.7 (*S*); 1-(*p*-OMe)phenylethanol: GC (80–180°C, 2°C/min), t_R/min: 35.6 (*R*), 36.2 (*S*); 1-(*p*-Br)phenylethanol: GC (80–180°C, 2°C/min), t_R/min: 41.8 (*R*), 42.1 (*S*); 1-(*o*-Br)phenylethanol: GC (80–150°C, 2°C/min), t_R/min: 30.3 (*R*), 30.8 (*S*); 1-(1-naphtyl)ethanol: HPLC (hexane:2-PrOH 95:5, flow 0.7 ml/min), t_R/min: 23.5 (*S*), 34.5 (*R*); 1-tetralol: GC (80–150°C at 2°C/min rate then 150–180°C at 1°C/min), t_R/min: 33.6 (*S*), 34.6 (*R*).

4.3. General procedure for synthesis of amino alcohols 7–11

(*R*)-1,2-Epoxy-3-ferrocenylpropane (100 mg, 0.4 mmol) was dissolved in a MeOH:H_2O 1:1 mixture (10 ml) and treated with an excess (2–4 equiv.) of the appropriate amine. The solution was maintained at 45°C until TLC analysis showed the complete conversion of the substrate. After addition of water the reaction mixture was partitioned with AcOEt and the organic phase extracted with 10% solution of citric acid. The acidic aqueous phase was then alkalinised with 1N NaOH and extracted with AcOEt. The final organic phase was dried over Na_2SO_4 and taken to dryness to afford a residue that was purified by Silica gel column chromatography using AcOEt–Et_3N 2–5% mixtures as eluant.

4.3.1. (*R*)-1-*N*-Methylamino-2-hydroxy-3-ferrocenylpropane, 7. 68% yield, mp 96°C (dec.), $[\alpha]_D = -11.5$ (*c* 0.37, C_6H_6); ^{1}H NMR: δ 2.27 (3H, s), 2.33 (1H, dd, $J = 9.1$ and 12.0), 2.34 (1H, dd, $J = 5.4$ and 14.2), 2.42 (1H, dd, $J = 7.1$ and 14.2), 2.49 (1H, dd, 3.2 and 12.0), 3.55 (1H, m), 3.95 (2H, m), 3.96 (5H, s), 3.98 (2H, m); ^{13}C NMR: δ 35.80, 35.85, 56.60, 67.70, 68.60, 68.96, 69.11, 70.00, 84.12. Anal. calcd for $C_{14}H_{19}FeNO$: C, 61.55; H, 7.01; N, 5.13. Found: C, 61.80; H, 7.14; N, 5.20%.

4.3.2. (*R*)-1-*N*-*tert*-Butylamino-2-hydroxy-3-ferrocenylpropane, 8. 65% yield, mp 100°C, $[\alpha]_D = -21.8$ (*c* 1.30, C_6H_6); ^{1}H NMR: δ 1.11 (9H, s), 2.47 (2H, m), 2.60 (1H, dd, $J = 6.9$ and 14.1), 2.71 (1H, dd, $J = 2.8$ and 11.7), 3.65 (1H, m), 4.06 (2H, bs), 4.10 (6H, bs), 4.13 (1H, m); ^{13}C NMR: δ 24.75, 35.98, 47.20, 51.82, 67.58, 67.66, 68.57, 68.92, 69.22, 70.18, 84.19. Anal. calcd for $C_{17}H_{25}FeNO$: C, 64.77; H, 7.99; N, 4.44. Found: C, 64.49; H, 8.09; N, 4.52%.

4.3.3. (*R*)-1-*N*-Benzylamino-2-hydroxy-3-ferrocenylpropane, 9. 74% yield, mp 69–70°C, $[\alpha]_D = -7.9$ (*c* 0.66, C_6H_6); ^{1}H NMR: δ 2.50 (1H, dd, $J = 2.9$ and 12.0), 2.51 (1H, dd, $J = 5.3$ and 14.0), 2.57 (1H, dd, $J = 6.7$ and 14.0), 2.75 (1H, dd, $J = 3.2$ and 12.0), 3.69 (1H, m), 3.76 (1H, d, $J = 13.2$), 3.82 (1H, d, $J = 13.2$), 4.10 (2H, m), 4.12 (6H, bs), 4.14 (1H, m), 7.28–7.35 (5H, m); ^{13}C NMR: δ 35.17, 53.72, 54.22, 67.67, 67.71, 68.60, 68.97, 69.11, 70.65, 84.28, 127.04, 128.09, 128.43, 140.08. Anal. calcd for $C_{20}H_{23}FeNO$: C, 68.78; H, 6.64; N, 4.01. Found: C, 68.95 H, 6.59; N, 3.96%.

4.3.4. 1-*N*-[(*R*)-1-Phenylethyl]amino-2-(*R*)-hydroxy-3-ferrocenylpropane, 10a. 75% yield, $[\alpha]_D = +39.8$ (*c* 0.6, $CHCl_3$), lit.[13] $[\alpha]_D = -40.0$ (*c* 0.32, $CHCl_3$) for (*S*,*S*)-enantiomer.

4.3.5. 1-*N*-[(*S*)-1-Phenylethyl]amino-2-(*R*)-hydroxy-3-ferrocenylpropane, 10b. 72% yield, $[\alpha]_D = -30.5$ (*c* 0.4, $CHCl_3$), lit.[13] $[\alpha]_D = +30.3$ (*c* 0.32, $CHCl_3$) for (*R*,*S*)-enantiomer.

4.3.6. 1-*N*-[(*R*)-1-Cyclohexylethyl]amino-2-(*R*)-hydroxy-3-ferrocenylpropane, 11. 62% yield, mp 65°C, $[\alpha]_D =$

−13.0 (*c* 0.55, $CHCl_3$); ^1H NMR: δ 0.98 (3H, d, $J=6.5$), 1.17–1.28 (5H, m), 1.66–1.77 (6H, m), 2.39 (1H, m), 2.45 (1H, dd, $J=8.8$ and 12.1), 2.48 (1H, dd, $J=5.7$ and 14.2), 2.58 (1H, dd, $J=6.8$ and 14.2), 2.68 (1H, dd, $J=3.4$ and 12.1), 3.59 (1H, m), 4.09 (2H, m), 4.12 (6H, bs), 4.15 (1H, m); ^{13}C NMR: δ 16.93, 26.45, 26.55, 26.70, 28.23, 29.63, 35.68, 43.20, 51.84, 57.30, 67.60, 68.57, 69.02, 69.09, 70.26, 84.45. Anal. calcd for $C_{21}H_{31}FeNO$: C, 68.29; H, 8.46; N, 3.79. Found: C, 68.46; H, 8.56; N, 3.84%.

4.4. Synthesis of (*R*,*R*)-1,1′-bis[(3-*N*-benzylamino-2-hydroxy)propyl]ferrocene, 12

According to the procedure described above for amino alcohols **7**–**11**, (*R*,*R*)-1,1′-bis[(2,3-epoxy)propyl]-ferrocene was treated with benzylamine to afford (*R*,*R*)-**12** in 58% yield; $[\alpha]_D=-22.9$ (*c* 1.15, C_6H_6); ^1H NMR: δ 2.42 (2H, dd, $J=5.5$ and 14.1), 2.45 (2H, dd, $J=8.9$ and 12.0), 2.49 (2H, dd, $J=7.0$ and 14.1), 2.69 (2H, dd, $J=3.2$ and 12.0), 3.62 (2H, m), 3.70 (2H, d, $J=13.2$), 3.76 (2H, d, $J=13.2$), 4.00 (8H, m), 7.22–7.30 (10H, m); ^{13}C NMR: δ 35.40, 53.60, 54.06, 68.43, 69.63, 69.79, 70.54, 84.30, 127.09, 128.12, 128.43, 129.01, 139.75. Anal. calcd for $C_{30}H_{36}FeN_2O_2$: C, 70.31; H, 7.08; N, 5.47. Found: C, 70.45; H, 7.15; N, 5.32%.

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