Diastereoselective 1,2-Addition of Organometallic Reagents to Chiral Formylferrocenes Leading to Enantiomerically Pure Ferrocenyl Amino Alcohols: Application to Asymmetric Dialkylzinc Addition to Aldehydes and Synthesis of Optically Active 1,2-Homodisubstituted Ferrocenes

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The chiral formylferrocenes **2**–**5** have been readily prepared in good yields by *ortho*-lithiation of the TMS-blocked or -unblocked aminoferrocenes and subsequent reaction with DMF. The stereochemistry of the reaction of **2** with organometallic reagents has been examined. Reactions of **2** with Grignard and organolithium reagents gave the corresponding amino alcohol **6** in good yields with moderate to high diastereomeric excesses (up to 99%). When a dialkylzinc was used as the nucleophile, a single diastereomer was obtained almost exclusively. This reaction may be rationalized in terms of an autocatalytic mechanism; the zinc alkoxide **7** generated in situ functions as an activator of dialkylzinc, which then adds to the formyl group. We have examined the asymmetric diethylzinc addition to benzaldehyde using formylferrocenes **2**–**5** or ferrocenyl amino alcohols **6a**, **13** as catalysts, especially with regard to the relationship between catalytic activity and the chirality of the diastereomeric ferrocenes. Alkylation with **2**, **3**, and **6a** gave (1*R*)-phenyl-1-propanol in good yields with high *ee* values (87–91% *ee*). On the other hand, reactions with **4**, **5**, and **13** gave the (*S*)-product in low yield and with low *ee* (38–57% *ee*). The low stereoselectivities can be attributed to stereochemical mismatching in the zinc alkoxides derived from **4** and **5**. With aromatic, straight-chain, or branched aliphatic aldehydes, the stereoselective alkylation successfully gave the corresponding alcohols in good to high optical purities when **2** or **3** was employed as the catalyst. The optically active 1,2-ferrocenediol and -diphosphane have been prepared by means of the stereospecific substitution reaction with the amino alcohol **13** on treatment with acetic anhydride, followed by hydrolysis or substitution with diphenylphosphane.

Introduction

Chiral ferrocenes are classified into those having central, planar, or C_2 chirality, and they generally have one or a combination of these three chiralities.[1] The unique structure of ferrocenes allows one to design a variety of chiral substituted derivatives. Suitably designed chiral ferrocenes may induce high stereoselectivities in organic reactions as either chiral auxiliaries, ligands, or building blocks.[2] A classical route to chiral ferrocenes is optical resolution of the racemate and limited quantities of compounds have been prepared by this method.[1,3] Recent successes in the synthesis of various chiral ferrocenes without optical resolution have now attracted considerable attention with regard to asymmetric synthesis.[4] For example, homochiral oxazoline and acetal can be prepared from achiral ferrocenecarboxylic acid[5] and formylferrocene,[6] respectively. The C_2-symmetrical 1,1′-ferrocenediol is obtained from asymmetric reduction of 1,1′-diacyl ferrocene and can be converted into the corresponding ferrocenediamine and -diphosphane derivatives.[7] The planar chiral ferrocene can be prepared by regioselective lithiation of the achiral ferroceneamide with a chiral lithium reagent.[8]

A chiral formylferrocene has recently been reported by Kagan et al. as an attractive precursor for ligands of transition metal catalysts in that the formyl group could be stereospecifically reduced or alkylated.[6] Herein, we wish to report the stereoselective alkylation of the aminoformylferrocene (**2**) with organometallic reagents, leading to a synthesis of ferrocenyl amino alcohols. An autocatalytic mechanism for the reaction with dialkylzinc is proposed, which accounts for the fact that no further catalyst is required. We would also like to discuss the application of the new class of chiral 1,2-amino alcohols to asymmetric dialkylzinc addition to an aldehyde and the synthesis of the optically active 1,2-ferrocenediol and -diphosphane through stereospecific substitution reactions with the amino alcohol.[9]

Results and Discussion

Preparation of the Chiral Formylferrocene and Its Reaction with Organometallic Reagents

The chiral formylferrocene, 1-[1(*S*)-dimethylaminoethyl]-2(*Rp*)-formylferrocene **2**, was readily prepared in good yield by *ortho*-lithiation of [1(*R*)-dimethylaminoethyl]ferrocene **1** and subsequent reaction with dimethylformamide (DMF)

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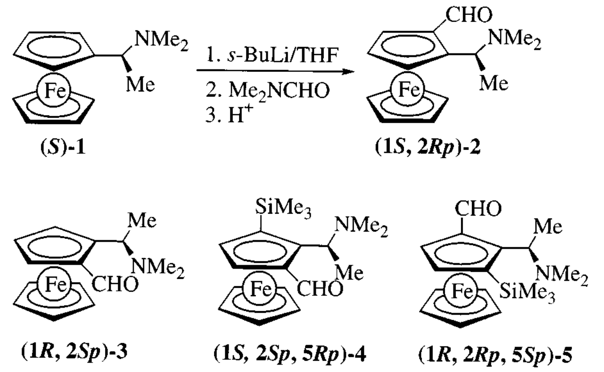
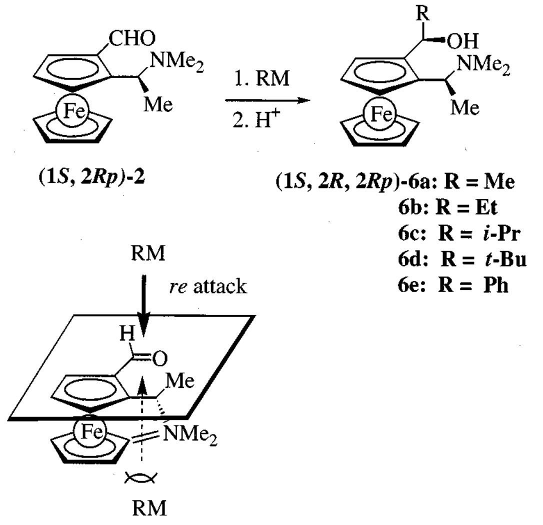
(Scheme 1).[10] Further chiral formylferrocenes **3**−**5** were similarly prepared starting from trimethylsilyl-blocked[11] or -unblocked amino ferrocenes. The ferrocenes **2**−**5** were found to be air-stable and could be stored for a long time (more than one year) at ambient temperature without noticeable decomposition. They have been characterized spectroscopically and analytically. The ferrocenes (1*S*,2*Rp*)-**2** and (1*R*,2*Sp*)-**3** represent enantiomers, and the silylferrocenes (1*S*,2*Sp*,5*Rp*)-**4** and (1*R*,2*Rp*,5*Sp*)-**5** are another pair of enantiomers; the silylferrocene (1*S*,2*Sp*,5*Rp*)-**4** could be a diastereomer of (1*S*,2*Rp*)-**2** if the TMS group is removed.[12]



Scheme 1

We first examined the stereochemistry of the reaction of **2** with organometallic reagents, specifically Grignard reagents, organolithium, and dialkylzinc compounds (Scheme 2). The results of these reactions are summarized in Table 1. Reactions of **2** with methyl- and ethylmagnesium bromides gave the corresponding amino alcohol **6** in good yield as a diastereomeric mixture with 75% diastereomeric excess (*de*). The reaction proceeded much more stereoselectively when more bulky Grignard reagents such as isopropyl- or *tert*-butylmagnesium halides were used, the *de* values being in excess of 99%. Reaction with methyllithium gave the product with low diastereoselectivity, and the selectivity remained low even when the sterically hindered *tert*-butyllithium was used. Reactions with phenylmagnesium and -lithium led in both cases to the corresponding amino alcohol with greater than 99% *de*. The absolute configurations of the major diastereomers **6** were determined by ^{1}H NMR with reference to the literature value; we could assign them as (1*S*,2*R*,2*Rp*).[13] Organometallic reagents attack the formyl group from the top, away from the sterically hindered lower cyclopentadienyl ring. Since *re* face attack is observed, the carbonyl group is directed towards the *ortho* amino group substituent.[14]

One of the previously reported preparative methods for ferrocenyl amino alcohol involves sequential lithiation of the aminoferrocene **1** and trapping with an aldehyde.[13] However, this method often affords a mixture of diastereomers with low *de* (0−75%). Consequently, alkylation of the formylferrocene is superior to this method for the preparation of diastereomerically pure ferrocene compounds.



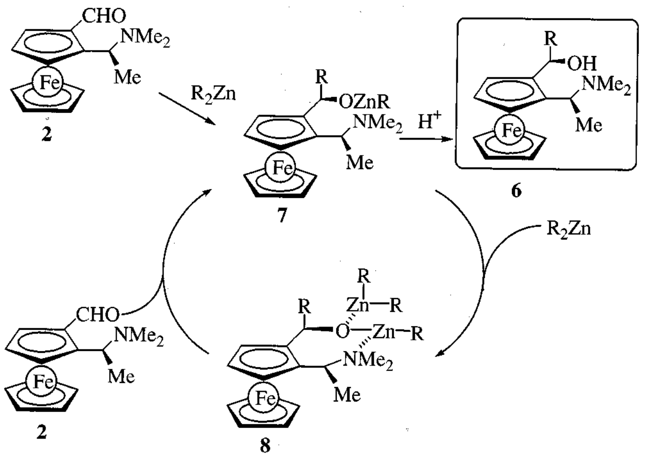
Scheme 2

Table 1. Reaction of the chiral formylferrocene (1*S*,2*Rp*)-**2** with organometallic reagents (RM)

Entry	RM[a]	Yield [%][b]	*de* [%][c]
1	MeMgI	93	74
2	EtMgI	90	75
3	*i*PrMgBr	88	>99
4	*t*BuMgCl	78	>99
5	PhMgBr	57	>99
6	MeLi	88	54
7	*t*BuLi	73	77
8	PhLi	68	>99
9[d]	Me_2Zn	80	>99
10[d]	Et_2Zn	96	>99

[a] 1-[1(*S*)-dimethylaminoethyl]-2(*R*)-formylferrocene (**2**) (1 mmol), RM (1 mmol); THF (5 mL), −78 °C, room temp., 15 h. − [b] Isolated yield. − [c] Determined by ^{1}H and ^{13}C NMR. − [d] The reaction was carried out at 0 °C for 15 h in toluene (5 mL).

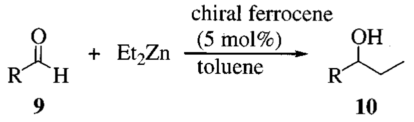
Interestingly, when dimethyl- or diethylzinc was used as the nucleophile, essentially just a single diastereomer was obtained, even though the alkyl group is not sterically hindered. This major diastereomer proved to be the same as that obtained from the reactions with Grignard reagents or methyllithium. It is noteworthy that this reaction proceeded smoothly without a catalyst, even though it is well-established that asymmetric alkylation of aldehydes with dialkylzinc needs a certain catalyst, such as a Lewis acid, a sulfonamide, or an amino alcohol (including a ferrocenyl amino alcohol). While our work was in progress, Brocard et al. reported a related reaction utilizing a formylferrocene possessing only planar chirality.[15] The reaction with dialkylzinc may be rationalized in terms of an autocatalytic (or auto-activation) mechanism, as shown in Scheme 3.[16] In the initial step of the reaction, a small amount of zinc alkoxide **7** is generated, which functions as an activator of dialkylzinc. With further dialkylzinc, the zinc alkoxide **7** forms the complex **8**, which reacts with further formylferrocene to give more **7** and hence the autocatalytic cycle can be repeated. This hypothesis has been confirmed as described in the next section.



Scheme 3

Asymmetric Dialkylzinc Addition to Aldehydes in the Presence of the Formylferrocene

Since the zinc alkoxide **7** was formed stereoselectively in the autocatalytic reaction system, it could be envisaged as functioning as an asymmetric catalyst for the alkylation of an external aldehyde that was added to the reaction system. We thus examined the addition of diethylzinc to benzaldehyde using **2**−**5** (actually their corresponding alkoxides in the reaction system) as catalysts with regard to the relationship between the catalytic activity and chirality of these diastereomeric ferrocenes (Scheme 4). The reactions were performed using 5 mol% of the formylferrocene in toluene solution at 0 °C and were allowed to proceed for 15 h.



Scheme 4

As shown in Table 2, the alkylations with **2** and **3** gave the (*R*)- and (*S*)-isomers of 1-phenyl-1-propanol, respectively, in good yields with high *ee* values (87−91% *ee*) (runs 1 and 2).[17] On the other hand, **4** and **5** showed not only lower catalytic activity than **2** and **3**, but also gave the product with low *ee* (38−57% *ee*). The absolute configurations of the generated 1-phenyl-1-propanol were consistent within the pairs **2**/**4** and **3**/**5**, suggesting that the central absolute configurations of the α-amino substituents of the ferrocenes should be the main factor in determining the asymmetric induction. The low *ee* values achieved with **4** and **5** may either be due to a mismatching of the stereochemistry or due to the steric effects of the bulky TMS group. As mentioned above, the actual catalyst should be the zinc alkoxide **7**; the ferrocenyl amino alcohol may be used as a catalyst instead of the formylferrocene. We next examined the reaction using the TMS-free ferrocenyl amino alcohols, (1*S*,2*R*,2*Rp*)-**6a** and (1*S*,2*S*,2*Sp*)-**13**, which were stereoselectively obtained from **2** and **4**, respectively, by reaction with dimethylzinc (the preparative method for **13** will be discussed later). A similar stereochemical outcome was obtained using either stereoisomer; with **6a** the (*R*)-alcohol was obtained in high *ee* (81%), while the use of **13** resulted in low stereoselectivity (*R*; 27% *ee*). From this result, we may conclude that the TMS group does not affect the stereoselectivity, but that stereochemical mismatching in the zinc alkoxides derived from **4** and **5** is most likely responsible for the low stereoselectivities.[18]

Table 2. Ethylation of benzaldehydes with diethylzinc catalyzed by formylferrocenes

Entry	Catalyst	Yield [%][a]	*ee* [%][b]	Configuration
1	(1*S*,2*Rp*)-**2**	94	91	*R*
2	(1*R*,2*Sp*)-**3**	92	87	*S*
3	(1*S*,2*Sp*,5*Rp*)-**4**	48	38	*R*
4	(1*R*,2*Rp*,5*Sp*)-**5**	56	57	*S*
5	(1*S*,2*R*,2*Rp*)-**6a**	93	81	*R*
6	(1*S*,2*S*,2*Sp*)-**13**	84	27	*R*

[a] Isolated yield after PTLC. − [b] Determined by HPLC using Daicel Chiralcel OD column (*i*PrOH/hexane = 10:90) and/or by GC using Astec Chiraldex B-PH chiral capillary column.

Table 3 shows the typical results of the ethylation of representative aldehydes using **2**−**5** as catalysts. With aromatic, straight-chain, or branched aliphatic aldehydes, the stereoselective alkylation successfully gave the corresponding alcohols with moderate to high optical purities when **2** and **3** were employed as catalysts. The use of ferrocenes **4** and **5** again led to low selectivities (36% *ee*) in the reaction with cyclohexanecarbaldehyde. Only a slight difference in *ee* values between 4-methoxy- and 4-nitrobenzaldehyde may be taken as evidence that the electronic effect on the reaction is negligible.

Transformation of the Amino Alcohol to Optically Active 1,2-Ferrocenediol and 1,2-Ferrocenediphosphane

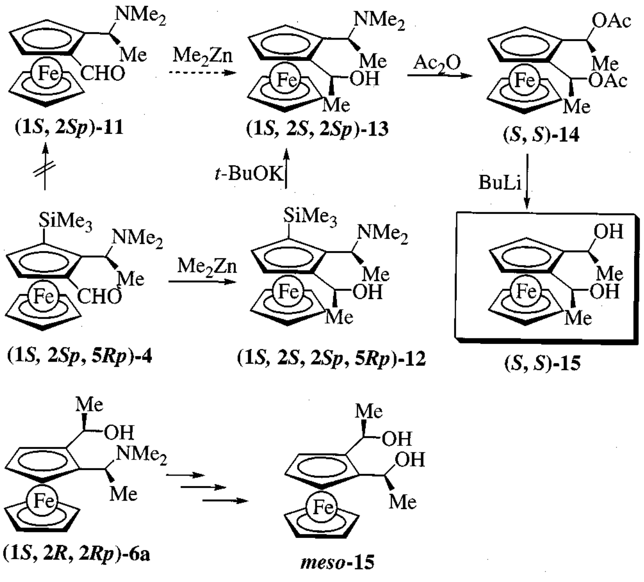
The C_2-symmetrical 1,1′-ferrocenediol is of current interest as it can be expected to act as a chiral ligand in metal complexes and as a precursor of 1,1′-disubstituted ferrocenes such as the diamine or diphosphane, which may serve as new classes of chiral ligands for metal complex catalysts.[7] We are also interested in 1,2-ferrocenediol as another new chiral ligand, which may be prepared through retentive α-substitution of **6a** and/or **13** by acetate. The ferrocenyl amino alcohol (1*S*,2*S*,2*Sp*)-**13** was prepared in good overall yield (68%) by stereoselective methylation of **4** with dimethylzinc followed by desilylation.[11] On treating **13** overnight with acetic anhydride, we obtained the 1,2-diacetate (*S*,*S*)-**14**, treatment of which with *n*BuLi gave (*S*,*S*)-**15** in good yield (Scheme 5). Optical rotation measurements confirmed this to be an optically active compound. On the other hand, conversion of (1*S*,2*R*,*Rp*)-**6a** to its 1,2-diol by a similar procedure led to a non-optically active compound, i.e. *meso*-**14**.

Reaction of (*S*,*S*)-**14** with an excess of diphenylphosphane afforded the air-sensitive diphenylphosphane with retention of configuration, which could be isolated as the borane-protected diphosphane (*S*,*S*)-**16** on treatment with BH_3SMe_2 (Scheme 6).[7]

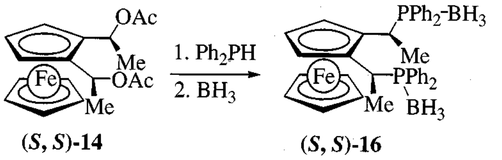
Table 3. Ethylation of aldehydes with diethylzinc catalyzed by **2−5**

Entry	Catalyst	Aldehyde	Yield [%][a]	*ee* [%][b]	Configuration
1	**2**	4-methoxybenzaldehyde	97	93	*R*
2	**3**	4-methoxybenzaldehyde	97	99	*S*
3	**2**	4-nitrobenzaldehyde	89	87	*R*
4	**3**	4-nitrobenzaldehyde	88	91	*S*
5	**2**	1-naphthaldehyde	91	88	*R*
6	**2**	ferrocenecarbaldehyde	90	81	*R*
7	**2**	cinnamaldehyde	85	80	*R*
8	**2**	cyclohexanecarbaldehyde	87	82	*R*
9	**3**	cyclohexanecarbaldehyde	98	80	*S*
10	**4**	cyclohexanecarbaldehyde	79	36	*R*
11	**5**	cyclohexanecarbaldehyde	43	36	*S*
12	**2**	isobutyraldehyde	73	81	*R*
13	**2**	pivaldehyde	55	80	*R*
14	**2**	3-phenylpropanal	88	83	*R*
15	**2**	octanal	86	55	*R*
16	**3**	octanal	99	56	*S*

[a] Isolated yield after PTLC. − [b] Determined by HPLC using Daicel Chiralcel OD column (*i*PrOH/hexane = 10:90) and/or by GC using Astec Chiraldex B-PH chiral capillary column.



Scheme 5



Scheme 6

Conclusions

Reactions of the chiral formylferrocenes **2−5** with Grignard and organolithium reagents have been shown to give the corresponding amino alcohol **6** in good yields with moderate to high diastereomeric excesses (up to 99%). When dialkylzinc was used as the nucleophile, one diastereomer was formed almost exclusively. The asymmetric addition of diethylzinc to aldehydes was found to proceed with high stereoselectively (up to 95% *ee*) in the presence of catalytic amounts of the formylferrocenes **2** or **3** or ferrocenyl amino alcohol **6a**. On the other hand, reactions with **4**, **5**, and **13** gave the (*S*)-product in low yield and with low *ee* (38−57% *ee*). The low stereoselectivities can be ascribed to stereochemical mismatching in the zinc alkoxides derived from **4** and **5**. The optically active 1,2-ferrocenediol and -diphosphane could be obtained by means of the stereospecific substitution reaction with the amino alcohol **13** on treatment with acetic anhydride, followed by hydrolysis or reaction with diphenylphosphane.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM A-400 NMR (400 MHz) spectrometer with samples in $CDCl_3$ solution. Chemical shifts are reported in δ units downfield from Me_4Si used as an internal reference. − Infrared spectra were recorded on a JASCO Herschel FT-IR-230A spectrometer. − HPLC analyses were carried out on a Hitachi L-7100 apparatus equipped with a UV detector using Daicel Chiralcel OB, OJ, and OD columns (0.46 mm × 25 cm) eluting with 2-propanol/*n*-hexane (1:9 → 1:99). − GC-MS analyses were performed on a Hewlett-Packard 5980/5972 instrument equipped with a chiral capillary column (Asteck, Ciraldex G-TA) (0.25 mm × 30 m) using helium as the carrier gas. − Optical rotations were determined on a JASCO DIP-370 apparatus. − Elemental analyses were carried out using a Yanaco CHN CORDER MT-5. − Column chromatography was performed on a Yamazen YFLC-254 and a Michael Miller column equipped with a UV detector using Merck silica gel 60. Preparative TLC was carried out using 20 × 20 cm glass plates coated with a 2 mm thick layer of Merck kieselgel 60 PF_{254}.

General Procedure for the Preparation of Chiral Formylferrocene: A two-necked, round-bottomed flask containing a magnetic stirring bar was charged with [1(*S*)-dimethylaminoethyl]ferrocene **1** (>99% *ee*) (4.00 g, 15.6 mmol) and dry diethyl ether (50 mL) under a slight pressure of nitrogen. The flask was cooled in an ice bath, whereupon a hexane solution of *n*BuLi (1.5 M, 13 mL, 19.5 mmol) was added by means of a syringe through the septum under magnetic stirring. After 2 h, DMF (2.5 mL, 31.0 mmol) was added at the same temperature. When the addition was complete, the ice bath was removed and the mixture was allowed to warm to room temperature and stirred for a further 17 h. The reaction was then quenched with water, and the resulting solution was extracted with diethyl ether (3 × 20 mL). The combined extracts were washed (brine), dried (K_2CO_3), and filtered, and the solvent was removed in a rotary evaporator to leave a brown residue. The crude oily product solidified on washing with hexane at −78 °C. Recrystallization of the solid from hexane/chloroform gave the pure 1-[1(*S*)-dimethylaminoethyl]-2(*Rp*)-formylferrocene **2**. Yield: 2.5 g (8.77 mmol, 56%). Brown solid; m.p. 62−64 °C. − $[\alpha]_D^{25} = +176.4$ ($c = 1.0$, MeOH). − ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.48$ (d, $J = 6.8$ Hz, 3 H, CH_3), 2.09 (s, 6 H, NCH_3), 4.15 (q, $J = 6.8$ Hz, 1 H, CHN), 4.23 (s, 5 H, CpH), 4.54 (s, 1 H, CpH), 4.58 (s, 1 H, CpH), 4.81 (s, 1 H, CpH), 10.11 (s, 1 H, CH=O). − ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (CH_3), 40.3 (NCH_3), 55.4 (CHN), 68.5, 69.3, 70.2, 71.1, 72.3, 91.4, 193.1 (C=O). − IR (KBr): $\tilde{\nu} = 1672$ (C=O) cm^{-1}. − $C_{15}H_{19}FeNO$ (285.16): calcd. C 63.18, H 6.72, N 4.91; found C 63.21, H 6.71, N 4.87.

1-[1(*R*)-Dimethylaminoethyl]-2(*Sp*)-formylferrocene (3): The title compound was obtained in 60% yield by lithiation of (*R*)-**1** followed by formylation with DMF. Brown solid; m.p. 61−63 °C. − $[\alpha]_D^{25} = -176.7$ ($c = 0.77$, MeOH). − ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.48$ (d, $J = 6.8$ Hz, 3 H, CH_3), 2.09 (s, 6 H, NCH_3), 4.15 (q, $J = 6.8$ Hz, 1 H, CHN), 4.23 (s, 5 H, CpH), 4.54 (s, 1 H, CpH), 4.58 (s, 1 H, CpH), 4.81 (s, 1 H, CpH), 10.11 (s, 1 H, CH=O). − ^{13}C NMR ($CDCl_3$): $\delta = 14.5$ (CH_3), 40.3 (NCH_3), 55.4 (CHN), 68.5, 69.3, 70.2, 71.1, 72.3, 91.4, 193.1 (C=O). − IR (KBr): $\tilde{\nu} = 1671$ (C=O) cm^{-1}. − $C_{15}H_{19}FeNO$ (285.16): calcd. C 63.17, H 6.72, N 4.91; found C 63.15, H 6.74, N 4.69.

1-[1(*S*)-Dimethylaminoethyl]-2(*S*)-formyl-5(*Rp*)-trimethylsilylferrocene (4): The title compound was obtained in 61% yield by lithiation of 1-[1(*S*)-dimethylaminoethyl]-2(*Rp*)-trimethylsilylferrocene followed by formylation with DMF. Brown solid; m.p. 137−139 °C. − $[\alpha]_D^{25} = -798.3$ ($c = 1.0$, MeOH). − ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.30$ (s, 9 H, $SiCH_3$), 1.77 (d, $J = 6.8$ Hz, 3 H, CH_3), 2.03 (s, 6 H, NCH_3), 3.11 (q, $J = 6.8$ Hz, 1 H, CHN), 4.22 (s, 5 H, CpH), 4.48 (d, $J = 2.4$ Hz, 1 H, CpH), 4.94 (d, $J = 2.4$ Hz, 1 H, CpH), 10.50 (s, 1 H, CHO). − ^{13}C NMR: $\delta = 0.0$ ($SiCH_3$), 22.7 (CH_3), 43.2 (NCH_3), 59.9 (CHN), 68.6, 69.9, 75.7, 77.6, 103.9, 194.4 (C=O). − IR (KBr): $\tilde{\nu} = 1660$ (C=O) cm^{-1}. − $C_{18}H_{27}FeNOSi$ (357.34): calcd. C 60.50, H 7.62, N 3.92; found C 60.62, H 7.55, N 3.88.

1-[1(*R*)-Dimethylaminoethyl]-2(*Rp*)-formyl-5(*Sp*)-trimethylsilylferrocene (5): The title compound was obtained in 62% yield by lithiation of 1-[1(*R*)-dimethylaminoethyl]-2(*S*)-trimethylsilylferrocene[11] followed by formylation with DMF. Brown solid; m.p. 138−140 °C. − $[\alpha]_D^{25} = +766.9$ ($c = 1.0$, MeOH). − ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 0.30$ (s, 9 H, $SiCH_3$), 1.77 (d, $J = 6.8$ Hz, 3 H, CH_3), 2.03 (s, 6 H, NCH_3), 3.11 (q, $^1J = 6.8$ Hz, 1 H, CHN), 4.22 (s, 5 H, CpH), 4.48 (d, $J = 2.4$ Hz, 1 H, CpH), 4.94 (d, $J = 2.4$ Hz, 1 H, CpH), 10.50 (s, 1 H, CHO). − ^{13}C NMR: $\delta = 0.0$ ($SiCH_3$), 22.7 (CH_3), 43.2 (NCH_3), 59.9 (CHN), 68.6, 69.9, 75.7, 77.6, 103.9, 194.4 (C=O). − IR (KBr): $\tilde{\nu} = 1660$ (C=O) cm^{-1}. − $C_{18}H_{27}FeNOSi$ (357.35): calcd. C 60.50, H 7.62, N 3.92; found C 60.44, H 7.71, N 3.87.

General Procedure for the Alkylation of Chiral Formylferrocene with Grignard or Organolithium Reagents: A 50 mL Schlenk tube containing a magnetic stirring bar was charged with (1*S*,2*Rp*)-**2** (>99% *de*) (143 mg, 0.50 mmol) and dry THF (5.0 mL) under a slight pressure of nitrogen. Methylmagnesium iodide (1.0 M THF solution, 0.6 mL, 0.6 mmol) or methyllithium (1.0 M diethyl ether solution, 0.6 mL, 0.6 mmol) was then added by means of a syringe through the septum under magnetic stirring at −78 °C. The resulting mixture was stirred at the same temperature for 15 min. and then allowed to warm to room temperature over a period of 2 h. The reaction was subsequently quenched with water, and the resulting solution was extracted with diethyl ether (3 × 20 mL). The combined extracts were washed (brine), dried (K_2CO_3), and filtered, and the solvent was removed in a rotary evaporator to leave a brown residue. The crude product was filtered through a short column of alumina (2 × 4 cm) eluting with hexane/ethyl acetate, 4:1, to give a diastereomeric mixture of 1-[1(*S*)-dimethylaminoethyl]-2(*Rp*)-[1(*R*)-hydroxyethyl]ferrocene **6a** as a brown oil. The diastereomeric excess was determined from the integrals of well-resolved peaks in the ^1H and ^{13}C NMR spectra. Yield: 141 mg (0.47 mmol, 93%). Major diastereomer: ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.27$ (d, $J = 6.5$ Hz, 3 H, CH_3CHN), 1.51 (d, $J = 6.6$ Hz, 3 H, CH_3CHO), 2.14 (s, 6 H, NCH_3), 4.0−4.2 (several peaks, 9 H, CpH and CHN), 4.98 (q, $J = 6.5$ Hz, 1 H, CHOH). − ^{13}C NMR ($CDCl_3$): $\delta = 6.7$ (CH_3CHN), 19.3 (CH_3CHO), 38.5 (NCH_3), 57.1 (NCH), 64.0, 65.1, 66.0, 67.3, 68.9, 89.2, 91.5. Minor diastereomer (distinct signals): ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.24$ (d, $J = 6.6$ Hz, CH_3CHN), 1.68 (d, $J = 6.6$ Hz, CH_3CHO), 2.08 (s, NCH_3), 4.46 (q, $J = 6.5$ Hz, CHOH). − ^{13}C NMR ($CDCl_3$): $\delta = 7.5$ (CH_3CHN), 25.0 (CH_3CHO), 40.6 (NCH_3), 57.4 (CHN), 65.0, 65.6, 66.8, 67.1, 68.8 (CHOH), 86.8, 94.1. − IR (neat): $\tilde{\nu} = 3181$, 3093 (OH) cm^{-1}. − $C_{16}H_{23}FeNO$ (301.20): calcd. C 63.80, H 7.70, N 4.65; found C 63.75, H 7.75, N 4.62.

1-[1(*S*)-Dimethylaminoethyl]-2(*Rp*)-[1(*R*)-hydroxypropyl]ferrocene (6b): The title compound was obtained from the reaction of (1*S*,2*Rp*)-**2** with ethylmagnesium bromide as a brown oil. Yield: 140 mg (0.45 mmol, 90%). Major diastereomer: ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.12$ (t, $J = 7.3$ Hz, 3 H, CH_3), 1.21 (d, $J = 6.6$ Hz, 3 H, CH_3CHN), 1.60−1.70 (m, 1 H, one of CH_2), 1.84−1.98 (m, 1 H, one of CH_2), 2.07 (s, 6 H, NCH_3), 3.96 (s, 5 H, CpH), 4.0−4.15 (several peaks, 4 H, CpH and CHN), 4.61 (dd, $J = 3.2$, 9.5 Hz, 1 H, CHOH). − ^{13}C NMR ($CDCl_3$): $\delta = 6.8$ (CH_3CHN), 11.4 (CH_3), 26.9 (CH_2), 38.6 (NCH_3), 57.1 (CHN), 65.3, 66.4, 67.1, 69.1, 69.6, 89.2, 91.5. Minor diastereomer (distinct signals): ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.07$ (t, $J = 7.6$ Hz, CH_3), 1.16 (d, $J = 6.6$ Hz, CH_3CHN), 2.05 (s, NCH_3). − ^{13}C NMR ($CDCl_3$): $\delta = 7.5$ (CH_3CHN), 11.7 (CH_3CHO), 32.1 (CH_2), 38.5 (NCH_3), 57.2 (CHN), 65.0, 66.8, 68.4, 69.0, 70.9 (CHOH), 86.9, 93.9. − IR (neat): $\tilde{\nu} = 3172$, 3093 (OH) cm^{-1}. − $C_{17}H_{25}FeNO$ (315.23): calcd. C 64.77, H 7.99, N 4.44; found C 64.53, H 8.01, N 4.36.

1-[1(*S*)-Dimethylaminoethyl]-2(*Rp*)-[1(*R*)-hydroxy-2-methylpropyl]ferrocene (6c): The title compound was obtained from the reaction of (1*S*,2*Rp*)-**2** with isopropylmagnesium bromide as a brown oil. Yield: 145 mg (0.44 mmol, 88%). − ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.08$ (d, $J = 6.6$ Hz, 3 H, CH_3CH), 1.24 (d, $J = 6.8$ Hz, 3 H, CH_3CH), 1.30 (d, $J = 6.8$ Hz, 3 H, CH_3CHN), 2.1 (m, 1 H, CH_3CH), 2.15 (s, 6 H, NCH_3), 4.04 (s, 5 H, CpH), 4.1−4.3 (several peaks, 4 H, CpH and CHN), 4.62 (d, $J = 4.1$ Hz, 1 H, CHOH). − ^{13}C NMR ($CDCl_3$): $\delta = 6.9$ (CH_3CHN), 17.9 (CH_3CH), 22.0 (CH_3CH), 31.4 (CH_2), 38.6 (NCH_3), 57.2 (CHN), 65.3, 66.9, 67.2, 69.3, 73.1 (CHOH), 89.0, 91.4. − IR (neat): $\tilde{\nu} = 3180$, 3092 (OH) cm^{-1}. − $C_{18}H_{27}FeNO$ (329.26): calcd. C 65.66, H 8.27, N 4.25; found C 65.68, H 8.24, N 4.37.

1-[1(*S*)-Dimethylaminoethyl]-2(*Rp*)-[1(*R*)-hydroxy-2,2-dimethylpropyl]ferrocene (6d): The title compound was obtained from the reaction of (1*S*,2*Rp*)-**2** with *tert*-butylmagnesium chloride [yield: 134 mg (0.39 mmol, 78%)] or *tert*-butyllithium [yield: 124 mg (0.36 mmol, 73%)] as a brown oil. Major diastereomer: ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 1.18$ [s, 9 H, $(CH_3)_3$], 1.32 (d, $J = 6.6$ Hz, 3 H, CH_3CHN), 2.17 (s, 6 H, NCH_3), 4.04 (s, 5 H, CpH), 4.1−4.3

(several peaks, 4 H, CpH and CHN), 4.53 (s, 1 H, C*H*OH). − ^{13}C NMR (CDCl$_3$): δ = 7.3 (*C*H$_3$CHN), 27.6 [(CH$_3$)$_3$], 35.6 [*C*(CH$_3$)$_3$], 38.5 (NCH$_3$), 57.1 (CHN), 65.4, 66.4, 68.0, 69.6, 76.2 (CHOH), 88.5, 90.5. Minor diastereomer (distinct signals): ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.94 [s, (CH$_3$)$_3$], 2.07 (s, NCH$_3$), 3.50 (q, *J* = 7.1 Hz, CHN). − ^{13}C NMR (CDCl$_3$, 400 MHz): δ = 9.2 (*C*H$_3$CHN), 26.6 [(CH$_3$)$_3$], 35.4 [*C*(CH$_3$)$_3$], 39.4 (NCH$_3$), 56.2 (CHN), 73.4 (CHOH). − IR (neat): ṽ = 3182, 3094 (OH) cm^{-1}. − $C_{19}H_{29}FeNO$ (343.28): calcd. C 66.48, H 8.51, N 4.08; found C 66.36, H 8.54, N 4.10.

1-[1(*S*)-Dimethylaminoethyl]-2(*Rp*)-[1(*R*)-hydroxy-1-phenylmethyl]-ferrocene (6e): The title compound was obtained from the reaction of (1*S*,2*Rp*)-**2** with phenylmagnesium bromide [yield: 102 mg (0.28 mmol, 57%)] or phenyllithium [yield: 123 mg (0.34 mmol, 68%)] as a brown oil. − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.35 (d, *J* = 6.4 Hz, 3 H, CH$_3$), 2.22 (s, 6 H, NCH$_3$), 3.48 (m, 1 H, CpH), 3.95 (t, *J* = 2.4 Hz, 1 H, CpH), 4.05 (s, 5 H, CpH), 4.18 (m, 1 H, CpH), 4.23 (q, *J* = 6.4 Hz, 1 H, CHN), 5.94 (s, 1 H, C*H*OH), 7.3−7.6 (m, 5 H, Ph). − ^{13}C NMR (CDCl$_3$): δ = 6.9 (CH$_3$CHN), 38.6 (NCH$_3$), 57.3 (CHN), 65.1, 67.3, 68.7, 69.1, 71.5 (CHOH), 88.7, 92.8, 127.0, 127.2, 127.7, 142.0. − IR (KBr): ṽ = 3180, 3092 (OH) cm^{-1}. − $C_{21}H_{25}FeNO$ (363.27): calcd. C 69.43, H 6.94, N 3.86; found C 69.47, H 6.92, N 3.85.

General Procedure for the Alkylation of Chiral Formylferrocene with Dialkylzinc: A 50 mL Schlenk tube containing a magnetic stirring bar was charged with (1*S*,2*Rp*)-**2** (>99% *de*) (143 mg, 0.50 mmol) and dry toluene (5.0 mL) under a slight pressure of nitrogen. A hexane solution of diethylzinc (1.0 M, 0.6 mL, 0.6 mmol) was then added by means of a syringe through the septum under magnetic stirring at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and at room temperature for a further 17 h. The reaction was then quenched with water, and the precipitate formed was removed by filtration through Celite. The aqueous filtrate was extracted with diethyl ether (3 × 20 mL). The combined extracts were washed (brine), dried (K$_2$CO$_3$), and filtered, and the solvent was removed in a rotary evaporator to leave a brown residue. The crude product was filtered through a short column of alumina (2 × 4 cm) eluting with hexane/ethyl acetate, 4:1, to give diastereomerically pure **6b** as a brown oil. Yield: 151 mg (0.48 mmol, 96%). − $[\alpha]_D^{25}$ = −35.3 (*c* = 0.33, CHCl$_3$). − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.12 (t, ^1J = 7.3 Hz, 3 H, CH$_3$), 1.21 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHN), 1.60−1.70 (m, 1 H, one of CH$_2$), 1.84−1.98 (m, 1 H, one of CH$_2$), 2.07 (s, 6 H, NCH$_3$), 3.96 (s, 5 H, CpH), 4.0−4.15 (several peaks, 4 H, CpH and CHN), 4.61 (dd, *J* = 3.2, 9.5 Hz, 1 H, C*H*OH). − ^{13}C NMR (CDCl$_3$): δ = 6.8 (CH$_3$), 11.4 (*C*H$_3$CHN), 26.9, 38.6 (NCH$_3$), 57.1 (CHN), 65.3, 66.4, 67.1, 69.1, 69.6, 89.2, 91.5. − $C_{17}H_{25}FeNO$ (315.23): calcd. C 64.77, H 7.99, N 4.44; found C 64.81, H 7.96, N 4.41.

Diastereomerically Pure 6a: The title compound was obtained from the reaction of (1*S*,2*Rp*)-**2** with dimethylzinc as a brown oil. Yield: 120 mg (0.40 mmol, 80%). − $[\alpha]_D^{25}$ = −5.2 (*c* = 0.29, CHCl$_3$). − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.27 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CHN), 1.51 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CHO), 2.14 (s, 6 H, NCH$_3$), 4.0−4.2 (several peaks, 9 H, CpH and CHN), 4.98 (q, *J* = 6.5 Hz, 1 H, C*H*OH). − ^{13}C NMR (CDCl$_3$): δ = 6.7 (*C*H$_3$CHN), 19.3 (*C*H$_3$CHO), 38.5 (NCH$_3$), 57.1 (NCH), 64.0, 65.1, 66.0, 67.3, 68.9, 89.2, 91.5. − $C_{16}H_{23}FeNO$ (301.20): calcd. C 63.80, H 7.70, N 4.65; found C 63.81, H 7.76, N 4.61.

1-[1(*S*)-Dimethylaminoethyl]-2(*Sp*)-[1(*S*)-hydroxyethyl]-5(*Rp*)-trimethylsilylferrocene [(1*S*,2*S*,2*Sp*,5*Rp*)-12]: The title compound was obtained from the reaction of (1*S*,2*Sp*,5*Rp*)-**4** with dimethylzinc as a brown oil. Yield: 168 mg (0.45 mmol, 90%). − $[\alpha]_D^{25}$ = −107.14 (*c* = 1.064, CHCl$_3$). − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 0.29 (s, 9 H, SiCH$_3$), 1.51 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CHN), 1.56 (br. s, 1 H, OH), 1.86 (d, *J* = 7.1 Hz, 3 H, C*H*$_3$CHO), 2.07 (s, 6 H, NCH$_3$), 2.85 (q, *J* = 7.1 Hz, 1 H, CHN), 4.00 (d, *J* = 2.5 Hz, 1 H, CpH), 4.09 (s, 5 H, CpH), 4.40 (d, *J* = 2.5 Hz, 1 H, CpH), 5.08 (q, *J* = 6.4 Hz, 1 H, C*H*OH). − ^{13}C NMR (CDCl$_3$): δ = 0.0 (SiCH$_3$), 20.4 (*C*H$_3$CHN), 22.5 (*C*H$_3$CHO), 44.0 (NCH$_3$), 54.7 (CHN), 61.0, 63.8, 68.8, 69.5, 71.1 (CHOH), 92.6, 99.4. − IR (neat): ṽ = 3170, 3095 (OH) cm^{-1}. − $C_{19}H_{31}FeNOSi$ (373.39): calcd. C 61.12, H 8.37, N 3.75; found C 61.23, H 8.48, N 3.74.

Preparation of 1-[1(*S*)-Dimethylaminoethyl]-2(*Sp*)-[1(*S*)-hydroxyethyl]ferrocene [(1*S*,2*S*,2*Sp*)-13] (by desilylation of the silylferrocene): A 100 mL single-necked, round-bottomed flask containing a magnetic stirring bar was charged with (1*S*,2*S*,2*Sp*,5*Rp*)-**12** (1.87 g, 5.01 mmol) and dimethyl sulfoxide (80 mL). Potassium *tert*-butoxide (0.616 g, 5.51 mmol) was added portionwise and following the addition the mixture was stirred at 40 °C for 2 h. The reaction was then quenched with water, and the aqueous solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed (brine), dried (K$_2$CO$_3$), filtered, and the solvent was removed in a rotary evaporator to leave a brown residue. The crude product was purified by column chromatography on alumina (hexane/ethyl acetate, 4:1) to give pure (1*S*,2*S*,2*Sp*)-**13**. Yield: 151 mg (5.0 mmol, 99%). − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.47 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CHN), 1.85 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$CHO), 2.09 (s, 6 H, NCH$_3$), 2.72 (q, *J* = 7.0 Hz, 1 H, CHN), 3.96 (dd, *J* = 1.4, 2.4 Hz, 1 H, CpH), 4.03 (t, *J* = 2.6 Hz, 1 H, CpH), 4.13 (s, 5 H, CpH), 4.23 (m, 1 H, CpH), 5.05 (q, *J* = 6.5 Hz, 1 H, C*H*OH). − ^{13}C NMR (CDCl$_3$): δ = 20.0 (*C*H$_3$CHN), 21.6 (*C*H$_3$CHO), 43.9 (NCH$_3$), 61.5 (CHN), 64.0, 64.4, 66.2, 69.0, 71.3 (CHO), 89.6, 91.5. − IR (neat): ṽ = 3182, 3094 (OH) cm^{-1}. − $C_{16}H_{23}FeNO$ (301.20): calcd. C 63.80, H 7.70, N 4.65; found C 63.55, H 7.75, N 4.45.

Preparation of 1,2-Bis[1(*S*)-diacetoxyethyl]ferrocene [(*S*,*S*)-14]: A mixture of (1*S*,2*S*,2*Sp*)-**13** (151 mg, 5.0 mmol) and acetic anhydride (30 mL) was stirred at room temperature for 2 days. The mixture was then slowly poured into aqueous NaHCO$_3$ solution and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed (brine), dried (MgSO$_4$), and filtered, and the solvent was removed in a rotary evaporator to leave a brown residue. The crude product was purified by column chromatography on alumina (hexane/ethyl acetate, 10:1) to give pure (*S*,*S*)-**14** as a brown oil. Yield: 163 mg (4.6 mmol, 92%). − $[\alpha]_D^{25}$ = +51.1 (*c* = 1.16, CHCl$_3$). − ^{1}H NMR (CDCl$_3$, 400 MHz): δ = 1.27 (d, *J* = 6.5 Hz, 3 H, C*H*$_3$CH), 1.51 (d, *J* = 6.6 Hz, 3 H, C*H*$_3$CH), 2.14 (s, 6 H, CH$_3$CO), 4.0−4.2 (several peaks, 9 H, CpH), 4.98 (q, *J* = 6.5 Hz, 1 H, C*H*OH). − ^{13}C NMR (CDCl$_3$): δ = 19.1 (*C*H$_3$CH), 21.1 (*C*H$_3$CH), 21.2 (CH$_3$CO), 22.1 (CH$_3$CO), 67.0, 67.2, 67.6, 68.5, 69.1 (CHO), 69.4 (CHOH), 84.1, 89.0, 170.0 (C=O), 170.2 (C=O). − IR (neat): ṽ = 1734 cm^{-1}. − $C_{18}H_{22}FeO_4$ (358.21): calcd. C 60.35, H 6.19; found C 60.33, H 6.21.

Preparation of 1,2-Bis[(1*S*)-dihydroxyethyl]ferrocene [(*S*,*S*)-15]: A 100 mL Schlenk tube containing a magnetic stirring bar was charged with (*S*,*S*)-**14** (163 mg, 4.6 mmol) and dry diethyl ether (50 mL) under a slight pressure of nitrogen. A hexane solution of *n*BuLi (1.5 M, 30 mL, 45.0 mmol) was added by means of a syringe through the septum under magnetic stirring at 0 °C and the resulting mixture was stirred at this temperature for 1 h. The reaction was then quenched with water and the aqueous solution was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed (brine), dried (MgSO$_4$), and filtered, and the solvent was removed in a rotary evaporator to leave a brown residue. The crude product was purified by column chromatography on silica gel (hexane/ethyl acetate, 10:1) to give pure (*S*,*S*)-**15**. Brown solid; m.p. 73–75 °C. Yield: 114 mg (4.2 mmol, 91%). – $[\alpha]^{25}_{D} = +38.7$ (*c* = 0.15, $CHCl_3$). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.47 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.51 (d, *J* = 6.3 Hz, 3 H, CH_3), 4.0–4.3 (several peaks, 3 H, CpH), 4.21 (s, 5 H, CpH), 4.72 (q, *J* = 6.3 Hz, 1 H, CHO), 4.80 (q, *J* = 6.4 Hz, 1 H, CHO). – ^{13}C NMR ($CDCl_3$): δ = 22.7 (CH_3), 23.9 (CH_3), 64.1, 65.4, 65.7, 67.0, 67.2 (CHOH), 68.7 (CHOH), 89.4, 92.8. – IR (KBr): $\tilde{\nu}$ = 3311 cm^{-1}. – $C_{14}H_{18}FeO_2$ (274.14): calcd. C 61.34, H 6.62; found C 61.23, H 6.66.

Preparation of 1,2-Bis[1(*S*)-diphenylphosphanylethyl]ferrocene (Diborane Complex) [(*S*,*S*)-16]: (*S*,*S*)-**14** (320 mg, 1.0 mmol) was dissolved in acetic acid (10 mL) under argon. Diphenylphosphane (186 mg, 10.0 mmol) was added and the reaction mixture was heated to 40 °C for 3 h. The solid that formed was dried in vacuo (0.7 Torr, 2 h) and dissolved in THF (15 mL). An excess of BH_3SMe_2 in THF (2.0 M, 10 mL) was added and the mixture was stirred for 1 h at room temperature. Unreacted borane was subsequently destroyed by the slow addition of MeOH (4 mL). After concentration to a volume of 4 mL, the crude mixture was directly purified by column chromatography (hexane/ethyl acetate, 7:1) to furnish the protected diphosphane complex. Yield: 0.39 g (0.61 mmol, 61%). Orange solid; m.p. 90–91 °C. – $[\alpha]^{25}_{D} = -6.1$ (*c* = 0.18, $CHCl_3$). – ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.50–1.8 (br. s, 6 H), 0.79 (dd, *J-J* = 7.3, *J-J* = 14.9 Hz, 3 H, CH_3), 1.73 (dd, *J* = 7.3, 14.9 Hz, 3 H, CH_3), 3.25 (dq, *J-J* = 6.6 Hz, *J-J* = 7.5 Hz, 1 H, CHP), 3.84 (s, 5 H, CpH), 3.92 (m, 1 H, CpH), 4.00 (dq, *J-J* = 6.6 Hz, *J-J* = 7.5 Hz, 1 H, CHP), 4.11 (t, *J* = 2.7 Hz, 1 H, CpH), 4.48 (br. s, 1 H, CpH), 7.20–8.00 (m, 20 H). – ^{13}C NMR ($CDCl_3$): δ = 19.5 (d, *J* = 0.05 Hz), 20.9 (d, *J* = 0.05 Hz), 28.6 (d, *J* = 0.30 Hz), 30.1 (d, *J* = 0.33 Hz), 66.1, 67.4, 67.5, 68.5, 69.6, 69.8, 86.5, 88.1, plus aromatic signals. – IR (KBr): $\tilde{\nu}$ = 3055, 2977, 2940, 2398, 1064, 741 cm^{-1}. – $C_{38}H_{42}B_2FeP_2$ (638.15): calcd. C 71.52, H 6.63; found C 71.73, H 6.41.

General Procedure for the Asymmetric Alkylation of Aldehydes with Dialkylzinc in the Presence of the Chiral Formylferrocene: A 50 mL Schlenk tube containing a magnetic stirring bar was charged with (1*S*,2*Rp*)-**2** (>99% *de*) (14 mg, 0.050 mmol) and dry toluene (5.0 mL) under a slight pressure of nitrogen. A hexane solution of diethylzinc (1.0 M, 1.5 mL, 1.5 mmol) was then added by means of a syringe through the septum under magnetic stirring at 0 °C. The resulting mixture was stirred at this temperature for 0.5 h and then benzaldehyde (106 mg, 1.0 mmol) was added. Stirring was continued for 15 h at 0 °C. The reaction was subsequently quenched with 0.5 M HCl and the aqueous layer was extracted with diethyl ether (3 × 20 mL); the amine ferrocene remained in the acidic aqueous layer. The combined extracts were washed (brine) and dried ($MgSO_4$). GC-MS analysis of the ethereal solution revealed the presence of 1-phenyl-1-propanol. After evaporation of the solvent, the product (127.9 mg, 0.94 mmol, 94% yield) was isolated by preparative TLC (hexane/ethyl acetate, 5:1). The enantiomeric excess was determined by HPLC analysis using a Daicel Chiralcel OD column and by GC on a chiral capillary column (Chiraldex G-TA, 30 m).

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