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Chiral ferrocenyl amino alcohols for enantioselective additions of diethylzinc to aldehydes

Stéphanie Bastin,[a] Mihaela Ginj,[a] Jacques Brocard,[a] Lydie Pélinski[a,*] and Guy Novogrocki[b]

[a]*Laboratoire de Catalyse de Lille, UMR CNRS 8010, ENSCL 59 652 Villeneuve d'Ascq, France*
[b]*Laboratoire de Cristallochimie et physicochimie du solide, UPRESA 8012, ENSCL 59 652 Villeneuve d'Ascq, France*

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Abstract—Optically active ferrocenyl amino alcohols have been prepared from commercially available L-alaninol, L-leucinol and L-valinol. They have been utilized as chiral ligands in the catalytic addition of diethylzinc to aldehydes. The influence of the substituents on the stereogenic centers of the ligand has been studied. Enantioselectivities up to 95% have been obtained.

1. Introduction

The synthesis of optically active secondary alcohols through enantioselective additions of organometallic reagents has been widely used in stereoselective organic synthesis.[1] Among the organometallic reagents, dialkylzincs have received special attention due to the development of chiral catalysts that enable improvement of the chemoselectivity, the activity and the enantioselectivity of the addition.[2] Thus, a wide variety of chiral catalysts, i.e. amino alcohols,[3] diamines,[4] diols[5] and amino sulfur derivatives[6] promote efficiently this enantioselective alkylation. In particular, chiral organometallic compounds, and especially ferrocene[7] and tricarbonyl(arene)chromium complexes,[8] have emerged as highly efficient chiral catalysts for this reaction. As a consequence, much effort has been devoted to the study of chiral 1,2-disubstituted bidentate ferrocene ligands because of the inherent nature of their planar chirality.[9] These amino alcohols, possessing both planar and central stereogenicities, provide high enantioselectivities (up to 99% e.e.) for the ethylation of aldehydes. More recently, Bolm et al. have reported the synthesis of a ferrocene derivative containing a chiral oxazoline unit and they have demonstrated the importance of the planar chirality in the addition of dialkylzinc to aldehydes.[10] Indeed, chiral ferrocenyl amino alcohols possessing only one single stereogenic centre alpha to the ferrocenyl nucleus exhibit only modest enantioselectivities (41% e.e.).[11] Moreover, Watanabe et al. reported that the presence of a ferrocenyl moiety on the nitrogen atom of ephedrine and norephedrine based ligands plays an important role in the enantiodifferentiation occurring during this alkylation reaction.[12] We have had an ongoing interest in the synthesis of chiral ferrocenyl amino alcohols and their application in enantioselective alkylations to aldehydes with diethylzinc.[13] On the basis of the above-mentioned data, we sought to design new enantiomerically pure ligands possessing both the ferrocenyl unit and the norephedrine skeleton expecting a synergy of the characteristics of both moieties. In a previous communication,[14] we reported on the synthesis of such ligands and their use in the enantioselective addition of diethylzinc to benzaldehyde. Moreover, we showed that the replacement of the phenyl group of the norephedrine skeleton by a ferrocenyl unit led to an enhancement in the enantioselectivity when used as the catalyst in the addition of diethylzinc to benzaldehyde. Herein, we report our full results on the synthesis of ferrocenyl amino alcohols and their catalytic properties for the asymmetric alkylation of various aldehydes by diethylzinc.

2. Results and discussion

2.1. Synthesis of ligands

The amino function of natural L-alaninol **1a**, L-leucinol **1b** and L-valinol **1c** was first protected with an excess of

* Corresponding author. Tel.: +33-3-20434893; fax: +33-3-20436585; e-mail: lydie.pelinski@ensc-lille.fr

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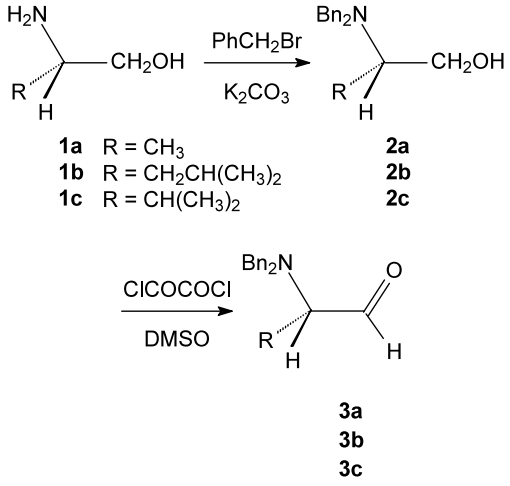
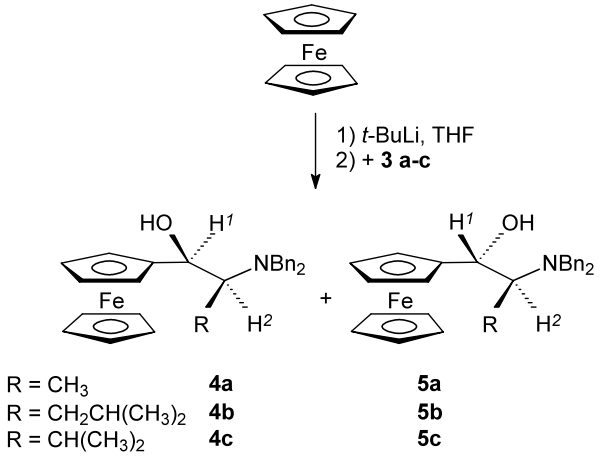
benzyl bromide in the presence of K_2CO_3 leading, respectively, to the amino alcohols **2a**, **2b**, and **2c** in 97, 83 and 78% isolated yields, respectively (Scheme 1). The *N*,*N*-dibenzylamino alcohols **2a**–**c** were then transformed quantitatively into the amino aldehydes **3a**–**c** by a Swern oxidation.



Scheme 1. Synthesis of amino aldehydes **3a**–**c**.

On the other side, ferrocenyllithium,[15] prepared by reaction of ferrocene with *t*-BuLi in THF at −78°C, was added to the amino aldehydes **3a**, **3b** and **3c** providing a mixture of diastereomers **4a**/**5a**, **4b**/**5b** and **4c**/**5c**, respectively (Scheme 2). The yields and the ratios of the diastereomers are summarized in Table 1. The low yields of the addition reaction could be explained by the difficulty in the synthesis of the ferrocenyllithium and by of the steric hindrance of the amino aldehydes. In agreement with the literature,[16] the non-chelation controlled addition of ferrocenyllithium onto the amino aldehydes afforded the 'erythro' isomer **4** as the major diastereomer. This addition process follows the Felkin Anh model. We observed that an increase of the bulkiness of the alkyl group attached to the stereogenic centre led to a decrease in the diastereoselectivity of the ferrocenyllithium addition reaction. Indeed, the diastereoselectivity dropped to 58% in the presence of an isobutyl group on the amine function whereas the addition proceeds with 82 and 84% d.e. in the presence of an isopropyl or a methyl group, respectively. This phenomenon can be attributed to the steric difference between the dibenzylamino residue and the isobutyl group. The ratios of diastereomers were determined by HPLC on the crude isolated product and both diastereomers were separated by silica gel column chromatography. The coupling constant values $J_{1,2}$ (Scheme 2, Table 1) allowed to be established unambiguously the stereochemistry of each diastereomer. The structure of **5a** was confirmed by X-ray structural analysis and the ORTEP view is shown in Figure 1.



Scheme 2. Synthesis of ferrocenyl amino alcohols **4a**–**c** and **5a**–**c**.

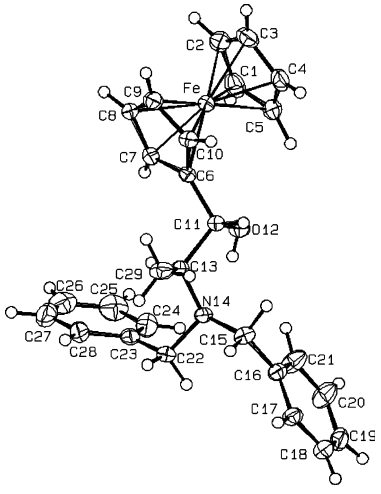


Figure 1. X-Ray crystal structure of **5a**.

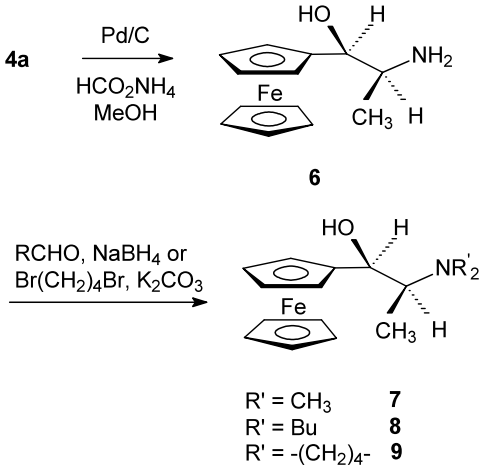
The cleavage of the two benzyl groups led to the primary amine which could be variously bisalkylated. Indeed, the two benzyl groups of the ferrocenylamino alcohol **4a** were cleaved in the presence of a mixture of

Table 1. Addition of ferrocenyllithium to amino aldehydes **3a-3c**

Amino aldehyde	Yield (%)[a]		Ratio of diastereomers (%)[b]		Coupling constants $J_{1,2}$ (H)[c]			
3a	**4a**/**5a**	64	**4a**/**5a**	92/8	**4a**	6	**5a**	9.5
3b	**4b**/**5b**	55	**4b**/**5b**	79/21	**4b**	4	**5b**	9
3c	**4c**/**5c**	51	**4c**/**5c**	91/9	**4c**	5	**5c**	8.5

[a] Isolated yield after column chromatography.
[b] Determined by HPLC analysis on a chiral stationary phase.
[c] Determined by ^{1}H NMR spectroscopy.

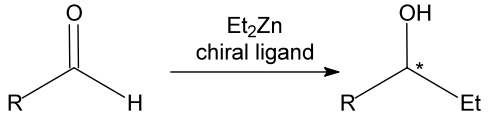
ammonium formate and Pd–C in methanol providing **6** in 60% isolated yield. Then, the *N*,*N*-dimethyl derivative **7** was obtained in 57% yield from **4a** by treatment with formaldehyde and $NaBH_4$ in methanol. Unfortunately, the direct dibutylation of **6** with an excess of butyl iodide in the presence of potassium carbonate led only to monoalkylation of the amino group. Thus, the *N*,*N*-dibutylamino alcohol **8** was obtained by two consecutive reactions of butanal on **6** followed by the reduction with $NaBH_4$ in 36% global yield. The reaction of 1,4-dibromobutane in the presence of potassium carbonate led to the pyrrolidinyl amino alcohol **9** in 57% yield (Scheme 3).



Scheme 3. Synthesis of ferrocenyl amino alcohols **7**–**9**.

2.2. Asymmetric catalyses

In order to examine the catalytic behavior of the ligands, the reaction of diethylzinc with benzaldehyde has been first investigated. The reaction of diethylzinc with benzaldehyde was carried out in toluene at 20°C in the presence of 10 mol% of ferrocenyl amino alcohols (Scheme 4). The results are summarized in Table 2.



Scheme 4. Addition of diethylzinc to aldehydes.

Catalysts afforded 1-phenylpropanol in high yields (86–100%) and in moderate to high enantiomeric excesses (14–95% e.e.). First, our study was focused on the influence of the configuration of the carbon bearing the hydroxyl group and the steric hindrance of the carbon bearing the amino function. It appeared clearly that the absolute configuration of the 1-phenylpropanol correlates with the configuration of the hydroxyl-bearing stereocenter of the ligand (entries 1–2 and 4–5). For example, (*R*)-1-phenylpropanol was obtained in 90% e.e. in the presence of **4a** (entry 1), whereas the opposite (*S*)-1-phenylpropanol was produced with the diastereomer **5a** (73% e.e.) (entry 4). An identical control of the sense of the asymmetric induction expected by the configuration of the alcohol moiety of the catalyst was also observed by Corey when using chiral catalysts derived from ephedrine and pseudoephedrine.[17] The enhancement of the bulkiness on the

Table 2. Addition of diethylzinc to aldehydes in the presence of ferrocenyl amino alcohols **4a**–**c**, **5a**–**b**, **6**–**9**

Entry	Aldehyde	Ligand	Time (h)	Yield (%)[a]	E.e. (%)[b]	Config.[c]
1	Ph	**4a**	17	97	90	*R*
2	Ph	**4b**	22	95	66	*R*
3	Ph	**4c**	72	95	14	*R*
4	Ph	**5a**	5	96	73	*S*
5	Ph	**5b**	6	99	53	*S*
6	Ph	**6**	48	86	21	*R*
7	Ph	**7**	2	100	94	*R*
8	Ph	**7**[d]	3.5	98	94	*R*
9	Ph	**7**[e]	24	96	50	*R*
10	Ph	**7**[f]	5.5	100	94	*R*
11	Ph	**8**	1	100	95	*R*
12	Ph	**9**	1.5	96	95	*R*
13	4-ClC_6H_4	**4a**	26	96	89	*R*
14	4-$OMeC_6H_4$	**4a**	26	92	86	*R*
15	4-ClC_6H_4	**7**	2	98	95	*R*
16	4-$OMeC_6H_4$	**7**	2	96	91	*R*
17	$PhCH{=}CH_2$	**7**	2	100	70	*R*

[a] Determined by ^1H NMR, the by products or the other products being benzyl alcohol and unreacted benzaldehyde.
[b] Determined by GC analysis on FS-Cyclodex β-I/P (30 m×0.24).
[c] Determined from the comparison of the sign of the specific rotation with the literature data.
[d] Using 5 mol% catalyst.
[e] Using 2 mol% catalyst.
[f] The reaction was carried out at 0°C.

carbon bearing the amino function led to a decrease in enantioselectivity (compare entries 1 versus 2 and 3, and 4 versus 5). The presence of an isopropyl group in **4c** involves a low e.e. of 14% and a reaction time of 72 h (entry 3) and consequently its diastereomer **5c** was not studied further.

Ligand **4a** was found to be the most efficient of the series to catalyze the diethylzinc addition. Thus, with the aim of improving the enantioselection, we thought to modify this ligand, particularly by changing the nitrogen substituents. Interestingly, the substituents on the nitrogen atom influence only slightly the selectivity of the transformation, the highest e.e. being obtained with butyl and pyrrolidinyl groups (compare entries 1, 7, 11 and 12). On the other hand, when applying the unsubstituted ligand **6**, a decrease of the enantioselectivity and of the yield were obtained (entry 6).

The reported data show that reaction conditions, temperature and quantity of catalyst, can influence the enantioselectivity.[18] It turned out that a lowering of the temperature had no effect on the selectivity of the reaction. Indeed, carrying out the reaction at either room temperature or 0°C led to 94% e.e. (entries 7 and 10). Diminishing the amount of catalyst **7** from 10 to 5 mol% did not significantly affect the enantioselectivity (entries 7 and 8). However, decreasing the amount of 7 to 2 mol% is detrimental to the enantioselectivity, the e.e. dropped from 94 to 50% (entry 9). Under these reaction conditions, a prolonged reaction time was required. Most interestingly, it is noticeable that the ligands **7** and **8** are more enantioselective than their *N*-methylephedrine[18,19] and *N*,*N*-dibutylnorephedrine[20] analogues. These results suggest that the hindrance of the ferrocenyl group, compared to a phenyl group, plays an important role in the enantioselection. In particular, the gain in e.e. brought about by such coordination is 30% for the *N*,*N*-dimethylated amino alcohol. In a similar manner, Jones reported on the properties of the *N*,*N*-dialkylnorephedrine. A beneficial effect has been reported for the enantioselectivity of the asymmetric alkylation of benzaldehyde in complexing the phenyl group of the above amino alcohols by a $Cr(CO)_3$ unit.[8b]

The catalysts **4a** and **7** were examined for the ethylation of other aromatic aldehydes (entries 13–17, Table 2). *para*-Substituted benzaldehydes afforded the corresponding secondary alcohols in up to 95% e.e.

A great number of theoretical studies on the mechanism of the addition of dialkylzinc to aldehydes has been reported, defining the intermediates and the possible transition states involved in the reaction and providing an understanding of the origin of the asymmetric induction.[21]

Taking these studies into account, we can attempt to provide a qualitative rationale for the stereochemical outcome of the diethylzinc addition catalyzed by the diastereomers **4a** and **5a**. As illustrated in Figure 2, diethylzinc reacts firstly with the ligand **4a** to give the corresponding zinc aminoalkoxide **10** and then converts to the zinc monoalkoxide–diethylzinc complex **11**. Benzaldehyde coordinates at the less hindered face of the five-membered ring chelate. The ethyl group transfers from the diethylzinc to the aldehyde both from the *Re*-face and *Si*-face leads to the *anti*-5/4/4-fused tricyclic transition state **12**-Pro-*R* and **13**-Pro-*S*, respectively. In the transition state **12**-Pro-*R*, the steric repulsion between Et and Ph is absent. Consequently, this transition state is the favored structure and leads to (*R*)-1-phenylpropanol. On the other hand, the strong steric interaction between the Et and Ph groups disfavors the transition state **13**-Pro-*S*, which leads to (*S*)-1-phenylpropanol.

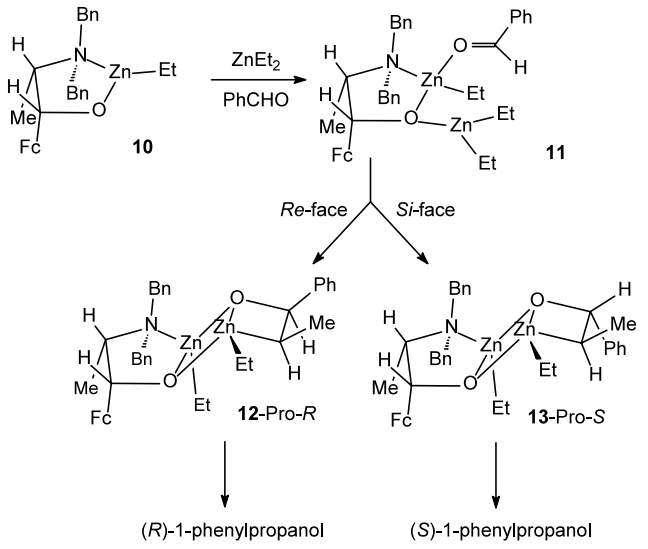


Figure 2. Transition structures derived from amino alcohol **4a**.

In the case of the transition structures derived from amino alcohol **5a** (**14** and **15**) represented in Figure 3, an absence of steric repulsion between Et and Ph is observed in the transition state **14**-Pro-*S*, which leads to (*S*)-1-phenylpropanol, and then explained the inversion of the configuration between both diastereomers.

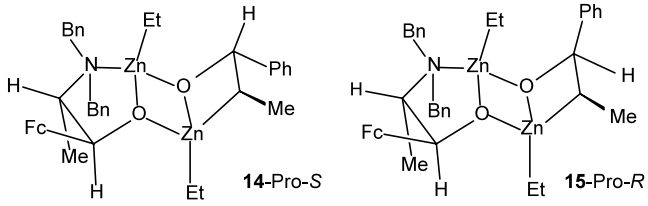


Figure 3. Transition structures derived from amino alcohol **5a**.

3. Conclusion

In summary, nine new enantiopure ferrocenyl amino alcohols have been synthesized. We have shown that the nature and stereochemistry of the substituents in

these ligands have an important influence in their ability to act as catalysts for the enantioselective addition of diethylzinc to aldehydes. We have demonstrated that ferrocenyl amino alcohol **4a** represents an efficient promoter in this catalytic reaction. Application of these amino alcohols as catalytic precursors for other asymmetric transformations are in progress.

4. Experimental

4.1. General

The reactions were performed in oven-dried glassware. All manipulations of air- and moisture-sensitive compounds were carried out under an atmosphere of nitrogen by using standard Schlenk techniques. Tetrahydrofuran and toluene were distilled from sodium/benzophenone ketyl immediately prior to use. Benzaldehyde was distilled under reduced pressure and stored under nitrogen in a Schlenk tube wrapped in an aluminum foil. All other reagents were used as received from common commercial sources. Column chromatography was performed on SiO_2 (Merck, 70–230 mesh, Kieselgel 60). Routine ^1H and ^{13}C NMR spectra were performed in $CDCl_3$ using tetramethylsilane as an internal standard and recorded at rt on a Bruker AC 300 spectrometer operating at 300 and 75 MHz for the two nuclei, respectively. Chemical shifts are given in ppm, and coupling constant (J) are given in hertz. Mass spectra were obtained with a RIBER 10-10 or Concept II H-H (Kustros Analytical Ltd) (FAB) mass spectrometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at wavelength 589 nm (sodium D line). HRMS were performed on a JEOL JMS-700m Station mass spectrometer. Enantiomeric excesses were determined using a gas chromatograph equipped with a chiral column (FS-Cyclodex β-I/P, 30 m×0.24). HPLC analyses were performed on a Shimadzu apparatus equipped with a UV detector and a Chiralcel OD (5×250 mm DAICEL) column. Melting points were determined on a Kofler apparatus and are uncorrected. Spectroscopic analysis of **2a**–**c** and **3a**–**c** were according to the published data.[22]

4.2. General procedure for the protection of amino alcohols

Benzyl bromide (1.264 mL, 10.66 mmol) and K_2CO_3 (1.474 g, 10.66 mmol) were dissolved in a mixture of acetone and water (4/1, 20 mL). The amino alcohol (5.33 mmol) in acetone (60 mL) was added dropwise. After 10 h under reflux, the reaction mixture was extracted by CH_2Cl_2 (3×20 mL) and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvent in vacuo, the crude product was purified by column chromatography (petroleum ether/diethylether = 9:1).

4.2.1. (*S*)-2-(*N*,*N*-Dibenzylamino)-1-propanol 2a. Following the general procedure starting from (*S*)-alaninol **1a** (400 mg), (*S*)-2-(*N*,*N*-dibenzylamino)-1-propanol was obtained as oil (1.32 g, 97%).

4.2.2. (*S*)-2-(*N*,*N*-Dibenzylamino)-4-methyl-1-pentanol 2b. Following the general procedure starting from (*S*)-leucinol **1b** (625 mg), (*S*)-2-(*N*,*N*-dibenzylamino)-4-methyl-1-pentanol was obtained as oil (1.3 g, 83%).

4.2.3. (*S*)-2-(*N*,*N*-Dibenzylamino)-3-methyl-1-butanol 2c. Following the general procedure starting from (*S*)-valinol **1c** (550 mg), (*S*)-2-(*N*,*N*-dibenzylamino)-3-methyl-1-butanol was obtained as oil (1.18 g, 78%).

4.3. General procedure for the oxidation of amino alcohols

Oxalyl chloride (410 μL, 4.71 mmol) in dry CH_2Cl_2 (5 mL) under nitrogen was cooled at −60°C. DMSO (696 μL, 9.80 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the mixture was stirred for 15 min. Amino alcohol (3.92 mmol) in CH_2Cl_2 (10 mL), was added dropwise to the mixture. After 30 min, triethylamine (2.99 mL, 21.57 mmol) was added. After 15 min, the solution was hydrolyzed by water at rt, extracted by CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The residue was used without purification in the next step.

4.3.1. (*S*)-2-(*N*,*N*-Dibenzylamino)propanal 3a. Following the general procedure starting from amino alcohol (1 g), (*S*)-2-(*N*,*N*-dibenzylamino)propanal was obtained as an oil (1.1 g, 96%).

4.3.2. (*S*)-2-(*N*,*N*-Dibenzylamino)pentanal 3b. Following the general procedure starting from amino alcohol (1.16g), (*S*)-2-(*N*,*N*-dibenzylamino)pentanal was obtained as an oil (1.09 g, 90%).

4.3.3. (*S*)-2-(*N*,*N*-Dibenzylamino)butanal 3c. Following the general procedure starting from amino alcohol (1.11g), (*S*)-2-(*N*,*N*-dibenzylamino)butanal was obtained as an oil (1.07 g, 98%).

4.4. General procedure for the synthesis of ferrocenyl amino alcohols

Ferrocene (440 mg, 2.37 mmol) and *t*-BuOK (33 mg, 0.296 mmol) in dry THF (20 mL) were cooled at −78°C under nitrogen. *t*-BuLi (1.7 M in pentane, 1.58 mL, 2.37 mmol) was added dropwise. The mixture was stirred at −78°C for 1 h. The amino aldehyde (1.58 mmol) was dissolved in THF (20 mL) and added to the reaction mixture. After 2 h, the mixture was allowed to warm up to rt, hydrolyzed by H_2O (10 mL) and extracted by ether (3×20 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under vacuum. The product was purified by column chromatography (eluent petroleum ether/diethyl ether gradient).

4.4.1. (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ferrocenyl-1-propanol 4a. Yellow oil (638 mg, 59%). $[\alpha]_D^{20} = +14$ (c 0.54, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta =$ 1.11 (d, $J = 6.5$ Hz, 3H), 2.85 (qd, $J = 6$ and 6.5 Hz, 1H), 3.37 (d, $J = 14$ Hz, 2H), 3.68 (d, $J = 14$ Hz, 2H), 4.08 (m, 1H), 4.14–4.17 (m, 3H), 4.16 (s, 5H), 4.39 (d,

$J=6.0$ Hz, 1H), 7.18–7.39 (m, 10H). ^{13}C (75 MHz, $CDCl_3$): $\delta=9.2$, 54.0, 54.5, 57.9, 65.6, 67.5, 67.6, 68.3, 69.6, 71.4, 92.6, 126.8, 128.1, 128.7, 139.8. MS (FAB): m/z 462 (M^++Na), 440 (M^++H), 420. HRMS (C.I.): calcd for $C_{27}H_{30}FeNO$ m/z 440.1677, found m/z 440.1678.

4.4.2. (1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ferrocenyl-1-propanol 5a. Yellow crystals (56 mg, 5%). Mp 163°C, $[\alpha]_D^{20}=-20$ (c 0.92, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=0.91$ (d, $J=6.5$ Hz, 3H), 2.52 (qd, $J=6.5$ and 9.5 Hz, 1H), 3.32 (d, $J=13.5$ Hz, 2H), 3.86 (d, $J=13.5$ Hz, 2H), 4.00 (m, 1H), 4.03 (m, 2H), 4.10 (m, 1H), 4.15 (d, $J=9.5$ Hz, 1H), 4.18 (s, 5H), 7.23–7.32 (m, 10H). MS (FAB): m/z 478 (M^++K), 462 (M^++Na), 440 (M^++H), 420. ^{13}C (75 MHz, $CDCl_3$): $\delta=8.2$, 53.3, 60.5, 65.0, 66.9, 67.4, 68.2, 68.6, 70.1, 90.2, 127.2, 128.5, 129.0, 138.8. HRMS (C.I.): calcd for $C_{27}H_{30}FeNO$ m/z 440.1677, found m/z 440.1672.

4.4.3. (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ferrocenyl-4-methyl-1-pentanol 4b. Yellow crystals for **4b** (334 mg, 44%). Mp 118°C, $[\alpha]_D^{20}=-141$ (c 1.74, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=0.72$ (d, $J=6.5$ Hz, 3H), 0.88 (d, $J=6.5$ Hz, 3H), 1.28–1.37 (m, 1H), 1.50 (m, 1H), 1.73 (m, 1H), 2.79 (ddd, $J=4$, 6.5 and 6.5 Hz, 1H), 3.48 (d, $J=13.5$ Hz, 2H), 3.56 (d, $J=13.5$ Hz, 2H), 4.04 (m, 1H), 4.09 (m, 1H), 4.13 (m, 1H), 4.17 (s, 5H), 4.31 (m, 1H), 4.61 (d, $J=4.0$ Hz, 1H), 7.23–7.31 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=22.9$, 24.7, 34.0, 54.8, 59.6, 66.1, 67.2, 67.3, 67.9, 68.6, 91.8, 127.0, 128.3, 129.0, 140.0. HRMS (C.I.): calcd for $C_{30}H_{36}FeNO$ m/z 482.2147, found m/z 482.2146.

4.4.4. (1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ferrocenyl-4-methyl-1-pentanol 5b. Yellow oil (84 mg, 11%). $[\alpha]_D^{20}=-120$ (c 0.75, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=0.58$ (d, $J=6.5$ Hz, 3H), 0.69 (d, $J=6.5$ Hz, 3H), 0.98–1.13 (m, 2H), 1.39 (m, 1H), 2.43 (ddd, $J=4.5$, 6 and 9 Hz, 1H), 3.45 (d, $J=13.5$ Hz, 2H), 3.87 (d, $J=13.5$ Hz, 2H), 4.05 (m, 3H), 4.13 (m, 1H), 4.16 (d, $J=9.0$ Hz, 1H), 4.21 (s, 5H), 7.21–7.39 (m, 10H). ^{13}C (75 MHz, $CDCl_3$): $\delta=22.7$, 22.9, 25.8, 35.5, 51.8, 62.9, 65.1, 66.8, 67.7, 68.5, 70.7, 90.9, 127.0, 128.4, 129.1, 139.4. MS (FAB): m/z 482 (M^++H). HRMS (C.I.): calcd for $C_{30}H_{36}FeNO$ m/z 482.2147, found m/z 482.2142.

4.4.5. (1*S*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ferrocenyl-3-methyl-1-butanol 4c. Yellow oil for **4c** (342 mg, 46%). $[\alpha]_D^{20}=-11$ (c 1.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=1.00$ (d, $J=6.5$ Hz, 3H), 1.16 (d, $J=6.5$ Hz, 3H), 2.16–2.23 (m, 1H), 2.52 (dd, $J=5.2$ and 7.7 Hz, 1H), 3.57 (d, $J=13.5$ Hz, 2H), 3.64 (d, $J=13.5$ Hz, 2H), 4.04 (m, 1H), 4.13 (m, 1H), 4.16 (s, 5H), 4.21 (m, 1H), 4.32 (m, 1H), 4.72 (d, $J=5.2$ Hz, 1H), 7.19–7.31 (m, 10H). ^{13}C (75 MHz, $CDCl_3$): $\delta=$ 21.4, 21.5, 27.6, 55.4, 66.7, 67.1, 67.2, 67.3, 67.5, 67.9, 68.2, 68.6, 69.7, 92.8, 126.9, 128.1, 128.2, 129.0, 129.1, 139.9. HRMS (C.I.): calcd for $C_{29}H_{34}FeNO$ m/z 468.4421, found m/z 468.4416.

4.4.6. (1*R*,2*S*)-2-(*N*,*N*-Dibenzylamino)-1-ferrocenyl-3-methyl-1-butanol 5c. Purification of **5c** by column chromatography is not possible, diastereomer **5c** is obtained as a mixture with ferrocene and **4c**. ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=0.70$ (d, $J=7.0$ Hz, 3H), 0.86 (d, $J=7.0$ Hz, 3H), 1.80–1.91 (m, 1H), 2.38 (dd, $J=3.5$ and 8.5 Hz, 1H), 3.66 (d, $J=12.5$ Hz, 2H), 3.70 (d, $J=12.5$ Hz, 2H), 3.90–4.26 (m, 4H), 4.27 (s, 5H), 4.55 (d, $J=8.5$ Hz, 1H), 7.22–7.38 (m, 10H).

4.5. (1*S*,2*S*)-2-Amino-1-ferrocenyl-1-propanol 6

A mixture of ferrocenyl amino alcohol **4a** (400 mg, 0.91 mmol), Pd/C 5% (800 mg) and ammonium formate in MeOH (20 mL) was stirred under reflux for 15 min under nitrogen. The reaction was monitored by thin-layer chromatography (eluent diethyl ether). Pd/C was removed by filtration through a pad of Celite 545, the filtrate was washed with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo to afford the amino alcohol **6** as a yellow–orange powder (188 mg, 80%). Mp 94°C, $[\alpha]_D^{20}=+74$ (c 1.04, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=$ 0.98 (d, $J=6.5$ Hz, 3H), 2.97 (qd, $J=4.8$ and 6.5 Hz, 1H), 4.15–4.22 (m, 4H), 4.22 (s, 5H), 4.27 (m, 1H). ^{13}C (75 MHz, $CDCl_3$): $\delta=51.2$, 65.0, 67.9, 68.0, 68.4, 68.7, 74.5, 90.0. δ MS (FAB): m/z 298 (M^++K), 282 (M^++Na), 259 (M^+). HRMS (C.I.): calcd for $C_{13}H_{17}FeNO$ m/z 259.0660, found m/z 259.0661.

4.6. (1*S*,2*S*)-2-(*N*,*N*-Dimethylamino)-1-ferrocenyl-1-propanol 7

A mixture of ferrocenyl amino alcohol **6** (336 mg, 1.29 mmol) and 37% aqueous solution of formaldehyde (971 μL) in MeOH (20 mL) was stirred under reflux for 30 min. The reaction mixture was allowed to cool down to rt and $NaBH_4$ (73 mg, 1.93 mmol) was slowly added. The reaction was run at rt for 1 h, treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified on silica gel chromatography (petroleum ether/diethyl ether/triethylamine gradient) giving the amino alcohol **7** as a yellow powder (214 mg, 57%). Mp 48–50°C, $[\alpha]_D^{20}=+7$ (c 0.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=0.88$ (d, $J=7$ Hz, 3H), 2.26 (s, 6H), 2.44 (qd, $J=4$ and 7 Hz, 1H), 4.12 (m, 3H), 4.19 (s, 5H), 4.31 (m, 1H), 4.58 (d, $J=4$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=9.2$, 42.6, 64.8, 66.0, 66.9, 67.2, 67.6, 68.6, 70.5, 91.2. HRMS (C.I.): calcd for $C_{15}H_{21}FeNO$ m/z 287.0973, found m/z 287.0978.

4.7. (1*S*,2*S*)-2-(*N*,*N*-Dibutylamino)-1-ferrocenyl-1-propanol 8

The ferrocenyl amino alcohol **6** (100 mg, 0.386 mmol) and butyraldehyde (250 μL, 1.54 mmol) were dissolved in ethanol (20 mL) in the presence of molecular sieves 3 Å (3g). The reaction mixture was stirred for 30 min at rt. $NaBH_4$ (147 mg, 3.86 mmol) was added slowly. The reaction was run for 1 h at rt, treated with H_2O (20

mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the crude monoalkylated product used without purification in the next step. This latter was dissolved in CH_2Cl_2 (20 mL) in the presence of butyraldehyde (250 μL, 1.54 mmol) and molecular sieves 4 Å (3 g). The reaction mixture was heated under reflux for 1 h 30 m. Molecular sieves was removed by filtration through a pad of Celite. After evaporation of CH_2Cl_2, the crude product was dissolved in MeOH (20 mL) and $NaBH_4$ was added slowly to the reaction mixture. The reaction was stirred at rt for 1 h and quenched with water (20 mL), extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were then dried over Na_2SO_4, concentrated in vacuo. The resulting crude product was purified on silica gel chromatography (petroleum ether/diethyl ether gradient) affording the ferrocenyl amino alcohol **8** as a yellow oil (52 mg, 36%). $[\alpha]_D^{20}=+31$ (*c* 0.35, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$+D_2O): $\delta=$ 0.86 (t, $J=7$ Hz, 6H), 0.89 (d, $J=7$ Hz, 3H), 1.16–1.38 (m, 8H), 2.20–2.28 (m, 4H), 2.86 (qd, $J=5.5$ and 7 Hz), 4.06 (m, 1H), 4.11 (m, 2H), 4.19 (s, 5H), 4.26 (m, 1H), 4.35 (d, $J=5.5$ Hz, 1H). ^{13}C (75 MHz, $CDCl_3$): $\delta=9.8$, 14.1, 20.5, 31.0, 50.9, 59.8, 66.0, 66.9, 67.3, 67.5, 68.6, 70.7, 90.9. HRMS (C.I.): calcd for $C_{21}H_{34}FeNO$ m/z 372.1990, found m/z 372.1982.

4.8. (1*S*,2*S*)-2-(Pyrrolidinyl)-1-ferrocenyl-1-propanol 9

A mixture of ferrocenyl amino alcohol **6** (100 mg, 0.386 mmol), 1,4-dibromoethane (146 μL, 1.2 mmol) and potassium carbonate (106 mg, 0.772 mmol) in MeOH (30 mL) was stirred under reflux for 24 h. The reaction mixture was treated with H_2O (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purified on silica gel chromatography (petroleum ether/diethyl ether/triethylamine gradient) giving the amino alcohol **9** as a yellow powder (69 mg, 57%). Mp 66°C, $[\alpha]_D^{20}=$ −31 (*c* 0.16, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$+ D_2O): $\delta=0.86$ (d, $J=6.6$ Hz, 3H), 1.78 (m, 4H), 2.57 (m, 2H), 2.69 (m, 2H), 4.07 (m, 1H), 4.11 (m, 2H), 4.19 (s, 5H), 4.34 (m, 1H), 4.72 (d, $J=3.0$ Hz, 1H). MS (FAB) m/z: 352 (M^++K), 314 (M^++H), 199, 98. HRMS (C.I.): calcd for $C_{18}H_{24}FeNO$ m/z 326.2417, found m/z 326.2420.

4.9. General procedure for the condensation of diethylzinc on aldehydes

Aldehyde (1.1 mmol), chiral amino alcohol complex (0.11 mmol) and toluene were placed in a Schlenk tube with a valve and gas inlet. Diethylzinc (2.2 mL, 2.2 mmol, 1 M in hexane) was added to the reaction mixture via a syringe. The reaction mixture was stirred at rt and the progress of the reaction was monitored by GC. The reaction was quenched with aqueous HCl (1N, 10 mL), extracted with diethyl ether (3×20 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated in vacuo.

4.10. X-Ray crystallographic study

A yellow crystal of approximate dimensions 0.3×0.2× 0.15 mm was mounted on a glass fiber. X-Ray measurements were made using a Bruker SMART CCD area-detector diffractometer with Mo Kα ($\lambda=0.71073$ Å) at $T=298$ K. Crystal data: orthorhombic $P2_12_12_1$: $a=10.978(2)$, $b=11.011(2)$, $c=18.825(3)$ Å; $V=2275$ Å^3; formula unit $FeC_{27}NOH_{29}$ with $Z=4$; $\rho_{calcd}=1.283$ g cm^{-3}; $F(000)=928$; $\mu(MoK\alpha)=0.68$ mm^{-1}. 19823 reflections were collected ($1.5°<\theta<31.2°$). The structure was solved by direct methods and hydrogen atoms located on Fourier difference maps. Full-matrix least-squares refinement on F^2 based on 5962 independent reflections ($R_{int}=0.046$) converged with 358 parameters (U of hydrogen atoms were fixed at 1.2 times the U_{iso} of the atoms they were bound to). $R_1=0.0351$ (for the 3306 data with $I>2\sigma(I)$); $wR_2=0.0792$; GoF = 0.838. Flack parameter = −.007(.014) so the absolute structure is correct. $\Delta\rho_{max}=0.204$ $\Delta\rho_{min}=-.109$ e Å^{-3}.

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