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Synthesis of chiral ferrocenyl aminoalcohols involving a diastereospecific oxidation: use in asymmetric catalysis

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Abstract

The synthesis of six new chiral ferrocenic aminoalcohols has been performed. One step of this synthesis was a diastereospecific oxidation of diastereomeric mixtures of 1-[2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]alcohols by manganese dioxide: one diastereomer was oxidized, while the other stayed inert. The six new chiral compounds in association with $ZnEt_2$ proved to be good catalysts in the asymmetric ethylation of benzaldehyde (77 to 88% ee).

1. Introduction

Asymmetric reduction is a common method for the synthesis of chiral molecules, especially the reduction of prochiral ketones into the corresponding hydroxy compound (by BH_3).[1] The opposite reaction, i.e. enantio- or diastereostereoselective oxidation, has hardly been employed and represents interesting methodologies as well. Enantioselective oxidation methods found in the literature, aimed at resolving racemic alcohols, are methods using enzymes (for example, biocatalytic methods[2]) or using chiral auxiliaries or chiral catalysts (for example, for the syntheses of chiral sulfoxides by oxidation of sulfides,[3] of chiral epoxides from allylic alcohols[4a,b] or alkenes[4c,d]) or the kinetic resolution of chiral alcohols by hydrogen transfer.[5] To the best of our knowledge, diastereoselective oxidations, where one diastereomer is preferentially oxidized, have only been carried out with cyclic allylic alcohols in the presence of MnO_2. In these cases, the rate and selectivity of oxidation are related to the equatorial or axial position of the hydroxyl group.[6]

In our laboratory, we are interested in the synthesis of enantiomerically pure ligands.[7] During the synthesis of a series of chiral ferrocenic aminoalcohols, we have discovered that the oxidation of the two diastereomers (1′*R*,1*S*) and (1′*R*,1*R*) of 1-[2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]ethanol **2** by

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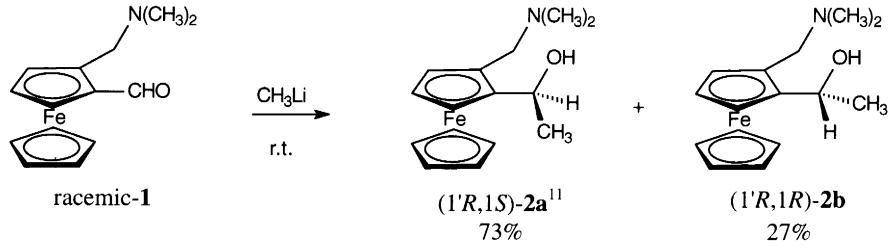
manganese dioxide was diastereospecific.[8] Here we would like to extend this unusual diastereospecific oxidation to other similar aminoalcohols and to report the synthesis of a series of chiral ferrocenyl aminoalcohols. These new compounds have been evaluated as ligands in the reaction of ethylation of benzaldehyde with diethylzinc.

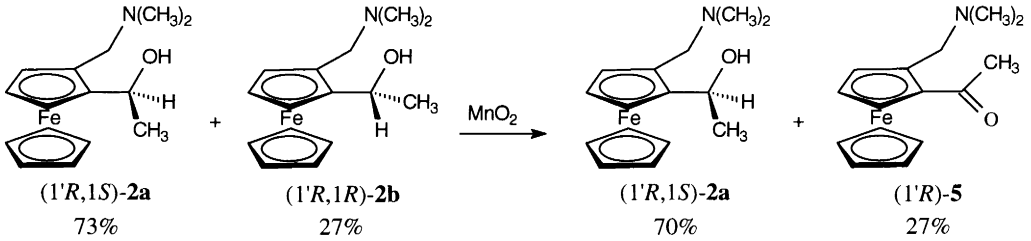
2. Results and discussion

The phenomenon of diastereospecific oxidation has been discovered during the oxidation of (1′*R*,1*S*)-1-[2-(*N*,*N*-dimethylaminomethyl)ferrocenyl]ethanol **2**.[8] This compound was obtained starting from (1′*R*)-2-(*N*,*N*-dimethylaminomethyl)ferrocenecarboxaldehyde **1**. The first step of the synthesis was the resolution of aminoaldehyde **1**. The Nicolosi's procedure,[9] which implies a lipase-promoted kinetic resolution, has allowed the preparation of enantiopure (1′*R*)-**1**[10] (ee >98%, determined by ^{1}H NMR in $CDCl_3$, using 1 equiv. of Pirkle's alcohol) by the use of *Candida rugosa* lipase (*CRL*). The action of CH_3Li on enantiopure (1′*R*)-**1** led to a diastereomeric mixture of alcohols **2** (Scheme 1).



Scheme 1.

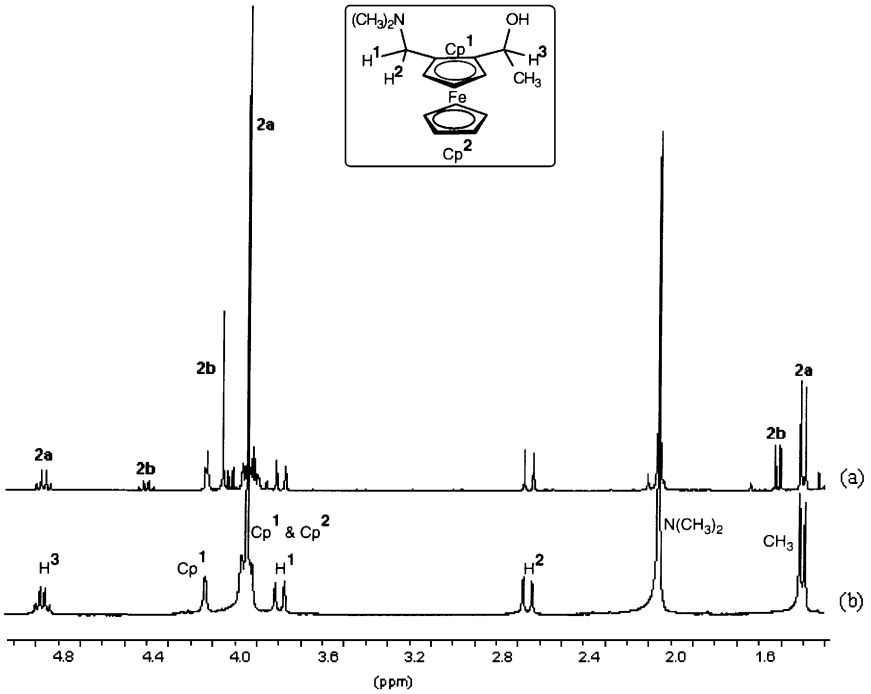
This reaction was stereoselective, leading to a 73:27 diastereomeric ratio (as determined by ^{1}H NMR). The separation of the diastereomers could not be achieved by column chromatography, so that the oxidation was attempted on the mixture in the presence of MnO_2, a typical achiral reagent for the oxidation of alcohols. The reaction was conducted in dichloromethane at 0°C; MnO_2 was added and the solution was allowed to warm to room temperature for 1 hour. After work-up, 27% of ketone **5** and 70% of the remaining alcohol **2** were recovered (Scheme 2). The ^{1}H NMR spectrum of the remaining alcohol showed only the presence of diastereomer **2a** (Scheme 3).



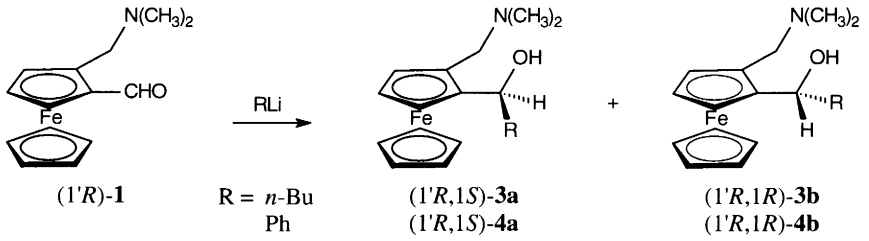
Scheme 2.

Obviously, the alcohol:ketone **2**:**5** ratio was almost the same as the **2a**:**2b** diastereomeric ratio before oxidation. This observation indicates that **2b** has been completely oxidized, while **2a** stayed totally inert, i.e., the oxidation was diastereospecific. To confirm this interesting result, we have synthesized other similar aminoalcohols derived from aldehyde (1′*R*)-**1** (Scheme 4, Table 1).

In fact, alcohols **3** and **4** were obtained by action of, respectively, *n*-BuLi and PhLi on (1′*R*)-**1**. The diastereomeric ratios were of the same order as for **2**.



Scheme 3. Comparison of the 300 MHz ^{1}H NMR spectra (realized at room temperature, in $CDCl_3$) of: (a) the mixture of diastereomers **2a** and **2b** before oxidation; and (b) the remaining alcohol after oxidation: a difference exists between the chemical shifts of H^3, Cp^2 and CH_3 of the two diastereomers



Scheme 4.

The mixtures of aminoalcohols were then oxidized under the same conditions than above. The ketones and the remaining alcohols were separated over column chromatography and analyzed by ^{1}H NMR. The results are summarized in Table 2.

Table 1
Action of RLi on aldehyde (1′*R*)-**1**; diastereomeric ratio of the resulting alcohols before oxidation

Entry	RLi	Resulting alcohol	(1′*R*,1*S*)/(1′*R*,1*R*) ratio[a]
1	CH_3Li	**2**	73 : 27
2	n-C_4H_9Li	**3**	62 : 38
3	C_6H_5Li	**4**	73 : 27

[a] As determined by ^{1}H NMR.

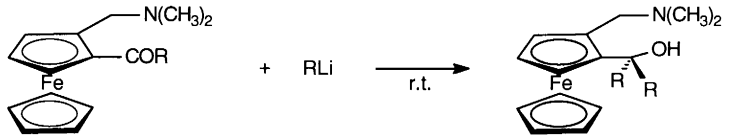
Once again, the final alcohol:ketone ratio was almost identical, within experimental error, to the initial **3a**:**3b** (**4a**:**4b**) diastereomeric ratio. In conclusion, the diastereospecific oxidation was observed with

Table 2
Oxidation of the mixtures of aminoalcohols **2**–**4**

Entry	Starting alcohol	Isolated remaining alcohol			Isolated ketone	
			Yield (%)	d.e. (%)		Yield (%)
1	**2**	(1'*R*,1*S*)-**2a**	70	> 98	(1'*R*)-**5**	27
2	**3**	(1'*R*,1*S*)-**3a**	65	> 98	(1'*R*)-**6**	30
3	**4**	(1'*R*,1*S*)-**4a**	65	> 98	(1'*R*)-**7**	27

aminoalcohols **3** and **4** as well. In fact, the major interest of this reaction for our synthesis is that the two diastereomers of **2**, **3** and **4** were not separable by column chromatography.[11] By action of MnO_2, only one diastereomer was oxidized, offering the possibility of isolating the other diastereomer. In this manner, we could recover pure aminoalcohols (1′*R*,1*S*)-**2a**, (1′*R*,1*S*)-**3a** and (1′*R*,1*S*)-**4a**, three new ligands.

Starting from ketones (1′*R*)-**5**, (1′*R*)-**6** and (1′*R*)-**7**, three other new chiral ligands, (1′*R*)-**8**, (1′*R*)-**9** and (1′*R*)-**10**, were developed. Effectively, those aminoketones were reduced by an alkyllithium compound, where the alkyl group was the same as the one borne by the carbonyl function (Scheme 5, Table 3).



R = CH_3 (1'*R*)-**5**; n-C_4H_9 (1'*R*)-**6**; C_6H_5 (1'*R*)-**7**

(1'*R*)-**8**; (1'*R*)-**9**; (1'*R*)-**10**

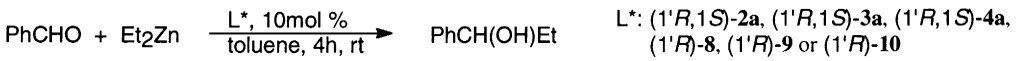
Scheme 5.

Table 3
Synthesis of chiral aminoalcohols (1′*R*)-**8**–**10**: action of RLi on aminoketones (1′*R*)-**5**–**7**

Entry	Aminoketone	RLi	Resulting aminoalcohol		
				Yield (%)	e.e. (%)[a]
1	(1'*R*)-**5**	CH_3Li	(1'*R*)-**8**	75	> 98
2	(1'*R*)-**6**	n-C_4H_9Li	(1'*R*)-**9**	81	> 98
3	(1'*R*)-**7**	C_6H_5Li	(1'*R*)-**10**	78	> 98

[a] Determined by ^1H NMR in $CDCl_3$, using 1 eq of Pirkle's alcohol.

New aminoalcohols (1′*R*,1*S*)-**2a**, (1′*R*,1*S*)-**3a**, (1′*R*,1*S*)-**4a**, (1′*R*)-**8**, (1′*R*)-**9** and (1′*R*)-**10**, derived from the preceding syntheses, are potential chiral ligands and their performances were evaluated in the catalytic ethylation of benzaldehyde by Et_2Zn[12] (Scheme 6, Table 4).



Scheme 6.

All aminoalcohols directed the catalytic process towards the same (1*S*)-1-phenylpropanol enantiomer. Aminoalcohol **4** gave the best result, i.e., 99% yield and 88% ee.

Table 4
Enantioselective ethylation of benzaldehyde by $ZnEt_2$ in the presence of 10 mol% of chiral amino-alcohols (1′*R*,1*S*)-**2a**–**4a** and (1′*R*)-**8**–**10**

Entry	Aminoalcohol	1-Phenylpropanol	
		Yield (%)[a]	e.e. (%)[b] (configuration)
1	(1'*R*,1*S*)-**2a**	97	81 (1*S*)
2	(1'*R*,1*S*)-**3a**	100	77 (1*S*)
3	(1'*R*,1*S*)-**4a**	99	88 (1*S*)
4	(1'*R*)-**8**	99	79 (1*S*)
5	(1'*R*)-**9**	99	81 (1*S*)
6	(1'*R*)-**10**	82	83 (1*S*)

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

3. Conclusion

The synthesis of six new chiral aminoalcohols and three new chiral aminoketones has been performed. The six enantiomerically pure aminoalcohols evaluated as ligands in the reaction of diethylzinc with benzaldehyde proved to have good inducing properties. This synthesis has highlighted the diastereo-specific oxidation of diastereomeric mixtures of aminoalcohols **2**, **3** or **4** with MnO_2, allowing three compounds — **2a**, **3a** and **4a** — to be isolated. Further studies are in progress to try to explain this phenomenon.

4. Experimental

The reactions were performed in glassware under an atmosphere of nitrogen. Diethyl ether was freshly distilled from sodium. Manganese dioxide was obtained from Acros and alkyllithium reagents from Aldrich. Column chromatography were performed on SiO_2 (Merck, 70–30 mesh, Kieselgel 60). ^{1}H NMR and ^{13}C NMR spectra were measured at room temperature with a Bruker AC 300 spectrometer for samples in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were obtained with a RIBER 10-10 (EI) or Kratos Concept II H-H (FAB) mass spectrometer. Optical rotations were measured at 20°C with a Perkin–Elmer 241 polarimeter at 589 nm. Enantiomeric excesses were determined by gas chromatography with a chiral column (FS-Cyclodex β-I/P, 30 m×0.24 mm). Elemental analyses were performed by the CNRS at Lyon.

*4.1. General procedure for preparation of aminoalcohols **2**–**4***

A solution of 2-(*N*,*N*-dimethylaminomethyl)ferrocenylcarbaldehyde **1** (540 mg, 2.0 mmol) in dry diethyl ether (20 ml) was stirred at room temperature under nitrogen. After 15 min, 1.5 equiv. of alkyllithium was slowly added. After 1 h, the solution was hydrolyzed with 20 ml of water-saturated diethyl ether and then with 20 ml of water. 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 the alcohols were purified through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine).

*4.1.1. (1′*R*)-1-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]ethanol* ***2***

The general procedure described above was applied with methyllithium (1.6 M, 3.0 mmol, 1.87 ml) to 90% of **2** in the form of an orange mixture of **2a** (73%) and **2b** (27%) (orange oil).

^{1}H NMR of the mixture: compound **2a**: δ 4.97 (q: J=6.5 Hz, 1H, C*H*-CH_3), 4.23 (m, 1H, C_5H_3), 4.08–4.00 (m, 2H, C_5H_3), 4.04 (s, 5H, C_5H_5), 3.89 (d: J=12.5 Hz, 1H, CH_2N), 2.75 (d: J=12.5 Hz, 1H, CH_2N), 2.16 (s, 6H, $N(CH_3)_2$), 1,50 (d: J=6.5 Hz, 3H, C*H*$_3$-CH). Compound **2b**: same δ as the major one except: δ 4.53 (q: J=6.5 Hz, 1H, C*H*-CH_3) and 1.61 (d: J=6.5 Hz, 3H, C*H*$_3$-CH).

*4.1.2. (1′*R*)-1-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]pentanol* ***3***

The general procedure described above was applied with *n*-butyllithium (2.5 M, 3 mmol, 1.2 ml) to 92% of **2** in the form of an orange mixture of **3a** (62%) and **3b** (38%) (orange oil).

^{1}H NMR of the mixture: compound **3a**: δ 4.75 (dd: J=9.2 Hz and J=3.1 Hz, 1H, C*H*-C_4H_9), 4.20 (m, 1H, C_5H_3), 4.15 (m, 1H, C_5H_3), 4.04 (s, 5H, C_5H_5), 4.00 (m, 1H, C_5H_3), 3.90 (d: J=12.4 Hz, 1H, CH_2N), 2.75 (d: J=12.4 Hz, 1H, CH_2N), 2.15 (s, 6H, $N(CH_3)_2$), 1.95–1.80 (m, 2H, CH_2 butyl group), 1.78–1.61 (m, 2H, CH_2 butyl group), 1.60–1.37 (m, 2H, CH_2 butyl group), 1.00 (t: J=7.1 Hz, 3H, C*H*$_3$-CH_2). Compound **3b**: same δ as the major one except: δ 4.29 (dd: J=9.2 Hz and J=3.1 Hz, 1H, C*H*-C_4H_9), 3.86 (d: J=12.4 Hz, 1H, CH_2N), 2.78 (d: J=12.4 Hz, 1H, CH_2N).

*4.1.3. (1′*R*)-1-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]-1-phenylmethanol* ***4***

The general procedure described above was applied with phenyllithium (1.6 M, 3 mmol, 1.87 ml) to 92% of **2** in the form of a mixture of **4a** (73%) and **4b** (27%) (orange oil).

^{1}H NMR of the mixture: compound **4a**: δ 7.6–7.3 (m, 5H, C_6H_5), 5.92 (s, 1H, C*H*-C_6H_5), 4.10 (m, 1H, C_5H_3), 4.06 (s, 5H, C_5H_5), 4.02 (d: J=12.6 Hz, 1H, CH_2N), 3.93 (m, 1H, C_5H_3), 3.47 (m, 1H, C_5H_3), 2.86 (d: J=12.6 Hz, 1H, CH_2N), 2.23 (s, 6H, $N(CH_3)_2$). Compound **4b**: δ 7.6–7.3 (m, 5H, C_6H_5), 5.46 (s, 1H, C*H*-C_6H_5), 4.06 (m, 1H, C_5H_3), 4.00 (m, 1H, C_5H_3), 3.95 (m, 1H, C_5H_3), 3.88 (s, 5H, C_5H_5), 3.83 (d: J=12.6 Hz, 1H, CH_2N), 2.84 (d: J=12.6 Hz, 1H, CH_2N), 2.18 (s, 6H, $N(CH_3)_2$).

4.2. General procedure for oxidation

Manganese dioxide (18.4 mmol, 1.6 g) was added to a mixture of alcohols (1.9 mmol) in dichloromethane (30 ml) at 0°C. The reaction was allowed to warm to room temperature. After 1 h, the solution was filtered and the solvent evaporated in vacuo. The remaining alcohol and the ketone were easily separated on silica gel (70% diethyl ether, 20% petroleum ether and 10% triethylamine).

*4.2.1. (1′*R*,1*S*)-1-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]ethanol* ***2a*** *and (1′*R*)-[2-(*N,N-*dimethylaminomethyl)ferrocenyl]methylketone* ***5***

The general procedure described above was applied to the mixture of the two diastereomers of **2** (545 mg, 1.9 mmol).

The remaining alcohol **2a** was isolated in 70% yield (381 mg), as a yellow oil; $[\alpha]_D$=−43 (*c* 0.285, $CHCl_3$); the ^{1}H NMR spectrum is identical to the corresponding major diastereomer; ^{13}C NMR: δ 92.14, 83.78 (C_5H_3, C IV), 70.76, 66.17, 65.33 (C_5H_3, C III), 68.98 (C_5H_5), 64.24 (*C*H-CH_3), 58.20 (CH_2), 44.32 ($N(CH_3)_2$), 19.41 (*C*H_3-CH); MS: (*m/z*) 287 (M^+, 56.9), 270 (19.8), 243 (100.0), 199 (32.7); anal. calcd for $C_{15}H_{21}FeNO$: C, 62.73; H, 7.37; N, 4.87. Found: C, 62.80; H, 7.35; N, 4.86.

Ketone **5** was isolated in 27% yield (147 mg), as a brown oil; $[\alpha]_D$=+403 (*c* 0.26, $CHCl_3$); ^{1}H NMR: δ 4.65 (m, 1H, C_5H_3), 4.55 (m, 1H, C_5H_3), 4.42 (m, 1H, C_5H_3), 4.15 (s, 5H, C_5H_5), 4.12 (d: J=12.7 Hz, 1H, CH_2N), 3.19 (d: J=12.7 Hz, 1H, CH_2N), 2.42 (s, 3H, CH_3CO), 2.25 (s, 6H, $N(CH_3)_2$); ^{13}C NMR:

δ 203 (CO), 95.02, 86.51 (C_5H_3, C IV), 75.51, 72.00, 70.41 (C_5H_3, C III), 70.44 (C_5H_5), 57.28 (CH_2), 45.07 ($N(CH_3)_2$), 28.58 (CH_3CO); MS: (*m/z*) 285 (M^+, 100.0), 270 (94.0), 242 (88.1), 228 (18.7), 163 (31.1), 121 (40.4); anal. calcd for $C_{15}H_{19}FeNO$: C, 63.17; H, 6.72; N, 4.91. Found: C, 63.52; H, 6.51; N, 4.89.

*4.2.2. (1′*R*,1*S*)-1-[2-(*N,N*-Dimethylaminomethyl)ferrocenyl]pentanol **3a** and (1′*R*)-butyl[2-(*N,N*-dimethylaminomethyl)ferrocenyl]ketone **6***

The general procedure described above was applied to the mixture of the 2 diastereomers of **3** (605 mg, 1.84 mmol).

Remaining alcohol **3a** was isolated in 65% yield (393 mg), as a yellow oil; $[\alpha]_D=-146$ (*c* 0.62, $CHCl_3$); the ^1H NMR spectrum is identical to the corresponding major diastereomer; ^{13}C NMR: δ 92.05, 83.62 (C_5H_3, C IV), 70.61, 68.02, 66.54 (C_5H_3, C III), 69.01 (C_5H_5), 65.39 (*C*H-*n*Bu), 58.23 (CH_2N), 44.32 ($N(CH_3)_2$), 33.68 (CH(OH)-*C*H_2), 28.90 (CH_2-*C*H_2-CH_2), 22.94 (*C*H_2-CH_3), 14.22 (*C*H_3-CH_2); MS: (*m/z*) 329 (M^+), 312, 285; anal. calcd for $C_{18}H_{27}FeNO$: C, 65.66; H, 8.26; N, 4.25. Found: C, 65.42; H, 8.27; N, 4.28.

Ketone **6** was isolated in 30% yield (180 mg), as a brown oil; $[\alpha]_D=+303$ (*c* 0.3, $CHCl_3$); ^1H NMR: δ 4.66 (m, 1H, C_5H_3), 4.54 (m, 1H, C_5H_3), 4.40 (m, 1H, C_5H_3), 4.15 (d: *J*=12.7 Hz, 1H, CH_2N), 4.13 (s, 5H, C_5H_5), 3.21 (d: *J*=12.7 Hz, 1H, CH_2N), 2.9–2.75 (m, 1H, $COCH_2Pr$), 2.75–2.58 (m, 1H, $COCH_2Pr$), 2.24 (s, 6H, $N(CH_3)_2$), 1.75–1.60 (m, 2H, CH_2 butyl group), 1.50–1.35 (m, 2H, CH_2 butyl group), 0.97 (t: *J*=7.3 Hz, 3H, C*H*$_3$-CH_2); ^{13}C NMR: δ 203.15 (CO), 96.12, 86.58 (C_5H_3, C IV), 75.24, 71.22 (C_5H_3, C III), 70.30 (C_5H_5), 57.34 (CH_2N), 45.09 ($N(CH_3)_2$), 40.08 (CO-*C*H_2), 26.32 (CH_2-*C*H_2-CH_2), 22.63 (*C*H_2-CH_3), 14.04 (*C*H_3-CH_2); MS: (*m/z*) 328 (MH^+), 283, 270; anal. calcd for $C_{18}H_{25}FeNO$: C, 66.06; H, 7.70; N, 4.28. Found: C, 66.30; H, 7.41; N, 4.32.

*4.2.3. (1′*R*,1*S*)-1-[2-(*N,N*-Dimethylaminomethyl)ferrocenyl]-1-phenylmethanol **4a** and (1′*R*)-[2-(*N,N*-dimethylaminomethyl)ferrocenyl]phenylketone **7***

The general procedure described above was applied to the mixture of the two diastereomers of **4** (642 mg, 1.84 mmol).

The remaining alcohol **4a** was isolated in 65% yield (417 mg), as a yellow oil; $[\alpha]_D=-176$ (*c* 0.5, $CHCl_3$); the ^1H NMR spectrum is identical to the corresponding major diastereomer; ^{13}C NMR: δ 141.90 (C_6H_5, C IV), 127.87 (C_6H_5, *meta*), 127.20 (C_6H_5, *ortho*), 127.11 (C_6H_5, *para*), 93.42, 83.20 (C_5H_3, C IV), 71.59, 70.91, 69.19 (C_5H_3, C III), 69.02 (C_5H_5), 64.32 (*C*H-C_6H_5), 58.31 (CH_2N), 44.27 ($N(CH_3)_2$); MS: (*m/z*) 349 (M^+, 61.9), 304 (100.0), 242 (17.6), 167 (33.3); anal. calcd for $C_{20}H_{23}FeNO$: C, 68.78; H, 6.64; N, 4.01. Found: C, 68.78; H, 6.63; N, 4.02.

Ketone **7** was isolated in 27% yield (172 mg), as a red oil; $[\alpha]_D=-285$ (*c* 0.1, $CHCl_3$); ^1H NMR: δ 7.82 (d: *J*=6.3 Hz, 2H, C_6H_5), 7.53 (t: *J*=6.3 Hz, 1H, C_6H_5), 7.44 (d: *J*=6.3 Hz, 2H, C_6H_5), 4.65 (m, 1H, C_5H_3), 4.51 (m, 1H, C_5H_3), 4.43 (m, 1H, C_5H_3), 4.17 (d: *J*=13.0 Hz, 1H, CH_2N), 4.14 (s, 5H, C_5H_5), 3.42 (d: *J*=13.0 Hz, 1H, CH_2N), 2.24 (s, 6H, $N(CH_3)_2$); ^{13}C NMR: δ 201.00 (CO), 140.42 (C_6H_5, C IV), 131.48 (C_6H_5, *meta*), 128.20 (C_6H_5, *ortho*), 128.00 (C_6H_5, *para*), 88.52 (C_5H_3, C IV), 75.49, 72.75, 70.31 (C_5H_3, C III), 70.30 (C_5H_5), 57.03 (CH_2N), 45.07 ($N(CH_3)_2$); MS: (*m/z*) 347 (M^+), 302, 177; anal. calcd for $C_{20}H_{21}FeNO$: C, 69.18; H, 6.09; N, 4.03. Found: C, 68.87; H, 6.20; N, 4.10.

*4.3. General procedure for the synthesis of aminoalcohols **8–10***

A solution of enantiopure aminoketone (0.50 to 0.55 mmol) in 20 ml of dry diethyl ether was stirred at room temperature under nitrogen. After 10 min, 1.5 equiv. of alkyllithium was slowly added via

syringe. After 1 h, the solution was hydrolyzed with 20 ml of water-saturated diethyl ether and then with 20 ml of water. The organic compounds were extracted with several portions of diethyl ether, the extracts were combined, washed twice with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the alcohol was purified through column chromatography (70% diethyl ether, 20% petroleum ether and 10% triethylamine).

*4.3.1. (1′*R*)-2-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]-2-propanol* ***8***

The general procedure described above was applied to aminoketone **5** (147 mg, 0.51 mmol) with methyllithium (1.5 M, 0.77 mmol, 512 μl).

Aminoalcohol **8** was obtained in 75% yield (115 mg), as a yellow oil. $[\alpha]_D$=–64 *(c* 0.6, $CHCl_3$); ^{1}H NMR: δ 4.12 (s, 5H, C_5H_5), 4.05 (d: J=12.6 Hz, 1H, CH_2N), 3.98 (m, 2H, C_5H_3), 3.96 (m, 1H, C_5H_3), 2.63 (d: J=12.6 Hz, 1H, CH_2N), 2.14 (s, 6H, $N(CH_3)_2$), 1.72 (s, 3H, $C(CH_3)_2$), 1.38 (s, 3H, $C(CH_3)_2$); ^{13}C NMR: δ 98.26, 80.74 (C_5H_3, C IV), 70.66, 67.18 (C_5H_3, C III), 69.21 (C_5H_5), 64.93 ($C(CH_3)_2$), 59.50 (CH_2), 44.07 ($N(CH_3)_2$), 32.68 (CH_3-$C(CH_3)$), 31.81 (CH_3-$C(CH_3)$); MS: (*m/z*) 301 (M^+, 87.1), 283 (100.0), 239 (60.4), 119 (42.5); anal. calcd for $C_{16}H_{23}FeNO$: C, 63.80; H, 7.70; N, 4.65. Found: C, 63.99; H, 7.80; N, 4.60.

*4.3.2. (1′*R*)-5-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]-5-propanol* ***9***

The general procedure described above was applied to aminoketone **6** (180 mg, 0.55 mmol) with *n*-butyllithium (2.5 M, 0.83 mmol, 331 μl).

Aminoalcohol **9** was obtained in 81% yield (171 mg), as a yellow oil. $[\alpha]_D$=−96 *(c* 0.6, $CHCl_3$); ^{1}H NMR: δ 4.14 (s, 5H, C_5H_5), 4.06 (d: J=12.4 Hz, 1H, CH_2N), 4.02 (m, 1H, C_5H_3), 3.98 (m, 1H, C_5H_3), 3.88 (m, 1H, C_5H_3), 2.60 (d: J=12.4 Hz, 1H, CH_2N), 2.15 (s, 6H, $N(CH_3)_2$), 2.0–1.1 (m, 12H, CH_2 butyl groups), 1.01 (t: J=7 Hz, 3H, CH_3 butyl group), 0.81 (t: J=7 Hz, 3H, CH_3 butyl group); ^{13}C NMR: δ 99.12, 80.84 (C_5H_3, C IV), 73.55, 70.22, 67.90 (C_5H_3, C III), 69.25 (C_5H_5), 65.11 ($C(n\text{Bu})_2$), 59.86 (CH_2N), 44.25 ($N(CH_3)_2$), 42.79, 42.16 (CH(OH)-CH_2), 26.78, 25.90 (CH_2-CH_2-CH_2), 23.67, 23.19 (CH_2-CH_3), 14.34, 14.12 (CH_3-CH_2); MS: (*m/z*) 385 (M^+, 36.5), 367 (32.5), 322 (62.8), 283 (100.0); anal. calcd for $C_{22}H_{35}FeNO$: C, 68.56; H, 9.15; N, 3.63. Found: C, 68.21; H, 9.20; N, 3.70.

*4.3.3. (1′*R*)-1-[2-(*N,N-*Dimethylaminomethyl)ferrocenyl]-1,1-diphenylmethanol* ***10***

The general procedure described above was applied to aminoketone **7** (172 mg, 0.5 mmol) with *t*-butyllithium (1.5 M, 0.74 mmol, 0.5 ml).

Aminoalcohol **10** was obtained in 78% yield (166 mg), as a yellow oil. $[\alpha]_D$=−169 *(c* 0.4, $CHCl_3$); ^{1}H NMR: δ 7.69–7.13 (m, 10H, $2C_6H_5$), 4.07 (m, 2H, C_5H_3), 3.96 (s, 5H, C_5H_5), 3.81 (m, 1H, C_5H_3), 3.68 (d: J=13 Hz, 1H, CH_2N), 2.67 (d: J=13 Hz, 1H, CH_2N), 1.98 (s, 6H, $N(CH_3)_2$); ^{13}C NMR: δ 150.01, 147.32, 127.51, 127.30, 127.25, 127.12, 126.43, 126.29 ($2C_6H_5$), 96.24, 82.20 (C_5H_3, C IV), 77.59, 70.71, 70.47 (C_5H_3, C III), 69.82 (C_5H_5), 65.41 ($C(C_6H_5)_2$), 59.13 (CH_2N), 44.27 ($N(CH_3)_2$); MS: (*m/z*) 425 (M^+, 55.8), 380 (100.0), 242 (20.21); anal. calcd for $C_{26}H_{27}FeNO$: C, 73.41; H, 6.40; N, 3.29. Found: C, 72.99; H, 6.50; N, 3.35.

4.4. General procedure for catalytic ethylation of benzaldehyde

A solution of aldehyde (1.1 mmol), chiral aminoalcohol (0.10 mmol) in 1.5 ml of dry toluene was placed at room temperature under nitrogen. Diethylzinc (4.0 ml, 4.4 mmol, 1.1 ml in toluene) was added to the reaction mixture via syringe. The solution was stirred and the reaction was monitored by GLC. After completion, aqueous HCl (1N, 10 ml) was added to quench the reaction. The mixture was extracted

with diethyl ether and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated under vacuum. The residue was purified by column chromatography. The absolute configuration of the alcohol was determined from the sign of the specific rotation.[13]

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