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Preparation of enantiopure 1,4-amino alcohols derived from [3]ferrocenophanes: use in the asymmetric addition of diethylzinc to benzaldehyde

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Abstract—A series of enantiopure 1,4-amino alcohols with a [3]ferrocenophane backbone have been synthesized. *Candida rugosa* lipases were used in a key step allowing the resolution of amino alcohol (1*S*,R_p)-**1**. Two other amino alcohols (1*S*,2*S*,R_p)-**2** and (1*S*,2*S*,R_p)-**3** were prepared starting from (1*S*,R_p)-**1**. The new ligands have been used in the asymmetric ethylation of benzaldehyde by diethylzinc and gave good catalytic properties. One of these ligands was particularly efficient, while the yield of the catalytic test reaction was near to 100% and the enantiomeric excess was about 80%. All the ligands directed the catalytic process towards the same (1*R*)-1-phenylpropanol.

1. Introduction

In recent years, considerable attention has been devoted to the preparation of optically active ligands. Among the latter, amino alcohols have been applied in various enantioselective catalyzed reactions. In particular, R_2Zn modified with chiral amino alcohols shows a high ability to promote the asymmetric alkylation of prochiral aldehydes and ketones.[1,2]

On the other hand, since its discovery, ferrocene and its derivatives have been widely studied.[3] Their substitution potential offers a large number of possibilities for synthesis and applications. For example, ferrocene compounds bearing a planar chirality[4] and/or a [3]ferrocenophane backbone[5] could present interesting properties. One famous application relevant to asymmetric catalysis is the alkylation of carbonyl compounds by dialkylzinc reagents.[6]

We have an ongoing interest in the synthesis and use of ferrocenyl compounds both as biomolecules[7] and chiral auxiliaries for asymmetric catalysis.[8] Herein, we report on the lipase-catalyzed synthesis of chiral 1,4-amino alcohols including a [3]ferrocenophane backbone and on their use in the ethylation of benzaldehyde by diethylzinc.

2. Synthesis of enantiopure 1,4-amino alcohols with a [3]ferrocenophane backbone

A retrosynthetic analysis of the access to the three targeted amino alcohols **1**, **2** and **3** is given in Figure 1.

The synthesis of enantiomerically pure 1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene **4** is described in the literature.[9] The resolution was attempted either by a fractionated crystallization of the amine with tartaric acid,[9b] but the resolution was only partial, or by the use of (*S*)-1-phenylethylamine as a chiral auxiliary,[9a] however a step of the synthesis needs to be realized in a steel autoclave. Hence we decided to develop a more efficient or easier method to reach total enantiomeric purity via a lipase-based resolution. Several attempts

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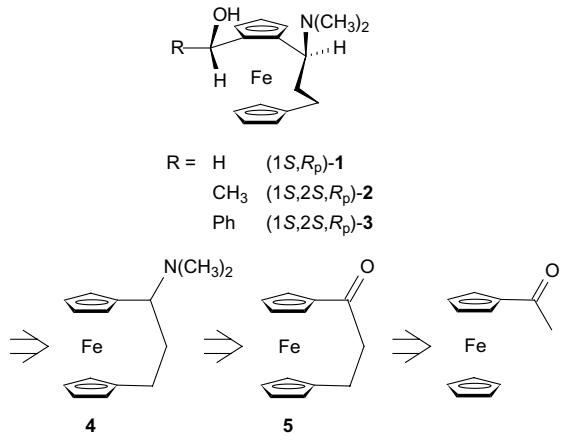

Figure 1. Strategy of synthesis of the three new aminoalcohols **1**, **2** and **3**.

could be realized either on secondary amine **4** or on amino alcohol **1**.

Cyclic ferrocenyl ketone **5** was obtained from the reaction between acetylferrocene and diethyl carbonate in the presence of NaH (Fig. 2). The reaction was conducted by refluxing in dry toluene for 2 h.[10] The resulting ketoester **6** was then reduced according to Clemmensen's procedure with a concomitant hydrolysis into the carboxylic acid **7** by heating to reflux in acetic acid for 3.5 h in the presence of a $Zn/HgCl_2/HCl$ mixture. A regioselective cyclization occurred between the two cyclopentadienyl units in the presence of trifluoroacetic acid.[11] No cyclization at the *ortho* position was observed.

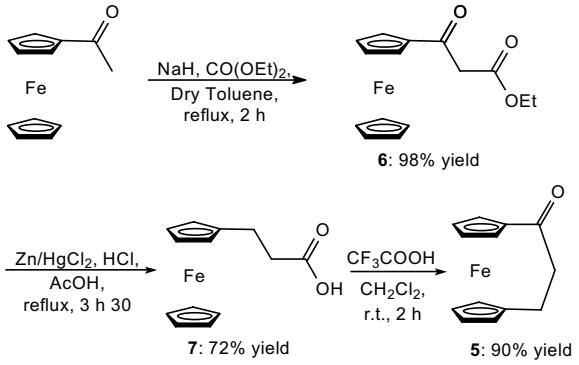

Figure 2. Synthesis of cyclic ketone **5**.

The next step consisted of preparing dimethylamine **4**. Methylamine was first condensed on ketone **5** in dry diethyl ether in the presence of molecular sieves 4 Å (Fig. 3). An 81/19 mixture of the two diastereomers of imine **8** was obtained. The proportion of each diastereomer (*Z*)-**8** and (*E*)-**8** was determined by ^1H NMR and NOESY analyses: the proximity of the NCH_3 group of stereoisomer (*E*)-**8** to the CH_2 of the cyclic alkyl chain (Fig. 3) was highlighted in the NOESY spectrum. The separation of these diastereomers was not necessary

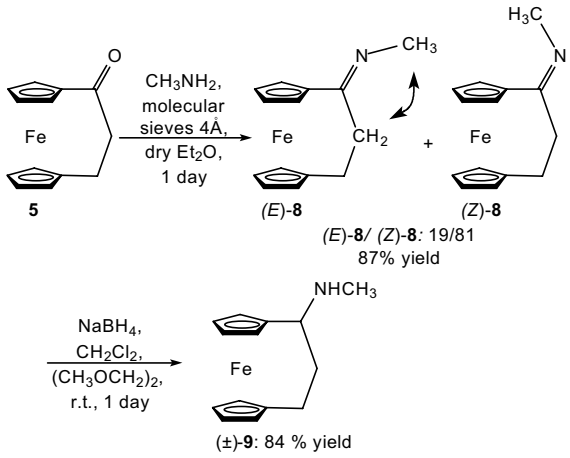

Figure 3. Synthesis of racemic secondary amine (±)-**9**.

(see below). The reduction of the mixture of imines **8** by $NaBH_4$ afforded the racemic methylamine (±)-**9**.

Our aim was to synthesize enantiopure amino alcohols using biocatalysis. As mentioned above, such a resolution could be attempted either on amine **9** or on amino alcohol **1**. Both were studied (vide infra).

Several attempts were made to resolve the racemic secondary amine (±)-**9**.[12] Unfortunately, neither the use of *Candida rugosa* nor that of *Candida antarctica B* lipases allowed a high enantiomeric excess to be reached (Fig. 4).

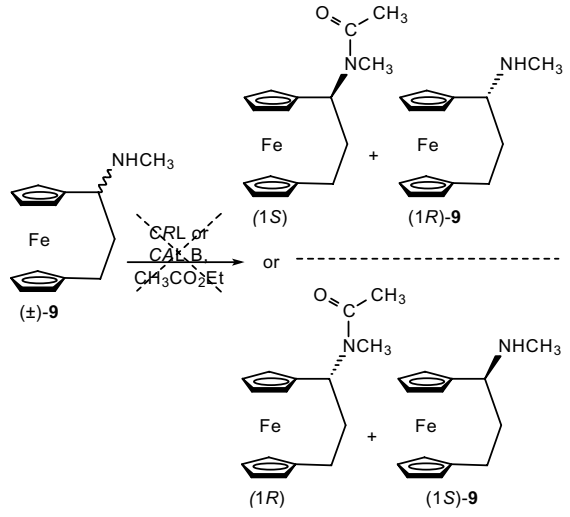

Figure 4. Attempts for optical resolution of secondary amine (±)-**9**.

We next prepared the amino alcohol **1**. This alcohol was obtained in three steps (Fig. 5). The secondary amine **4** was methylated by a $NaBH_4/HCHO$ mixture in H_2O/MeOH. The resulting dimethylamine **4** was then converted into the corresponding aminoaldehyde (±)-**10** by a deprotonation (*n*-BuLi)/addition (DMF) sequence. The addition of $NaBH_4$ onto aldehyde (±)-**10** produced racemic amino alcohol (±)-**1**.

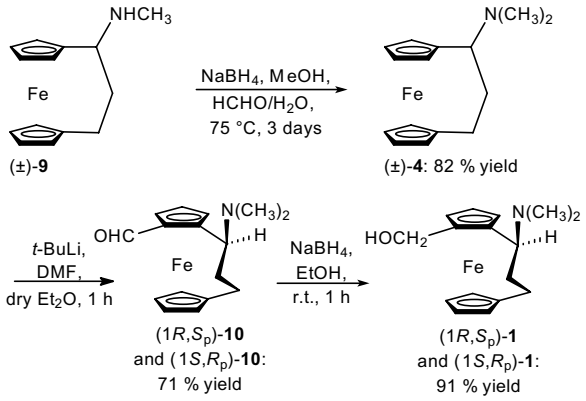

Figure 5. Synthesis of racemic (1*R*,S_p)-**1**/(1*S*,R_p)-**1**[14] (only one enantiomer is presented).

The regioselectivity at the *ortho* position can be attributed to the nitrogen assistance via coordination to the intermediate metallated Fc-Li species.[15] Four diastereomers could be formed. However, only two stereoisomers (a couple of enantiomers) were obtained. Indeed, the blocked structure of the cyclic amine **4** hinders free rotation, which involves the location of nitrogen near one of the two *ortho* positions of the cyclopentadienyl ring. As a result, a single *ortho* lithiation occurred (Fig. 6).[9a]

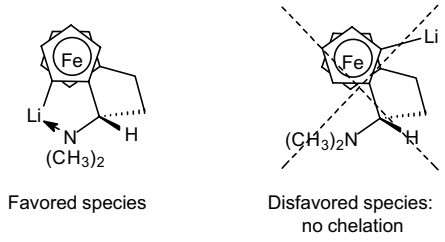

Figure 6. Stereoselective *ortho* lithiation of **4**.

The second attempt at the resolution using biocatalysis was achieved on the amino alcohol **1** (vide supra) by enzymatic resolution with *C. rugosa* lipases according to Nicolosi's procedure (Fig. 7).[16]

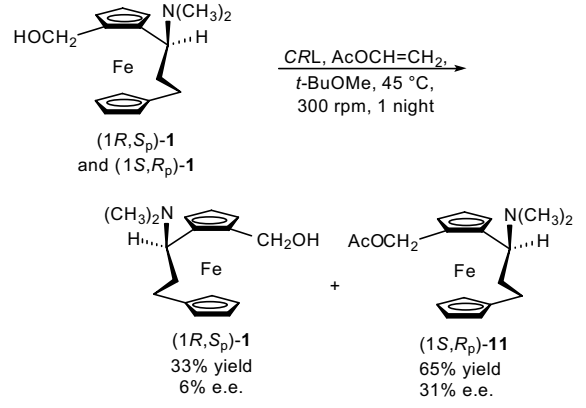

Figure 7. Enzymatic resolution of **1**.

Alcohol **1**, which was not converted, and acetate **11** were easily separated by chromatography on silica gel. The enantiomeric excesses were determined by ^{1}H NMR in $CDCl_3$, using 1 equiv of Pirkle's alcohol. In fact, a first analysis of the racemic mixture in the presence of this chiral agent showed that the singlet of $N(CH_3)_2$ of the two enantiomers was distinguished. The same differentiation was observed with the two doublets of the two diastereotopic protons $-CH_2-O$. The integration of each dedoubled signal allowed the determination of enantiomeric excesses. Unfortunately, the ee's were low (about 31% and 6%, respectively, for acetate **11** and recovered alcohol **1**).

A second lipase-promoted kinetic resolution was realized on the enantiomerically enriched ester **11** with *CR*L, in *t*-butylmethyl ether in the presence of butanol (Fig. 8).[16]

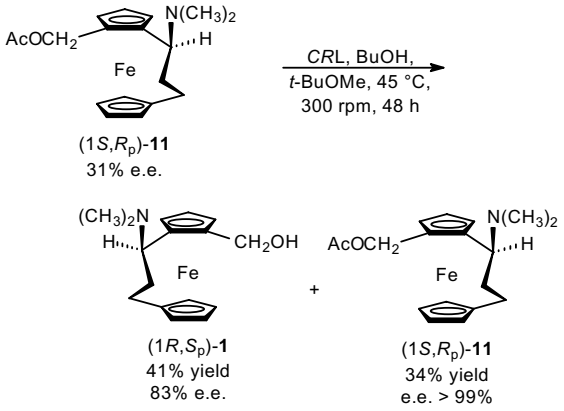

Figure 8. Enzymatic resolution of **11**.

In this manner, the enantiomerically pure ester (1*S*,R_p)-**11** was obtained $[\alpha]_D^{20} = -73.4$ (*c* 3.4, $CHCl_3$). This compound could then be converted into the enantiomerically pure alcohol (1*S*,R_p)-**1** by a simple and quantitative saponification by NaOH (Fig. 9). This alcohol is dextrogyre $\{[\alpha]_D^{20} = +145.3$ (*c* 0.6, $CHCl_3)\}$.

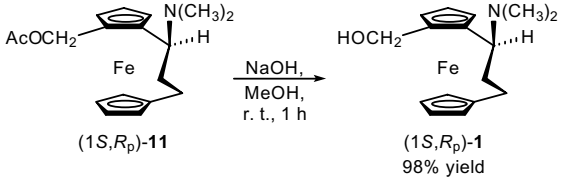

Figure 9. Saponification of (1*S*,R_p)-**11**.

Regarding the poor enantiomeric excess of ester **11** before resolution, we sought to realize the same reaction directly on racemic ester. Effectively, the enzymatic resolution yielded 43% of alcohol (1*R*,S_p)-**1** (72% ee) and 35% of ester (1*S*,R_p)-**11** (ee >99%). This excellent result could allow the first step of enzymatic resolution of alcohol **1** to be avoided and simply replaced by a classical acylation.

The absolute configurations of **1** and **11** were determined according to Sok et al.[17] Indeed, they proved that the dextro alcohol results from the laevo amine, which has got the (*S*)-configuration. Due to the presence of the nitrogen, the lithiation and the functionalization of only one *ortho* position involve the production of the 1,2-difunctionalized ferrocene having the (R_p)-configuration (cf. Fig. 6). The two other amino alcohols were synthesized from enantiomerically pure **1**.

Oxidation of (1*S*,R_p)-**1** by MnO_2 yielded enantiopure aminoaldehyde (1*S*,R_p)-**10** $[\alpha]_D^{20} = -558.8$ (*c* 0.1, $CHCl_3$). This compound was then treated with two different alkyllithiums (R = CH_3 or Ph) to produce the two secondary alcohols (Fig. 10).

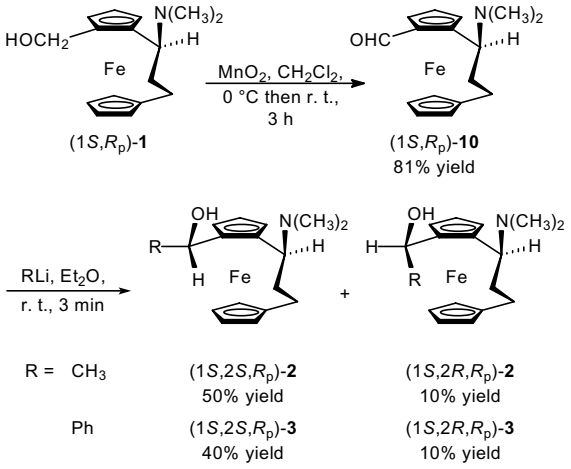

Figure 10. Synthesis of (1*S*,2*S*,R_p)-**2** and (1*S*,2*S*,R_p)-**3**.

The alkylation step with RLi produced the diastereomeric mixtures of amino alcohols (1*S*,2*S*,R_p)-**2**/(1*S*,2*R*,R_p)-**2** and (1*S*,2*S*,R_p)-**3**/(1*S*,2*R*,R_p)-**3**, which were separated by silica gel chromatography. Configurations of the new stereogenic centres were determined by ^{1}H NMR and according to Battelle's work on similar compounds.[18] Indeed, (1*S*,2*S*,R_p)-**2** exhibited a deshielded quadruplet at 5.07 ppm attributed to the hydrogen near the alcohol function Fc-C*H*(OH), whereas the corresponding quadruplet was located at 4.60 ppm for (1*S*,2*R*,R_p)-**2**. The proximity of this proton and iron can explain the deshielding observed. Compound (1*S*,2*S*,R_p)-**2** is dextrorotary $[\alpha]_D^{20} = +94.2$ (*c* 1.1, $CHCl_3$).

The same reasoning was applied to (1*S*,2*S*,R_p)-**3** and (1*S*,2*R*,R_p)-**3**: the hydrogen near the alcohol function of (1*S*,2*S*,R_p)-**3** appeared in the form of a deshielded singlet at 6.04 ppm, [vs 5.68 ppm for (1*S*,2*R*,R_p)-**3**]. The diastereoselectivity during the alkylation can be explained by the chelating of the nitrogen and oxygen atoms with lithium, which involved an attack preferentially on one side of the aldehyde function. Compound (1*S*,2*S*,R_p)-**3** is laevorotary $\{[\alpha]_D^{20} = -71.2$ (*c* 0.6, $CHCl_3)\}$.

3. Enantioselective addition of diethylzinc to benzaldehyde using 1, 2 and 3

The three new enantiomerically pure ferrocenyl amino alcohols were used as catalysts in the ethylation of benzaldehyde by diethylzinc (Fig. 11).

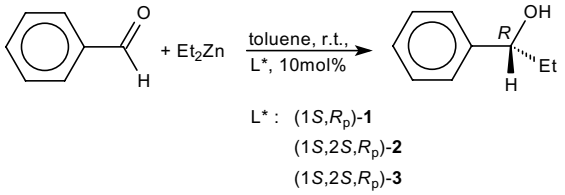

Figure 11. Catalytic ethylation of benzaldehyde by Et_2Zn.

The same procedure was applied for all three catalytic reactions. The ligand was then dissolved in dry toluene. Then, benzaldehyde and diethylzinc were added. The reaction was followed by GLC and stopped after complete conversion of the aldehyde. The results are collected in Table 1.

Table 1. Catalytic ethylation of benzaldehyde by Et_2Zn

Entry	Ligand	Time reaction (h)	1-Phenylpropanol	
			Yield[a] (%)	Ee (%) (configuration)[b]
1	(1*S*,R_p)-**1**	48	96	58 (1*R*)
2	(1*S*,2*S*,R_p)-**2**	24	96	80 (1*R*)
3	(1*S*,2*S*,R_p)-**3**	48	94	57 (1*R*)

[a] Determined by ^{1}H NMR. No more benzaldehyde was observed.
[b] Determined by GLC analysis on FS CYCLODEX β-I/P (30 m × 0.24 mm).

The ferrocenyl amino alcohols presented good catalytic properties as each reaction occurred with good yield (>94%). The enantiomeric excesses were moderate to good (between 57% and 80%). The three ligands directed the ethylation towards the same (1*R*)-1-phenylpropanol enantiomer.[19]

The probable stereochemical course of the reaction is postulated in Figures 12 and 13 based on a study of zinc complexes using molecular models and according to that proposed by Watanabe et al.[20] and Uemura et al.[21] for 1,4-amino alcohols.

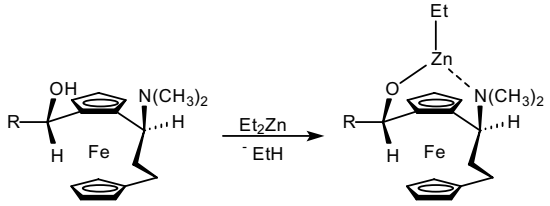

Figure 12. Complexation between diethylzinc and aminoalcohol.

A complexation between zinc and the amino alcohol occurred and produced a seven-membered ring (Fig. 12). Then benzaldehyde and a second molecule of diethylzinc

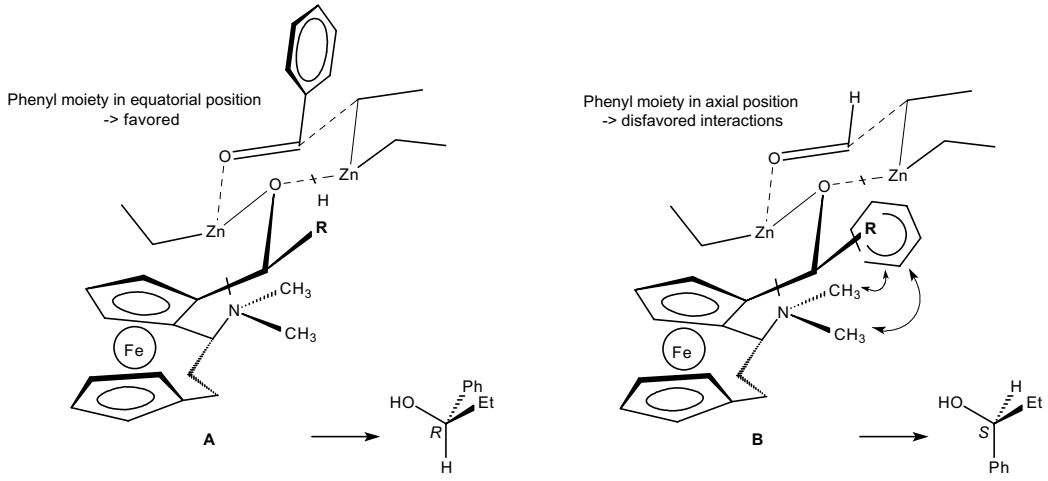

Figure 13. Proposed stereochemical course according to Uemura and Watanabe's models.

associated to form a six-membered ring adjacent to the previous one thus forming the transition state (Fig. 13). Usually in this transition state, the two cycles are in a chair–chair like conformation for steric reasons. However in our case, molecular models suggest that the adopted conformation could only be boat–chair: actually, the presence of the bridge between the two cyclopentadienyl rings causes an important rigidity avoiding the possibility for the complexes to adopt the chair–chair conformation.

Two transition states, **A** and **B**, could be considered. However, the phenyl group in **B** lies in an axial position, close to the two methyl groups of the nitrogen atom. Thus, the most favoured transition state seems to be **A** in which the phenyl group is in the equatorial position without any steric repulsion. The ethylation occurs on the *Re* face of benzaldehyde, leading to the formation of (1*R*)-phenylpropanol (Fig. 13). This is in accordance to the experimental results.

Amino alcohol (1*S*,2*S*,R_p)-**2** bearing the methyl group led to the best result, that is, 96% yield and 80% ee (entry 2). Surprisingly, compound (1*S*,2*S*,R_p)-**3** with the most hindered alcohol function (phenyl group) was not the best catalyst (57% ee, entry 3). In fact in the case of the acyclic ferrocenyl 1,4-amino alcohol series, it is well known that the steric hindrance of the hydroxyl group enhances the enantiomeric excesses. In our series, the cyclic chain in addition to the presence of the bulky phenyl substituent involves a loss of degree of liberty in the structure, preventing the formation of the ideal conformation to allow the best catalysis.

4. Conclusion

We have prepared a series of enantiopure [3]ferrocenophane-based amino alcohols (1*S*,R_p)-**1**, (1*S*,2*S*,R_p)-**2** and (1*S*,2*S*,R_p)-**3**. Total enantiomeric purity was reached via an enzymatic resolution of racemic **1**. These compounds were used as ligands in the reaction of diethylzinc with benzaldehyde. Compound (1*S*,2*S*,R_p)-**2** proved to induce interesting properties. All the ligands directed the catalytic process towards the formation of the same (1*R*)-1-phenylpropanol.

5. Experimental

5.1. General

The reactions were performed in glassware under an atmosphere of nitrogen. Catalytic reactions were performed under nitrogen by standard Schlenk techniques. Diethyl ether and toluene were freshly distilled over sodium prior to use. Alkyllithium reagents were purchased from Aldrich. *C. rugosa* lipases were purchased at Sigma. Column chromatographies were performed on SiO_2 (Merck, 70–230 mesh, Kieselgel 60). Melting points were determined on a Kopfler apparatus. Optical rotations were measured at an ambient temperature on a Perkin–Elmer 241 digital polarimeter. IR spectra were measured on a Perkin–Elmer Paragon 500 spectrometer using KBr pellets. NMR spectra were acquired at room temperature on a Bruker AC 300 spectrometer. ^{1}H NMR analyses were obtained at 300 MHz (s: singlet, d: doublet, t: triplet, dd: double doublet, m: multiplet); ^{13}C NMR analyses were obtained at 75.4 MHz. ^{1}H chemical shifts are quoted relative to TMS, and ^{13}C shifts relative to solvent signals. Carbon signals were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra (MALDI TOF) were obtained with an Applied Biosystem Voyager DE STR mass spectrometer. Mass spectra (CI) and HRMS were performed on a Jeol JMS-700 m Station mass spectrometer. Chiral GLC analyses were run on a FS CYCLODEX β-I/P (30 m × 0.24 mm) column.

5.2. Preparation of compounds

5.2.1. 1,1′-[1-(*N*-Methylimino)propanediyl]ferrocene (*Z*)-8 and (*E*)-8. To a solution of 1,1′-(1-oxopropanediyl)ferrocene **5**[13] (3.6 g, 15 mmol) in dry diethyl ether (75 mL) containing 10 g of molecular sieves 4 Å were added 24 mL (47 mmol) of methylamine. The solution

was stirred for 20 h at room temperature. The solution was filtered over Celite and the solvent removed under reduced pressure. A 81/19 mixture (3.45 g) of two diastereomers (*Z*)-**8** and (*E*)-**8** were obtained as orange crystals, mp 79 °C.

Compound (*Z*)-**8**: ^{1}H NMR δ 4.32 (4H, m, H *ortho* Cp and Cp′), 4.20 (2H, m, H *meta* Cp), 4.02 (2H, m, H *meta* Cp′), 3.21 (3H, s, NCH_3), 2.86 (2H, m, $CH_2C{=}N$), 2.49 (2H, m, CH_2Cp'); ^{13}C NMR δ 171.8 (C=N), 87.2 (CIV Cp), 73.7 (CIV Cp), 70.5–68.5 (CIII 2Cp), 46.9 ($CH_2C{=}N$), 41.6 (NCH_3), 27.7 (CH_2Cp').

Compound (*E*)-**8**: ^{1}H NMR δ 4.50–4.34 (4H, m, H *ortho* Cp and Cp′), 4.18 (2H, m, H *meta* Cp), 4.00 (2H, m, H *meta* Cp′), 3.26 (3H, s, NCH_3), 2.85 (2H, m, $CH_2C{=}N$), 2.48 (2H, m, CH_2Cp'); ^{13}C NMR δ 173.1 (C=N), 87.5 (CIV Cp), 72.8 (CIV Cp), 70.5–68.5 (CIII 2Cp), 45.2 ($CH_2C{=}N$), 39.4 (NCH_3), 28 (CH_2Cp); MS *m/e* (MALDI TOF, matrix: thap) 292 $[(M+K)]^+$, 276 $[(M+Na)]^+$, 258, 254 $[MH]^+$, 253 $[M]^+$, 247.

5.2.2. (±)-1,1′-[1-(*N*-Methylamino)propanediyl]ferrocene 9. To a solution of imine **8** (3.3 g, 13.2 mmol) in dichloromethane (80 mL) and 145 mL of ethylene glycol were added 523 mg (13.8 mmol) of $NaBH_4$. The solution was stirred at ambient temperature for 24 h. Water was then added. After 15 min, the solvent was removed under reduced pressure. The product was extracted with several portions of diethyl ether, the extracts combined, washed with water and then HCl 6 M. To the aqueous layer was added K_2CO_3 until a precipitate appears. An extraction with diethyl ether was realized followed by washing twice brine. The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine) yielded 84% (2.8 g) of **9** as orange crystals, mp 50 °C; ^{1}H NMR δ 4.23–4.06 (8H, m, 2Cp), 3.05 (1H, dd, $J = 7.3$ $J = 5.6$, CH–N), 2.36 (3H, s, NCH_3), 2.35 (1H, m, CH_2Cp), 2.13 (2H, m, CH_2C–N), 1.94 (1H, m, CH_2Cp); ^{13}C NMR δ 87.8 (CIV Cp), 86.4 (CIV Cp), 71.1–66.7 (CIII 2Cp), 58.5 (CH–N), 42.4 (CH_2C–N), 35.2 (NCH_3), 23.9 (CH_2Cp); MS *m/e* (MALDI TOF, matrix: thap) 294 $[(M+K)]^+$, 278 $[(M+Na)]^+$, 256 $[MH]^+$, 255 $[M]^+$, 191, 169.

5.2.3. (±)-1,1′-[1-(*N*,*N*-Dimethylamino)propanediyl]ferrocene 4. To a solution of methylamine **9** (3 g, 11.8 mmol) in methanol (100 mL) were added 95 mL of formaldehyde 37 wt % (solution in water). The solution was stirred at 0 °C for 10 min and then 8.55 g of $NaBH_4$ were added very carefully portionwise. The mixture was heated to reflux for 48 h. After cooling to ambient temperature, methanol was removed under reduced pressure. The product was extracted with several portions of diethyl ether and the extracts combined and washed twice with brine. The organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine) yielded 82% (2.6 g) of **4** as orange crystals, mp 90 °C; ^{1}H NMR δ 4.17–3.89 (8H, m, 2Cp), 2.82 (1H, dd, $J = 10.0$, 3.0, CH–N), 2.47 (1H, m, CH_2Cp), 2.19 (6H, s, $N(CH_3)_2$), 2.16 (1H, m, CH_2C–N), 2.13 (1H, m, CH_2C–N), 1.93 (1H, m, CH_2Cp); ^{13}C NMR δ 87.7 (CIV Cp), 80.5 (CIV Cp), 71,8–67.0 (CIII 2Cp), 65.4 (CH–N), 42.9 ($N(CH_3)_2$), 39.6 (CH_2C–N), 25.9 (CH_2Cp); MS *m/e* (MALDI TOF, matrix: thap) 308 $[(M+K)]^+$, 292 $[(M+Na)]^+$, 270 $[MH]^+$, 269 $[M]^+$, 225 $[M-NMe_2]^+$, 207, 191, 169.

5.2.4. (±)-2-Formyl-1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene 10. Dimethylamine **4** (860 mg, 3.2 mmol) was placed at room temperature under an inert atmosphere in a round-bottomed flask and then dissolved in dry diethyl ether (35 mL). After 5 min stirring, *t*-BuLi (2.7 mL, 4 mmol, 1.5 M in pentane) was added slowly and the solution stirred for another 1 h. Then, 0.5 mL of DMF (6.4 mmol) was added. The solution was stirred for 15 min, quenched with water-saturated diethyl ether (20 mL) and with brine (20 mL). The organic compounds were extracted with diethyl ether (2×20 mL) and the extracts combined, washed with brine (2×60 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine) yielded 71% (675 mg) of **10** as a red oil; IR (cm^{-1}) 3087, 2950, 2860, 2818, 2770, 1672, 1469, 1438, 1349, 1253, 1037, 1015, 810; ^{1}H NMR δ 10.38 (1H, s, –*CH*O), 4.82 (1H, m, Cp), 4.46 (1H, m, Cp), 4.41 (1H, m, Cp), 4.26 (2H, m, Cp), 4.01 (1H, m, Cp), 3.96 (1H, m, Cp), 2.77 (1H, dd, $J = 10.8$, 2.8, CH–N), 2.51 (1H, m, CH_2C–N), 2.51 (1H, m, CH_2Cp), 2.36 (1H, m, CH_2C–N), 2.27 (6H, s, $-N(CH_3)_2$), 1.95 (1H, m, CH_2Cp); ^{13}C NMR δ 196.2 (CHO), 89.5 (CIV Cp), 87.5 (CIV Cp), 78.6 (CIV Cp), 76.7–69.6 (CIII 2Cp), 66.9 (CH–N), 45.4 ($N(CH_3)_2$), 40.3 (CH_2C–N), 25.3 (CH_2Cp), MS *m/e* (MALDI TOF, matrix: thap) 336 $[(M+K)]^+$, 320 $[(M+Na)]^+$, 298 $[MH]^+$, 266, 253 $[M-NMe_2]^+$, 225, 207, 191.

5.2.5. (±)-2-(Hydroxymethyl)-1,1′-[1-(*N*,*N*-dimethylamino)-propanediyl]ferrocene 1. To a solution of aldehyde **10** (3 g, 10 mmol) in methanol (150 mL) was added $NaBH_4$ (14.8 g, 0.39 mol). The solution was stirred until discolouration. A hydrolysis was performed by adding water. Methanol was evaporated under reduced pressure. The product was extracted with several portions of diethyl ether and the extracts combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine) yielded 91% (2.72 g) of **1** as a dark orange oil; IR (cm^{-1}) 3381, 3205, 3078, 2953, 2858, 2816, 2783, 1470, 1429, 1350, 1205, 1016, 893, 839, 802; ^{1}H NMR δ 4.85 (1H, d, $J = 12.7$, CH_2O), 4.14 (1H, m, Cp), 4.10 (1H, d, $J = 12.7$, CH_2O), 4.05 (2H, m, Cp), 4.00 (1H, m, Cp), 3.94 (2H, m, Cp), 3.70 (1H, m, Cp), 2.60 (1H, m, CH_2Cp), 2.51 (1H, m, CH_2Cp), 2.47 (1H, m, CH–N), 2.32 (6H, s, $-N(CH_3)_2$), 2.22 (1H, m, CH_2C–N), 1.95 (1H, m, CH_2C–N); ^{13}C NMR δ 87.3 (CIV Cp), 86.3 (CIV Cp), 85.5 (CIV Cp), 71.5–66.1 (CIII 2Cp), 61.1 (CH_2O), 66.2 (CH–N), 44.9 ($N(CH_3)_2$), 37.5 (CH_2C–N), 25.1

(CH_2Cp), MS *m/e* (MALDI TOF, matrix: thap) 336 $[(M+K)]^+$, 320 $[(M+Na)]^+$, 298 $[MH]^+$, 266, 253 $[M-NMe_2]^+$, 225, 207, 191; HRMS (CI) Calcd for $C_{16}H_{21}FeNO$: 299.0973. Found: 299.0980.

5.2.6. Procedure for the enzymatic resolution of 2-(hydroxymethyl)-1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene 1. To a solution of alcohol **1** (1.43 g, 4.8 mmol) and 730 mg of *C. rugosa* lipases in *tert*-butylmethyl ether (30 mL) were added 20 mL (21.8 mmol) of vinyl acetate. The solution was stirred (300 rpm) at 45 °C for 14 h. The reaction mixture was then filtered over Celite. After evaporation of the solvent under reduced pressure, the residue was purified through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine to 90% diethyl ether and 10% triethylamine) yielded 33% (500 mg) of (1*S*,R_p)-11 (ee = 31%) and 65% (963 mg) of (1*R*,S_p)-**1** (ee = 6%).

5.2.7. (1*S*,R_p)-2-(Acetoxymethyl)-1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene 11. To a solution of racemic ester (1*S*,R_p)-**11** (500 mg, 1.5 mmol) and 20 g of *C. rugosa* lipases in *tert*-butylmethyl ether (50 mL) were added 4 mL of butanol. The solution was stirred (300 rpm) at 45 °C for 48 h. The reaction mixture was then filtered over Celite. After evaporation of the solvent under reduced pressure, the residue was purified through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine to 90% diethyl ether and 10% triethylamine) yielded 43% (192 mg) of (1*R*,S_p)-**1** (ee = 72%) and 35% (171 mg) of (1*S*,R_p)-11 (ee >99%). (1*S*,R_p)-**11**: orange oil; $[\alpha]_D^{20} = -73.4$ (*c* 3.4, $CHCl_3$); IR (cm^{-1}) 3087, 2951, 2862, 2815, 2765, 1737, 1468, 1447, 1372, 1357, 1239, 1031, 1021, 891, 841, 804; ^1H NMR δ 5.03 (2H, s, CH_2O), 4.19 (1H, m, Cp), 4.11–4.06 (3H, m, Cp), 3.98–3.96 (3H, m, Cp), 2.53 (1H, m, CH–N), 2.43 (2H, m, CH_2Cp), 2.23 (6H, s, –N(CH_3)$_2$), 2.15 (1H, m, CH_2C–N), 2.04 (3H, m, CH_3CO), 1.90 (1H, m, CH_2C–N); ^{13}C NMR δ 171.0 (C=O), 88.2 (CIV Cp), 83.7 (CIV Cp), 80.8 (CIV Cp), 72.3 (CIII Cp), 71.6–71.5 (2CIII Cp), 69.5 (2CIII Cp), 67.8 (CIII Cp), 67.6 (CIII Cp), 67.0 (CH–N), 62.5 (CH_2O), 45.2 (N(CH_3)$_2$), 39.0 (CH_2C–N), 25.1 (CH_2Cp), 21.0.3 (CH_3); MS *m/e* (MALDI TOF, matrix: thap) 380 $[(M+K)]^+$, 342 $[MH]^+$, 341 $[M]^+$, 297 $[M-NMe_2]^+$, 282 $[M-COOCH_3]^+$, 257, 239, 207, 191, 169; HRMS (CI) Calcd for $C_{18}H_{23}FeNO_2$: 341.1078. Found: 341.1082.

5.2.8. (1*S*,R_p)-2-(Hydroxymethyl)-1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene 1. To a solution of ester (1*S*,R_p)-**11** (400 mg, 1.2 mmol) in methanol (50 mL) was added 12 mL of a 1 M aqueous solution of NaOH (12 mol). The solution was stirred at ambient temperature for 1 h. Methanol was evaporated under reduced pressure. The product was extracted with several portions of diethyl ether, the extracts combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine to 90% diethyl ether and 10% triethylamine) yielded 98% (352 mg) of (1*S*,R_p)-**1** as orange crystals, mp 94 °C; $[\alpha]_D^{20} = +145.3$ (*c* 0.6, $CHCl_3$).

5.2.9. (1*S*,R_p)-2-Formyl-1,1′-[1-(*N*,*N*-dimethylamino)-propanediyl]ferrocene 10. Manganese dioxide (1.3 mg, 15 mmol) was added to a solution of alcohol (1*S*,R_p)-**1** (218 mg, 0.73 mmol) in dichloromethane (30 mL) at 0 °C. The reaction was allowed to warm to room temperature. After 3 h, the solution was filtered over Celite and the solvent evaporated under reduced pressure and purification through column chromatography (45% diethyl ether, 45% petroleum ether and 10% triethylamine to 90% diethyl ether and 10% triethylamine) yielded 81% (175 mg) of (1*S*,R_p)-**10** as a dark red oil; $[\alpha]_D^{20} = -558.8$ (*c* 0.1, $CHCl_3$).

5.2.10. (1*S*,2*S*,R_p)-2-(1-Hydroxyethyl)-1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene 2. A solution of aldehyde (1*S*,R_p)-**10** (160 mg, 0.54 mmol) in dry diethyl ether (20 mL) was stirred at room temperature under nitrogen. After 15 min, 0.5 mL of methyllithium (1.6 M, 0.81 mmol) was slowly added. After 3 min, the solution was hydrolyzed with 20 mL of water-saturated diethyl ether and then with 20 mL of brine. The organics were extracted with several portions of diethyl ether, and the extracts combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine) yielded 50% (84 mg) of (1*S*,2S,R_p)-**2** as yellow crystals (mp 112 °C) and 10% of (1*S*,2*R*,R_p)-**2** as an orange oil.

Compound (1*S*,2*S*,R_p)-**2**: $[\alpha]_D^{20} = +94.2$ (*c* 1.1, $CHCl_3$); IR (cm^{-1}) 3406, 3229, 3087, 2971, 2951, 2925, 2892, 2821, 2777, 1470, 1458, 1426, 1359, 1342, 1093, 1036, 991, 889, 876, 832, 802; ^1H NMR δ 5.07 (1H, q, J = 6.0, –CHO), 4.16 (1H, m, Cp), 4.12 (1H, m, Cp), 4.05 (1H, m, Cp), 3.97 (2H, m, Cp), 3.95 (1H, m, Cp), 3.64 (1H, m, Cp), 2.62 (1H, m, CH_2Cp), 2.51 (1H, m, CH_2C–N), 2.47 (1H, m, CH–N), 2.31 (6H, s, –N(CH_3)$_2$), 2.28 (1H, m, CH_2C–N), 1.93 (1H, m, CH_2C–N), 1.42 (3H, d, J = 6.0, CH_3); ^{13}C NMR δ 90.5 (CIV Cp), 87.5 (CIV Cp), 85.4 (CIV Cp), 71.9 (CIII Cp), 71.5 (CIII Cp), 71.2 (CIII Cp), 69.6 (CIII Cp), 67.9 (CIII Cp), 67.1 (CIII Cp), 66.5 (CH–N), 66.2 (CHO), 64.8 (CIII Cp), 44.9 (N(CH_3)$_2$), 37.2 (CH_2C–N), 25.4 (CH_2Cp), 20.3 (CH_3); MS *m/e* (MALDI TOF, matrix: thap) 352 $[(M+K)]^+$, 336 $[(M+Na)]^+$, 314 $[MH]^+$, 313 $[M]^+$, 251, 207, 191, 169, 148; HRMS (CI) Calcd for $C_{17}H_{23}FeNO$: 313.1129; Found: 313.1125.

Compound (1*S*,2*R*,R_p)-**2**: $[\alpha]_D^{20} = -9.4$ (*c* 0.4, $CHCl_3$); ^1H NMR δ 4.60 (1H, q, J = 6.3, –CHO), 4.49 (1H, m, Cp), 4.10 (1H, m, Cp), 4.08 (1H, m, Cp), 3.98 (2H, m, Cp), 3.95 (1H, m, Cp), 3.89 (1H, m, Cp), 2.56 (1H, m, CH_2C–N), 2.50 (1H, m, CH_2Cp), 2.48 (1H, m, CH–N), 2.33 (1H, m, CH_2C–N), 2.30 (6H, s, –N(CH_3)$_2$), 1.85 (1H, m, CH_2Cp), 1.44 (3H, d, J = 6.3, CH_3); ^{13}C NMR δ 94.7 (CIV Cp), 87.4 (CIV Cp), 82.8 (CIV Cp), 71.3 (CIII Cp), 70.6 (CIII Cp), 69.4 (CIII Cp), 68.5 (CIII Cp), 68.1 (CIII Cp), 68 (CIII Cp), 66.4 (CIII

Cp), 65.7 (CH–N), 63.9 (CHO), 44.5 ($N(CH_3)_2$), 38.2 (CH_2C–N), 24.2 (CH_2Cp), 23.1 (CH_3).

5.2.11. (1*S*,2*S*,R_p)-2-(1-Hydroxy-1-phenylmethyl)-1,1′-[1-(*N*,*N*-dimethylamino)propanediyl]ferrocene 3. A solution of aldehyde (1*S*,R_p)-**10** (160 mg, 0.54 mmol) in dry diethyl ether (20 mL) was stirred at room temperature under nitrogen. After 15 min, 0.4 mL of phenyllithium (2 M, 0.8 mmol) was slowly added. After 3 min, the solution was hydrolyzed with 20 mL of water-saturated diethyl ether and then with 20 mL of brine. The organics were extracted with several portions of diethyl ether, and the extracts were combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and purification through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine) yielded 40% (81 mg) of (1*S*,2*S*,R_p)-**3** as an orange oil and 10% of (1*S*,2*R*,R_p)-**3** as an orange oil.

Compound (1*S*,2*S*,R_p)-**3**: $[\alpha]_D^{20} = -71.2$ (*c* 0.6, $CHCl_3$); IR (cm^{-1}) 3166, 3086, 2951, 2900, 2847, 2821, 2776, 1470, 1448, 1348, 1324, 1239, 1201, 1038, 1018, 893, 843, 806, 736, 699, 668; ^1H NMR δ 7.48 (2H, d, $J = 7.4$, H *ortho* Ph), 7.34 (2H, t, $J = 7.4$, H *meta* Ph), 7.26 (1H, t $J = 7.4$, H *para* Ph), 6.04 (1H, s, –CH–O), 4.10 (1H, m, Cp), 4.05 (1H, m, Cp), 3.99 (1H, m, Cp), 3.92 (1H, m, Cp), 3.91 (1H, m, Cp), 3.83 (1H, m, Cp), 3.25 (1H, m, Cp), 2.70 (1H, m, CH_2Cp), 2.59 (1H, m, CH_2C–N), 2.53 (1H, m, CH–N), 2.42 (1H, m, CH_2C–N), 2.37 (6H, s, –$N(CH_3)_2$), 1.99 (1H, m, CH_2Cp); ^{13}C NMR δ 142.5 (CIV, Ph), 127.8 (CIII *meta* Ph), 127.0 (CIII *para* Ph), 126.7 (CIII *ortho* Ph), 91.6 (CIV Cp), 87.7 (CIV Cp), 84.6 (CIV Cp), 72.7 (CIII Cp), 72.2 (CIII Cp), 71.8 (CHO), 71.2 (CIII Cp), 71.0 (CIII Cp), 70.0 (CIII Cp), 67.2 (CIII Cp), 66.5 (CH–N), 65.9 (CIII Cp), 44.8 ($N(CH_3)_2$), 37.5 (CH_2C–N), 25.5 (CH_2Cp); MS *m/e* (MALDI TOF, matrix: thap) 414 $[(M+K)]^+$, 398 $[(M+Na)]^+$, 376 $[MH]^+$, 375 $[M]^+$, 331 $[M-NMe_2]^+$, 315, 207, 191, 169; HRMS (CI) Calcd for $C_{22}H_{25}FeNO$: 375.1286. Found: 375.1286.

Compound (1*S*,2*R*,R_p)-**3**: $[\alpha]_D^{20} = -95.2$ (*c* 0.2; $CHCl_3$); ^1H NMR δ 7.44 (2H, d, $J = 7.7$, H *ortho* Ph), 7.34 (2H, t, $J = 7.7$, H *meta* Ph), 7.27 (1H, t, $J = 7.7$, H *para* Ph), 6.04 (1H, s, –CH–O), 4.48 (1H, m, Cp), 4.18 (1H, m, Cp), 4.11 (1H, m, Cp), 4.08 (1H, m, Cp), 3.92 (1H, m, Cp), 3.89 (1H, m, Cp), 3.82 (1H, m, Cp), 3.43 (1H, m, CH–N), 3.29 (1H, m, CH_2C–N), 2.77 (6H, s, –$N(CH_3)_2$), 2.66 (1H, m, CH_2Cp), 2.46 (1H, m, CH_2C–N), 1.98 (1H, m, CH_2Cp); ^{13}C NMR δ 143.3 (CIV, Ph), 128.0 (CIII *meta* Ph), 127.7 (CIII *para* Ph), 126.6 (CIII *ortho* Ph), 93.4 (CIV Cp), 87.3 (CIV Cp), 72.7 (1CIV and 1CIII Cp), 72.5 (CIII Cp), 72.0 (CIII Cp), 70.2 (CH–N), (CIII Cp), 69.9 (CIII Cp), 69.8 (CHO), 68.6 (2CIII Cp), 43.0 ($N(CH_3)_2$), 36.3 (CH_2C–N), 25.5 (CH_2Cp).

5.2.12. General procedure for catalytic ethylation of benzaldehyde. A solution of chiral amino alcohol (33 μmol) in 1.5 mL of dry toluene was placed at room temperature under nitrogen. Benzaldehyde (34 μL, 0.33 mmol) then diethylzinc (0.6 mL, 0.66 mmol, 1.1 M in toluene) were added to the reaction mixture via syringe. The mixture was monitored by GC analysis until no more benzaldehyde was present. After completion, aqueous HCl (1 M, 10 mL) was added to quench the reaction. The mixture was extracted with Et_2O and the organic layer washed with brine, dried over Na_2SO_4 and evaporated under vacuum. After evaporation of the solvent, the crude oil was purified by column chromatography and the enantiomeric excess of 1-phenylpropanol determined by chiral gas chromatography (115 °C, 0.75 bar). The amino alcohols can be recovered after an acidic wash of the organic layer, addition of NaOH to the aqueous layer, followed by extraction.

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