On the Role of Planar Chirality in Asymmetric Catalysis: A Study toward Appropriate Ferrocene Ligands for Diethylzinc Additions†

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Received June 9, 1998

Employing a directed ortho-metalation route, chiral ferrocene-based hydroxyloxazolines have been synthesized, and their capability to serve as bidentate ligand precursors in the diethylzinc addition to benzaldehyde has been investigated. On the basis of the X-ray crystal structures of two ferrocenes, (S,R_p)-**6** and (S,S_p)-**10**, it became possible to determine the general importance of the element of planar chirality for diastereomeric ferrocene complexes in this process. Comparison of the assumed transition states revealed a preferential catalyst conformation which led to the design of an adequate arene compound [(*S*)-**20**] that displayed catalytic activity similar to that of (S,R_p)-**6**.

Introduction

For more than 40 years, the fascinating structural properties of ferrocene and its derivatives have caused an unrivalled interest in all fields of organometallic chemistry.[1] During the last 2 decades, special efforts have been made to design chiral bidentate ferrocene ligands.[2] Because 1,2-disubstituted ferrocenes, which by their nature are *planar chiral* compounds,[3] have proven to act as effective ligands in asymmetric catalysis,[4] syntheses toward this 1,2-disubstitution pattern have been widely sought.[5,6]

This search has led to a general strategy which as its key step involves a directed ortho-metalation on ferrocene precursors bearing ortho-directing auxiliary groups with stereogenic centers. As a consequence, the resulting ferrocenes are diastereoisomers, containing elements of both planar and central chirality. The most common approach in this direction is still based on the use of Ugi's *N,N*-dimethyl-α-ferrocenylethylamine.[7] Among others, Ito,[8] Kumada and Hayashi,[9] and Togni[10] have shown that this compound is the one of choice for the preparation of a variety of related ferrocenes where the original amino group can also be replaced by other heteroatoms in order to tune the required ligand properties.

In the same context, Sammakia,[11] Richards,[12] and Uemura[13] have introduced chiral 2-ferrocenyloxazolines derived from optically active amino alcohols. Kagan and co-workers employed a chiral acetal formed from ferrocenecarbaldehyde and 1,2,4-butanetriol.[14] This elegant approach allows the generation of ferrocenes with planar chirality only after removal of the chiral auxiliary. A complementary direct route toward planar asymmetry on ferrocenes was developed by Snieckus and consists of an enantioselective ortho-metalation using a butyllithium/sparteine system.[15]

Because of the mentioned procedures, a large structural variety of planar chiral ferrocenes is known today. Some of these ferrocenes have played a key role in the development of important catalytic systems, and among those, two have recently found considerable application in industrial processes.[16]

For most catalytic systems involving chiral ferrocenes with both central and planar chirality, the effect of the latter has never been studied in detail. The only exception is the series of PPFA-type ligands introduced by Kumada and Hayashi.[17] It is widely accepted that in this set of P,N-chelating ligands, the element of planar chirality is decisive for exerting control over both absolute configuration and enantiomeric excess. This has been

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† Dedicated with appreciation to Professor R. W. Hoffmann, Marburg, Germany, on the occasion of his 65th birthday.

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10.1021/jo981098r CCC: $15.00
Published on Web 10/07/1998

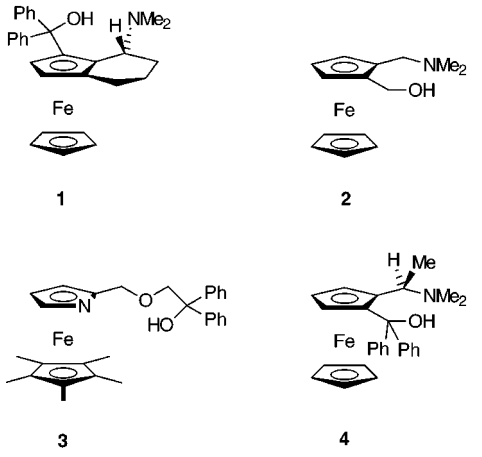


Figure 1.

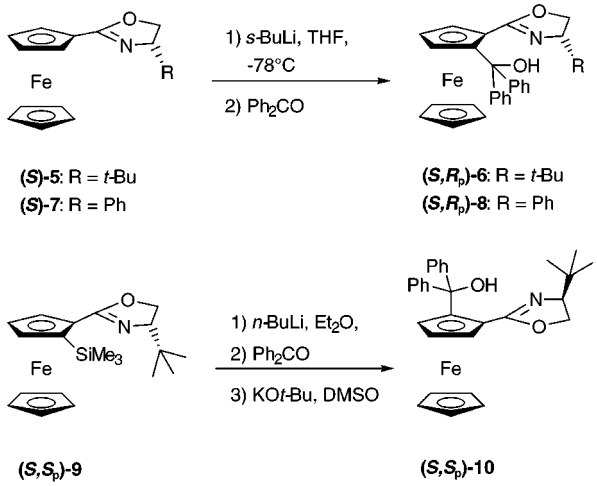
shown convincingly in Grignard cross couplings by comparing the impact of (S,R_p)-PPFA with that of its diastereomer (R,R_p)-PPFA and the planar chiral analogue (S_p)-FcPN.

A different conclusion was drawn by Pastor and Togni following their investigation of the impact of diastereomeric ferrocene ligands in the gold(I)-catalyzed asymmetric aldol reaction.[18] The principle of *chiral cooperativity* has been deduced from the observation that steric interactions in the side chain resulting from central chirality are responsible for both optimum diastereo- and enantioselectivity. Unfortunately, the corresponding ferrocene ligands with only planar chirality were omitted in this study.

We wondered whether these conclusions could be generalized and if they could establish a basis for other catalytic processes as well. As our test reaction, we chose the asymmetric alkylation of aldehydes by means of dialkylzincs.[19] Application of ferrocene-based ligands in this reaction was known, but the impact of the element of planar chirality on the stereochemical outcome had not yet been elucidated. Figure 1 shows the four known ferrocenes that have successfully been used in this transformation.

Ferrocene **1** was synthesized by Schlögl and co-workers, who plainly claimed central chirality to be the decisive element.[20] Nicolosi[21] and Fu[22] described complex **2** and azaferrocene **3**, respectively. DFPE **4** is a characteristic representative of a whole family of ferrocenes obtained by Butsugan, Watanabe, and co-workers via the common route from Ugi's amine.[23] Although several variations on **4** have been studied, no investigations on the effects of the chirality elements on the enantioselectivity in the alkylation reaction were reported.

Scheme 1



Results and Discussion

Synthesis of Ligands. Preparations of **1**−**4** include resolution steps. To avoid such procedures, we decided to synthesize a set of ortho-disubstituted ferrocenes with chiral oxazolinyl- and diphenylhydroxymethyl groups.[24,25] Starting materials (*S*)-**5** and (*S*)-**7** were readily available following known literature protocols (Scheme 1).[11,12b]

The synthesis of diastereomerically pure (S,R_p)-**6** from (*S*)-**5** has been recently reported by us.[26,27] As described in the literature,[11−13] lithiation of (*S*)-**5** was highly stereoselective, and a diastereomeric ratio of 27:1 was determined from the crude proton NMR spectrum by comparison of the signals of the respective *tert*-butyl groups. Ferrocene (S,R_p)-**8** was obtained from (*S*)-**7** using identical reaction conditions, albeit the chemical yield was lower [34% compared with 87% for (S,R_p)-**6**]. Its enantiomer, (R,S_p)-**8**, was synthesized from (*R*)-**7** following this route. Compound (S,S_p)-**10**, which has the same absolute central configuration as ferrocene (S,R_p)-**6** but opposite planar chirality, was synthesized by applying the standard procedure of temporarily blocking the preferred ortho position with TMS. Subsequent deprotonation at the remaining ortho position of silylated ferrocene (S,S_p)-**9**, followed by reaction of the lithiated intermediate with benzophenone and removal of the TMS protection group furnished (S,S_p)-**10** as a single diastereoisomer in good overall yield (Scheme 1).

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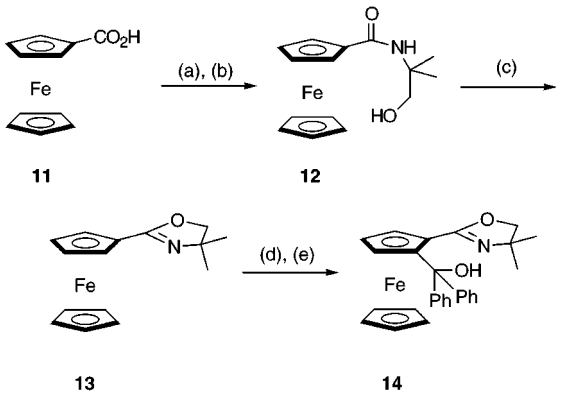
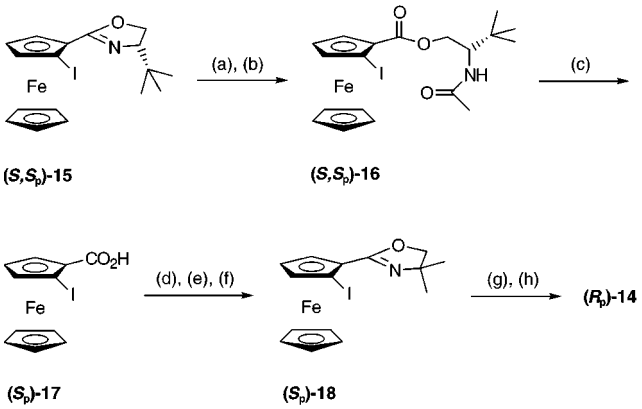
Scheme 2[a]



[a] Key: (a) $(COCl)_2$, CH_2Cl_2; (b) 2-amino-2-methylpropanol, NEt_3, CH_2Cl_2; (c) PPh_3, CCl_4, NEt_3; (d) *n*-BuLi, THF, −78 °C; (e) Ph_2CO, −30 °C.

Scheme 3[a]



[a] Key: (a) TFA, Na_2SO_4, THF; (b) Ac_2O, pyridine, CH_2Cl_2; (c) NaOH; (d) $(COCl)_2$, CH_2Cl_2; (e) 2-amino-2-methylpropanol, NEt_3, CH_2Cl_2; (f) PPh_3, CCl_4, NEt_3; (g) *n*-BuLi, THF; (h) Ph_2CO.

Starting from achiral 2-ferrocenyloxazoline **13**[28] that was synthesized from ferrocene carboxylic acid **11** and 2-amino-2-methylpropanol in the common two-step procedure following Richard's route,[12b,26] planar-chirality-inheriting ferrocene **14** was obtained as a racemate (Scheme 2).

Several attempts to separate this racemate by chemical resolution were unsuccessful. A direct synthesis toward enantiomerically pure **14** in analogy to Snieckus' approach[15] gave only racemic material. Finally, a separation by preparative HPLC proved successful and provided each of the two enantiomers of **14** in >99.8% optical purity.[29] Their respective absolute planar configuration was determined via chemical correlation (Scheme 3); diastereomerically pure 2-(α-iodoferrocenyl)oxazoline (S,S_p)-**15**, which was obtained from (*S*)-**5** in the usual way (deprotonation followed by reaction with iodine), was converted into the corresponding enantiomerically pure α-iodoferrocene carboxylic acid (S_p)-**17** by employing Meyers' procedure for transformation of the oxazoline.[30] In a reaction sequence identical to the one described above for the synthesis of **13**, planar chiral 2-(α-iodoferrocenyl)oxazoline (S_p)-**18** was then obtained from (S_p)-**17**. Finally, an iodine/lithium exchange followed by quenching of the resulting anion with benzophenone furnished (R_p)-**14**, which by analytical HPLC proved to be identical with the levorotatory enantiomer of **14** obtained from preparative HPLC resolution.

All new ferrocenes **6**, **8**, and **10**−**18** are air-stable solids that give the expected analytical and spectroscopical data. Interestingly for **6**, **8**, **10**, and **14**, the hydroxyl proton is strongly coordinated to the nitrogen of the oxazoline moiety, resulting in a stable seven-membered chelate ring. As a consequence in ^1H NMR spectra, these protons show significant downfield shifts to values between 9.1 and 9.6 ppm.

Asymmetric Catalyses. With compound (S,R_p)-**6**, several diethylzinc additions were performed using benzaldehyde as the standard substrate in order to find optimal reaction conditions. Applying 5 mol % of this ferrocene and using toluene as solvent at a temperature of 0 °C, (*R*)-1-phenylpropanol was obtained with 93% ee (Table 1, entry 2; Scheme 4).

A variety of other aldehydes were employed subsequently, and the corresponding secondary aldehydes were obtained in ee's of up to 95% (Table 2).[26]

We next investigated the diethylzinc addition to benzaldehyde by employing the whole set of ferrocene ligands described above (Table 3).

First, attention was focused on varying the absolute planar chirality while maintaining the central chirality. Thus, replacing ferrocene (S,R_p)-**6** by (S,S_p)-**10** had a dramatic impact on the reaction outcome. Use of the

Table 1. Enantiomeric Excesses Resulting from the Asymmetric Addition of Diethylzinc to Benzaldehyde in the Presence of (S,R_p)-6 as Chiral Ligand

entry	solvent	mol % of catalyst	reaction time [h]	yield [%][a]	ee [%][b]
1	toluene	10	5	91	93
2	toluene	5	6	83	93
3	toluene	1	26	65	86
4	*n*-hexane	5	6	94	90
5	diethyl ether	5	8	90	85

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis using a Chiralcel OD column.

Scheme 4

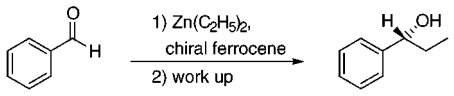


Table 2. Enantiomeric Excesses Resulting from the Asymmetric Addition of Diethylzinc to Several Aldehydes in the Presence of 5 mol % of (S,R_p)-6

entry	aldehyde	reaction time [h]	yield [%][a]	ee [%][b]	config
1	ferrocenecarbaldehyde	3	93	95	*R*
2	4-methoxybenzaldehyde	9	93	91	*R*
3	5-(4-chlorophenyl)-furancarbaldehyde	2	92	91[c]	*R*[d]
4	heptanal	26	94	87[e]	*R*
5	4-chlorobenzaldehyde	6	94	86	*R*
6	cinnamaldehyde	6	89	78	*R*

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis on a chiral stationary phase. [c] >99% ee after one recrystallization. [d] Tentatively assigned by assumption of an identical reaction pathway. [e] Determined by ^{13}C NMR spectroscopy of the corresponding MTPA esters.

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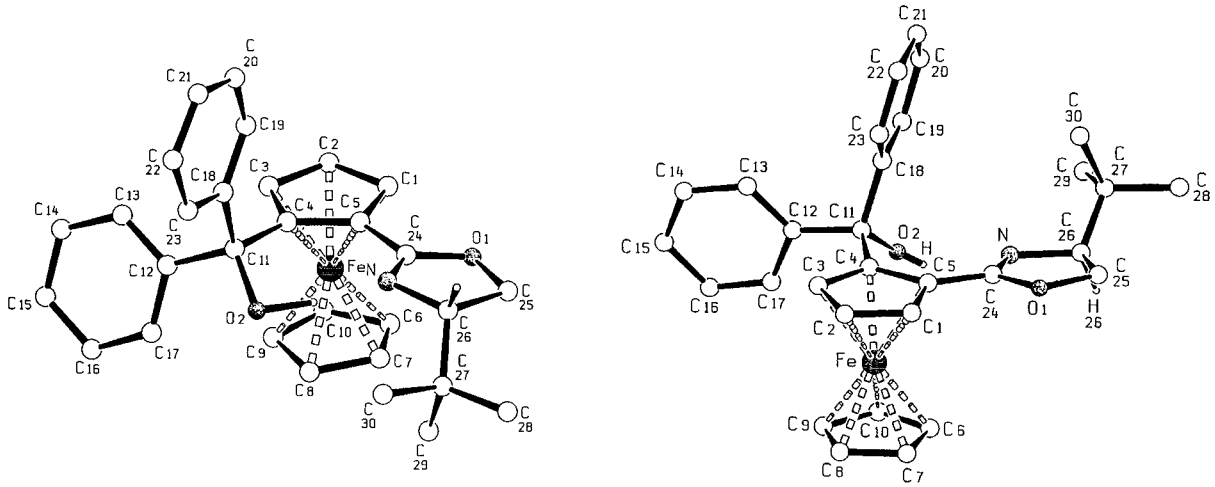

Figure 2. Solid-state structures (SCHAKAL plots) of (S,R_p)-**6** (left) and (S,S_p)-**10** (right).

Table 3. Enantiomeric Excesses Resulting from the Asymmetric Addition of Diethylzinc to Benzaldehyde in the Presence of 5 mol % of Different Chiral Ferrocenes

entry	ferrocene ligand	reaction time [h]	yield [%][a]	ee [%][b]	config[c]
1	(S,R_p)-**6**	6	83	93	*R*
2	(S,R_p)-**8**	5	99	94	*R*
3	(S,S_p)-**10**	59	55	35	*R*
4	(R_p)-**14**	20	97	51	*R*

[a] Isolated yield after column chromatography. [b] Determined by HPLC analysis using a Chiralcel OD column. [c] Determined by comparison with literature data (optical rotation and HPLC retention times).

latter not only required a much longer reaction time (26 h to go to at least half conversion) but also catalyzed the formation of product with only low ee (35%). Interestingly, the absolute configuration of the generated 1-phenylpropanol was unchanged. For the sake of a better understanding of these results, the solid-state structures of (S,R_p)-**6**[26] and (S,S_p)-**10** were determined (Figure 2).

Both compounds have one equatorial phenyl group, while the other phenyl substituent occupies an axial position with regard to the cyclopentadienyl backbone. Such a conformation is common for those ferrocene derivatives which bear two bulky groups in the α position. Because the hydroxyl proton is chelated within a seven-membered ring, the relative position of the *tert*-butyl group toward the axial phenyl substituent is firmly attached, which results in an overall fixed conformation. Thus in (S,R_p)-**6**, these two groups are placed anti with regard to the upper cyclopentadienyl ring, whereas in (S,S_p)-**10** both sterically demanding groups point in the same direction.

Because all other structural features are similar, this arrangement has to play the decisive role in causing the observed dramatic differences in the catalysis outcome. It has been demonstrated that ferrocene ligands maintain their general conformational characteristics when coordinating to a transition metal.[31] We assume that this is also the case with (S,R_p)-**6** and (S,S_p)-**10**, and therefore the replacement of the chelated proton by an ethylzinc moiety should not lead to any significant structural distortion. As a further consequence, in the resulting

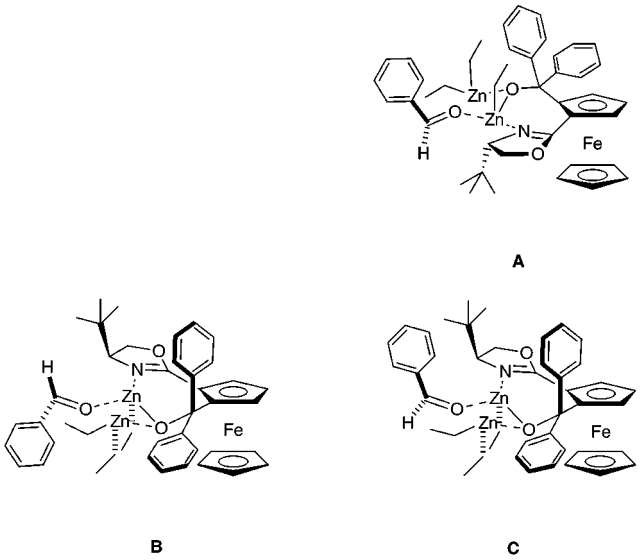

Figure 3.

zinc alkoxide (S,R_p)-**6** can be regarded as a kind of pseudo-C_2-symmetrical ligand. On the other hand, (S,S_p)-**10** must then be considered a ligand of unfavorable pseudo-C_s-symmetry.

Interestingly, in both cases the absolute configuration of the generated 1-phenylpropanol is *R*. The observed stereochemical outcome can be explained by considering the transition states of the types **A**−**C**, which are in agreement with the models proposed by Noyori[19b] and Corey (Figure 3).[32]

Taking into account the high ee obtained from catalysis employing pseudo-C_2-symmetrical (S,R_p)-**6**, one can assume a single transition state **A** to be dominant. In **A**, the substrate is coordinated in such an orientation that its large phenyl is opposite to the *tert*-butyl group. The ethyl transfer will then occur from the *re* side, giving the (*R*)-configurated alcohol.

A different assumption has to be made for catalysis with (S,S_p)-**10**. The low ee observed leads to the reasonable conclusion that at least two competing transition states must be involved. A transition state like **B** derives from minimizing the steric interactions between the

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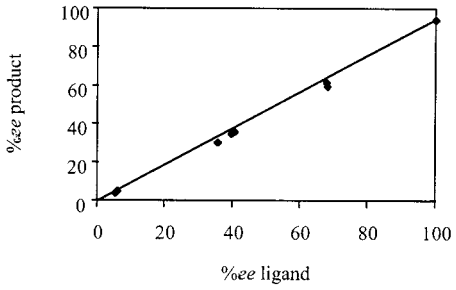


Figure 4.

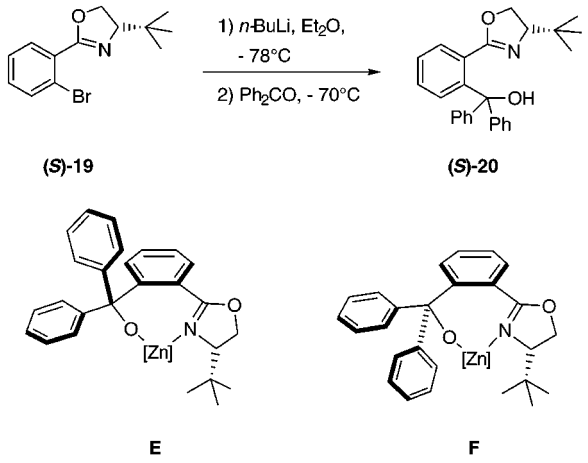
phenyl ring of the substrate and both the *tert*-butyl group and the axial phenyl substituent of the ferrocene ligand. Again, the ethyl transfer is accomplished from the *re* side and furnishes the (*R*)-configurated alcohol. An alternative coordination of the benzaldehyde to the central zinc atom such that its phenyl group points in the same direction as the two bulky substituents of the ferrocene is depicted in transition state **C**. Hence, ethyl transfer occurs from the *si* side, giving rise to the formation of the (*S*)-configurated product. Comparison of these two intermediates shows that steric interactions will find higher expression in **C**, and therefore, transition state **B** should be favored. From the obtained ee, a ratio of approximately 2:1 for these competing transition states can be deduced.

The results of the above experiments reveal the importance of well-balanced structural features of catalysts for achieving high enantioselectivity. The two ferrocenes (S,R_p)-**6** and (S,S_p)-**10** are diastereoisomers having central and planar elements of chirality. Only the absolute configuration of the central chirality is identical, whereas the planar one is opposite. The importance of this fact is indicated by the differences in efficiency and enantioselectivity of these two ferrocenes in catalyzing the addition reaction (Table 2, entries 1 and 3). Apparently, changing planar chirality has a significant impact on the stereochemical outcome of the catalysis, and both elements of chirality seem to determine the overall catalyst conformation by interacting in either a cooperative or noncooperative manner.[25b,h]

Planar chirality alone is not sufficient for high enantioselectivity. That was shown by catalysis with enantiomerically pure (R_p)-**14**. The ee of the product was moderate, and high conversion required prolonged reaction times (Table 2, entry 4). Thus, in the discussed systems of diastereomeric ferrocenes the element of planar chirality is essential but not sufficient for rendering catalysts effective. Optimal catalysts of this kind also require a stereogenic center and an additional bulky substituent in the oxazoline backbone.

Next, we tested whether the structural properties of the new chiral ferrocenes would allow any nonlinear effects in catalysis.[33] The use of mixtures of (S,R_p)-**8** and (R,S_p)-**8** as catalyst precursors showed the relationship between the enantiomeric purity of the ferrocene and the ee of the product to be linear (Figure 4). Hence, the formation of any catalytically inactive heterochiral aggregates during the course of the catalysis can be ruled out. This behavior had also been reported for the ligands

Scheme 5



1, **3**, and **4**. So far, compound **2** remains the only example of a ferrocene showing a positive nonlinear effect in the asymmetric ethylation of benzaldehyde. The presence of three bulky phenyl groups in the ligand framework of ferrocene **8** makes obvious that aggregation of any kind will be disfavored due to steric hindrance.[34] Thus, the presence of a sterically demanding environment around the ferrocene backbone leads to an essential conformational rigidity but also blocks intermolecular aggregation.

Having established a preferential catalyst conformation on the basis of the assumed transition states for (S,R_p)-**6** and (S,S_p)-**10**, we decided to investigate the consequences of more significant ligand modifications on catalyst activity and enantioselectivity. Thus, the iron fragment of the ferrocene was removed and replaced by a simple benzene group. Arene (*S*)-**20** was synthesized from the known (*S*)-2-(2-bromophenyl)oxazoline **19**[35] via halogen/lithium exchange, followed by reaction of the lithiated intermediate with benzophenone (Scheme 5).

When the diethylzinc addition was performed in the presence of (*S*)-**20** under conditions identical to those for (S,R_p)-**6**, (*R*)-1-phenylpropanol was isolated in 85% chemical yield with an ee of 92% after a reaction time of 5 h. This behavior is noteworthy because for other cases where the ferrocene has been substituted for a benzene group the selectivity was reported to be significantly altered.[25f]

In this case, the stereochemical transfer relies solely on the element of central chirality. Upon complexation to zinc, relatively rigid conformations are assumed to be formed. Two extreme cases are depicted in Scheme 5. In both of them, the arene backbone and the oxazoline are in plane. When one phenyl group points toward an equatorial position, the other one is located on either the opposite or the same side as the *tert*-butyl group of the oxazoline, leading to intermediates **E** and **F**, respectively. Comparing these two structures with the ones of the ferrocene-containing compounds and taking into account the results of all catalyses, it becomes reasonable to suggest that the reaction with (*S*)-**20** proceeds via pseudo-C_2-symmetrical arrangement **E**. During the catalysis, this structural organization would essentially be identical to that of (S,R_p)-**6**.

(33) (a) Kagan, J. B.; Girard, C.; Guillaneaux, D.; Rainford, D.; Samuel, O.; Zhand, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *30*, 345. (b) Bolm, C. In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman & Hall: London, 1996; p 9.

(34) As a further consequence of the high steric substitution pattern of these ferrocenes, it has also proven impossible to obtain homochiral compounds of the type ML_x from (S,R_p)-**6** and metal centers such as V^{IV}, Cu^{II}, or Zn^{II}: Bolm, C.; Muñiz-Fernández, K. Unpublished results.

(35) Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467.

In conclusion, we have presented new oxazoline-containing ferrocenes for dialkylzinc additions to aldehydes and demonstrated the importance of planar chirality in these systems. The comparison of the results of catalyses with diastereomeric ferrocenes (S,R_p)-**6** and (S,S_p)-**10** made evident how central and planar chirality cooperate with each other. We further revealed the relevance of pseudo-C_2-symmetrical conformations for such diastereomeric ferrocene-based catalysts. Its identification allowed the design of a more simple catalyst that lacks the planar chirality of the ferrocenes but adopts a similar conformational arrangement and leads to an identical course of catalysis.

Experimental Section

General. Ferrocene carboxylic acid was purchased from Fluka and Aldrich. *sec*-Butyllithium was purchased from Fluka (1.3 M in cyclohexane), and *n*-butyllithium was purchased from Merck-Schuchardt (1.6 M in *n*-hexane). 2-Amino-2-methylpropanol was obtained from Aldrich and used as received. Diethylzinc was purchased from Witco. Chiral amino alcohols were synthesized from the corresponding amino acids following a published procedure.[36] THF, diethyl ether, *n*-hexane, and toluene were distilled from sodium/benzophenone ketyl radical under argon. Dichloromethane was distilled from CaH_2 under argon. All other solvents were reagent grade and were used as received. Triethylamine was distilled from KOH and was stored over KOH under argon.

If not stated otherwise, "standard workup" refers to quenching the reaction mixture with distilled water, extracting it with methyl *tert*-butyl ether, washing the organic layer subsequently with brine and water, and drying the combined organic phases with anhydrous $MgSO_4$.

All syntheses of ferrocene derivatives and all catalyses were repeated at least twice in order to ensure reproducibility. Given yields are average values. The ee of 1-phenylpropanol and of ferrocene ligands **8** and **14** were determined by chiral HPLC using Chiralcel OD and Chiralpak AD columns, respectively.

(S,R_p)-2-(α-Diphenylhydroxymethyl)ferrocenyl-5-*tert*-butyloxazoline [(S,R_p)-6]. A solution of ferrocene (*S*)-**5**[11] (643 mg, 2.07 mmol) in 40 mL of freshly distilled THF was cooled to −78 °C and then treated dropwise with *sec*-BuLi (1.9 mL, 2.48 mmol, 1.3 M in cyclohexane). After being stirred for 2 h at this temperature, benzophenone (527 mg, 2.89 mmol) was added at −60 °C. The resulting solution was allowed to warm to room temperature overnight. Standard workup followed by column chromatography of the crude product [hexanes/ethyl acetate (70/30)] and recrystallization from *n*-hexane gave 887 mg (87%) of (S,R_p)-**6** as orange crystals. Mp: 148 °C. $[\alpha]_D = -345.9$ ($c = 1.2$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H); 3.56 (dd, $J = 9.9$, 9.3 Hz, 1H); 3.69−3.70 (m, 1H); 3.99−4.08 (m, 1H); 4.13 (dd, $J = 9.8$, 9.4 Hz, 1H); 4.24−4.26 (m, 1H); 4.27 (s, 5H); 4.72−4.73 (m, 1H); 7.08−7.18 (m, 5H); 7.20−7.34 (m, 3H); 7.50−7.54 (m, 2H); 9.19 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.12; 32.95; 66.04; 67.69; 68.51; 70.38; 70.57; 74.96; 75.25; 77.25; 100.61; 126.21; 126.58; 127.12; 127.37; 127.85; 146.35; 149.19; 167.59. MS (70 eV): *m*/*z* 493 (M, 59%); 428 (100). IR (KBr): 1647; 1207; 1008 cm^{-1}. Anal. Calcd for $C_{30}H_{31}FeNO_2$: C, 73.03; H, 6.33; N, 2.84. Found: C, 73.22; H, 6.28; N, 2.69.

(S,R_p)-2-(α-Diphenylhydroxymethyl)ferrocenyl-5-phenyloxazoline [(S,R_p)-8]. A solution of ferrocene (*S*)-**7**[11] (550 mg, 1.66 mmol) in 35 mL of freshly distilled THF was cooled to −78 °C and then treated dropwise with *sec*-BuLi (1.5 mL, 1.95 mmol, 1.3 M in cyclohexane). After being stirred for 1 h at this temperature, benzophenone (393 mg, 2.16 mmol) was added at −65 °C. The resulting solution was allowed to warm to room temperature overnight. Standard workup and evaporation of the solvents under reduced pressure afforded an orange solid that was a mixture of at least three different ferrocene derivatives according to NMR spectroscopy of the crude reaction mixture. Recrystallization of this solid from *n*-hexane (three times) yielded 288 mg (0.56 mmol, 34%) of (S,R_p)-**8** as an orange solid. Mp: 148 °C. $[\alpha]_D = -335.8$ ($c = 1.6$, $CHCl_3$). HPLC (Daicel Chiralpak AD, *n*-hexane/2-propanol = 97/3, 0.4 mL/min): $t = 26.3$ min. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75−3.76 (m, 1H); 4.03−4.09 (m, 1H); 4.28−4.29 (m, 1H); 4.30 (s, 5H); 4.48 (dd, $J = 9.9$, 8.2 Hz, 1H); 4.81−4.83 (m, 1H); 4.91 (dd, $J = 10.2$, 8.5 Hz, 1H); 7.10−7.18 (m, 5H); 7.20−7.40 (M, 8H); 7.52−7.54 (m, 2H); 9.07 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 66.17; 69.01; 69.44; 71.38; 71.44; 75.12; 75.98; 77.95; 101.28; 126.88; 127.04; 127.28; 127.76; 127.92; 128.18; 128.21; 128.53; 129.54; 142.88; 147.12; 149.93; 169.93. MS (70 eV): *m*/*z* 513 (M, 44%); 448 (100). IR (KBr): 1639; 1208 cm^{-1}. Anal. Calcd for $C_{32}H_{27}FeNO_2$: C, 74.86; H, 5.30; N, 2.73. Found: C, 74.75; H, 5.18; N, 2.66.

(R,S_p)-2-(α-Diphenylhydroxymethyl)ferrocenyl-5-phenyloxazoline [(R,S_p)-8]. This compound was synthesized from (*R*)-**7** by the procedure reported above for its enantiomer (S,R_p)-**8**. $[\alpha]_D = +337.2$ ($c = 0.8$, $CHCl_3$). HPLC (Daicel Chiralpak AD, *n*-hexane/2-propanol = 97/3, 0.4 mL/min): $t =$ 34.7 min.

(S,S_p)-2-(α-Diphenylhydroxymethyl)ferrocenyl-5-*tert*-butyloxazoline [(S,S_p)-10]. 2-(α-Trimethylsilyl)ferrocenyloxazoline [(S,S_p)-**9**,[11] 720 mg, 1.88 mmol] was dissolved under argon in 30 mL of freshly distilled diethyl ether and stirred at room temperature. At this temperature, the solution was treated with *n*-BuLi (1.4 mL, 2.24 mmol, 1.6 M in *n*-hexane). After being stirred for 2 h more, benzophenone (420 mg, 2.25 mmol) was added directly, and stirring was continued overnight. Standard workup and evaporation of the solvents left a reddish foam that was dried in vacuo (998 mg, 1.77 mmol, 94%). Without further purification, the crude product was directly dissolved under argon in 20 mL of absolute DMSO at room temperature. Freshly sublimed potassium *tert*-butoxide (476 mg, 4.24 mmol) was then added in small portions to this solution, and stirring was continued overnight. Standard workup gave a red solution that was reduced to a volume of approximately 3 mL under reduced pressure. Column chromatography of the crude product [hexanes/ethyl acetate (70/30)] yielded 663 mg (1.35 mmol, 72% yield over both steps) of (S,S_p)-**10** as a red foam. Recrystallization from *n*-hexane at −24 °C led to the formation of red crystals that proved suitable for X-ray crystal analysis. Mp: 160−161 °C. $[\alpha]_D = -359.5$ ($c = 1.3$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.42 (s, 9H); 3.67−3.68 (m, 1H); 3.86 (dd, $J = 10.2$, 7.4 Hz, 1H); 3.94−4.00 (m, 1H); 4.20 (dd, $J = 9.9$, 8.5 Hz, 1H); 4.24−4.26 (m, 1H); 4.28 (s, 5H); 4.74−4.75 (m, 1H); 7.05−7.15 (m, 5H); 7.21−7.35 (m, 3H); 7.48−7.53 (m, 2H); 9.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.02; 33.26; 65.70; 67.85; 68.56; 70.28; 70.66; 75.14; 75.37; 77.13; 100.72; 126.38; 126.51; 127.08; 127.30; 127.55; 127.78; 146.47; 149.31; 167.60. MS (70 eV): *m*/*z* 493 (M, 41%); 428 (100). IR (KBr): 2949; 1654; 1448; 1364; 1209 cm^{-1}. Anal. Calcd for $C_{30}H_{31}FeNO_2$: C, 73.03; H, 6.33; N, 2.84. Found: C, 72.99; H, 6.43; N, 2.74.

[*N*-2-(1-Hydroxy-2-methylpropyl)]ferrocenecarboxamide (12). To a solution of ferrocene carboxylic acid **11** (620 mg, 2.7 mmol) in 20 mL of freshly distilled dichloromethane under argon, oxalyl chloride (0.47 mL, 5.35 mmol) was slowly added via syringe. After about 0.5 h, all gas evolution had ceased, and the solvent was removed directly into a trap. After the resulting purple solid was dried for 2 h, it was dissolved in 15 mL of freshly distilled dichloromethane under argon, and the resulting solution was transferred via cannula to a second Schlenk tube, which contained a solution of 2-amino-2-methylpropanol (0.36 mL, 3.3 mmol) and triethylamine (0.75 mL, 5.4 mmol) in 15 mL of freshly distilled dichloromethane. The resulting mixture was allowed to stir at room temperature overnight and was then quenched with 50 mL of distilled water. The organic phase was separated, and the aqueous

(36) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, R. *J. Org. Chem.* **1993**, *58*, 3568.

phase was extracted twice with 20 mL of dichloromethane. After the combined organic phases were dried over $MgSO_4$, the solvent was removed in vacuo. The resulting orange-red solid was purified by column chromatography [dichloromethane/methanol (93/7)] to afford **12** (575 mg, 1.9 mmol, 71%) as an orange solid. Mp: 144 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 6H); 3.64 (br, 2H); 4.21 (s, 5H); 4.36 (br, 2H); 4.64 (br, 2H); 5.21 (br, 1H); 5.84 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.92; 56.28; 68.24; 69.85; 70.57; 70.74; 71.08; 75.97; 171.56. MS (70 eV): *m*/*z* 301 (M, 79%); 213 (100). IR (KBr): 1612 cm^{-1}. Anal. Calcd for $C_{15}H_{19}FeNO_2$: C, 59.82; H, 6.36; N, 4.65. Found: C, 59.44; H, 6.34; N, 4.61.

2-Ferrocenyl-4,4-dimethyloxazoline (13). To a solution of ferrocene **12** (575 mg, 1.9 mmol) in 50 mL of dry acetonitrile under argon were added triphenylphosphine (1.83 g, 7.0 mmol), triethylamine (1.6 mL, 4.5 mmol), and tetrachloromethane (1.6 mL, 16.6 mmol), and stirring was continued overnight. The resulting deep red solution was worked up with 250 mL of distilled water. This mixture was extracted eight times with 200 mL of hexanes, until the organic layer showed no orange color. The combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting orange solid was purified by column chromatography [hexanes/ethyl acetate (60/40)], yielding the product as a red solid. After recrystallization from *n*-hexane, **13** was obtained as deep red crystals (501 mg, 1.77 mmol, 93%). Mp: 102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 6H); 4.00 (s, 2H); 4.18 (s, 5H); 4.32−4.33 (m, 2H); 4.75−4.76 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.39; 67.31; 68.99; 69.63; 70.26; 78.75; 164.46. MS (70 eV): *m*/*z* 283 (M, 100%); 121 (52). IR (KBr): 1652; 1297 cm^{-1}. Anal. Calcd for $C_{15}H_{17}FeNO$: C, 63.63; H, 6.05; N, 4.95. Found: C, 63.48; H, 6.05; N, 4.88.

2-(α-Diphenylhydroxymethyl)ferrocenyl-4,4-dimethyloxazoline (14). A solution of 2-ferrocenyl-4,4-dimethyloxazoline (**13**, 995 mg, 3.53 mmol) in 40 mL of freshly distilled THF under argon was cooled to −70 °C and then treated dropwise with *n*-BuLi (2.6 mL, 4.16 mmol, 1.6 M in *n*-hexane). After the solution was stirred for 1.5 h, benzophenone (900 mg, 4.9 mmol) was added directly in one portion at a bath temperature of −35 °C, and stirring was continued overnight. Standard workup followed by removal of the solvents furnished a red oil which was purified by column chromatography [hexanes/ethyl acetate (70/30)]. The product was obtained in the form of an orange foam that was dried at the vacuum pump for several hours. After recrystallization from *n*-hexane, deep red crystals of **14** were obtained (1.002 g, 2.15 mmol, 61%).

Separation by preparative HPLC provided 140 mg of each enantiomer.[29] **(−)-14:** $[\alpha]_D = -348.7$ ($c = 0.62$, $CHCl_3$). HPLC (Daicel Chiralpak AD, *n*-hexane/2-propanol = 97/3, 0.4 mL/min): $t = 16.8$ min. **(+)-14:** $[\alpha]_D = 342.3$ ($c = 0.38$, $CHCl_3$). HPLC (Daicel Chiralpak AD, *n*-hexane/2-propanol = 97/3, 0.4 mL/min): $t = 12.4$ min.

Direct Synthesis of (R_p)-14 from (S_p)-18. (S_p)-**18** (490 mg, 1.20 mmol) was dissolved in 15 mL of freshly distilled diethyl ether under argon and cooled to −78 °C. At this temperature, *n*-BuLi (0.8 mL, 1.28 mmol, 1.6 M in *n*-hexane) was added very slowly, and the resulting deep red solution was stirred for 2 h. Benzophenone (262 mg, 1.44 mmol) was then added at −60 °C, and the reaction mixture was allowed to warm to room temperature overnight. Standard workup and purification as stated above gave 460 mg (82%) of (R_p)-**14**, which by analytical HPLC was identical to (−)-**14**. Mp: 123 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.67 (s, 3H); 1.30 (s, 3H); 3.64−3.65 (m, 1H); 3.78 (d, $J = 8.0$ Hz, 1H); 3.88 (d, $J = 8.0$ Hz, 1H); 4.21−4.22 (m, 1H); 4.28 (s, 5H); 4.67−4.69 (m, 1H); 7.07−7.15 (m, 5H); 7.21−7.35 (m, 3H); 7.51−7.54 (m, 2H); 9.23 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.38; 28.32; 66.51; 66.87; 67.59; 69.61; 70.73; 74.82; 76.61; 77.06; 78.91; 101.58; 126.12; 126.54; 127.03; 127.17; 127.50; 127.68; 146.27; 149.38; 165.92. MS (70 eV): *m*/*z* 465 (M, 58%); 400 (100). IR (KBr): 1650; 1447 cm^{-1}. Anal. Calcd for $C_{28}H_{27}FeNO_2$: C, 72.27; H, 5.85; N, 3.01. Found: C, 71.95; H, 6.01; N, 2.85.

(S,S_p)-2-(α-Iodoferrocenyl)-5-*tert*-butyloxazoline [(S,S_p)-15]. A solution of ferrocene (*S*)-**5**[11] (465 mg, 1.49 mmol) in 20 mL of freshly distilled THF was cooled to −78 °C and then treated dropwise with *sec*-BuLi (1.4 mL, 1.82 mmol, 1.3 M in cyclohexane). After being stirred for 2 h at this temperature, a solution of iodine (531 mg, 2.10 mmol) in 30 mL of THF was slowly added via a dropping funnel. The resulting solution was allowed to warm to room temperature overnight. The reaction mixture was quenched with saturated sodium thiosulfate solution and extracted with methyl *tert*-butyl ether. The organic layer was washed subsequently with brine and distilled water and finally dried over anhydrous $MgSO_4$. Column chromatography of the crude product [hexanes/ethyl acetate (70/30)] gave 385 mg (59%) of (S,S_p)-**15** as a deep orange-brown solid followed by a second fraction of 172 mg (37%) of unreacted starting material. Mp: 86 °C. $[\alpha]_D = -203.5$ ($c = 0.4$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H); 3.90 (dd, $J = 9.9$, 7.4 Hz, 1H); 4.05−4.16 (m, 2H); 4.12 (s, 5H); 4.27−4.29 (m, 1H); 4.54−4.55 (m, 1H); 4.60−4.62 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.52; 34.42; 39.19; 68.57; 70.09; 71.41; 73.11; 77.02; 78.87; 163.90. MS (70 eV): *m*/*z* 437 (M, 100%); 309 (91). IR (KBr): 2951; 1664; 1130; 974 cm^{-1}. Anal. Calcd for $C_{17}H_{20}FeINO$: C, 46.71; H, 4.61; N, 3.20. Found: C, 46.54; H, 4.51; N, 3.12.

(S,S_p)-α-Iodoferrocene [*N*-Acetyl-(2-*tert*-butyl-2-aminoethyl)] Carboxylic Ester [(S,S_p)-16]. A solution of ferrocene (S,S_p)-**15** (370 mg, 0.85 mmol) in 9 mL of freshly distilled THF was successively treated with 0.8 mL of water and 6.2 g of sodium sulfate and cooled to 0 °C before 0.35 mL of trifluoroacetic acid was added via syringe. The reaction mixture was stirred overnight and allowed to warm to room temperature. A further 1.7 g of sodium sulfate was added, and the reaction mixture was filtered through a G3 frit under argon. The sodium sulfate layer was washed with THF until it became clear. The organic solvents were removed in vacuo to leave a dark oil, which was immediately dissolved in 15 mL of freshly distilled dichloromethane. The solution was cooled to 0 °C, and 3 mL of acetic anhydride was added followed by 5 mL of pyridine. Stirring was continued overnight, and the resulting dark solution was quenched with 30 mL of 3 M HCl. The organic layer was extracted twice with 30 mL of 3 M HCl, washed with saturated sodium bicarbonate solution, and dried over anhydrous $MgSO_4$. The resulting deep red solution was reduced to a volume of approximately 2 mL, taken up in hexane/ethyl acetate (20/80), and filtered through a pad of silica. After evaporation of the solvents, (S,R_p)-**16** (355 mg, 84%) was obtained as an orange solid. Mp: 146−147 °C. $[\alpha]_D = -20.3$ ($c = 0.5$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H); 1.93 (s, 3H); 4.09−4.24 (m, 2H); 4.16 (s, 5H); 4.34−4.40 (m, 1H); 4.63−4.64 (m, 1H); 4.76−4.77 (m, 1H); 5.62 (d, $J = 9.8$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.23; 27.46; 34.59; 40.44; 56.46; 64.22; 71.01; 71.22; 73.07; 73.38; 80.36; 170.65; 171.38. MS (70 eV): *m*/*z* 497 (M, 38%); 356 (100). IR (KBr): 2951; 1664; 1477; 1366; 1130 cm^{-1}. Anal. Calcd for $C_{19}H_{24}FeINO_3$: C, 46.71; H, 4.61; N, 3.20. Found: C, 46.54; H, 4.51; N, 3.12.

(S_p)-α-Iodoferrocene Carboxylic Acid [(S_p)-17]. Ferrocene (S,S_p)-**16** (310 mg, 0.60 mmol) was dissolved in 15 mL of THF under argon at room temperature. Degassed water (15 mL) was added, followed by the addition of 3.2 mL of degassed aqueous NaOH (2.5 M, 8.00 mmol). The resulting deep orange solution was stirred at 55 °C for 16 h and at 70 °C for a further 4 h. The resulting dark black solution was cooled to room temperature under argon. It was extracted with dichloromethane, and the aqueous layer was acidified by slow addition of 3 M HCl, upon which a brown solid precipitated. The acidified phase was extracted with dichloromethane until it became clear, and the organic phase was dried over anhydrous $MgSO_4$. Removal of the solvent at reduced pressure gave (S_p)-**17** (201 mg, 94%) as an orange solid. Mp: 168 °C. $[\alpha]_D = -75.1$ ($c = 0.53$, CH_2Cl_2). ^{1}H NMR (300 MHz, CD_2Cl_2): 4.21 (s, 5H); 4.46−4.48 (m, 1H); 4.72 (br s, 1H); 4.87 (br s, 1H); 11.3 (vbr s, 1H). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 40.50; 70.59; 71.87; 71.95; 74.01; 74.18; 81.62; 81.73; 177.91. MS (70 eV): *m*/*z* 356 (M, 1%); 59 (100). IR (KBr): 3433; 1674; 1660; 1460; 1268 cm^{-1}. Anal. Calcd for $C_{11}H_9FeIO_2$: C, 37.12; H, 2.55. Found: C, 37.39; H, 2.91.

(R_p)-2-(α-Iodoferrocenyl)-4,4-dimethyloxazoline [(R_p)-18]. A solution of ferrocene (S_p)-**17** (275 mg, 0.77 mmol) in 15 mL of freshly distilled dichloromethane under argon was treated at room temperature by dropwise addition of oxalyl chloride (0.34 mL, 3.85 mmol) via syringe. After about 0.5 h, all gas evolution had ceased, and the solvent was directly removed into a trap. After drying for 2 h, the dark oil was dissolved in 10 mL of freshly distilled dichloromethane under argon, and the resulting solution was transferred via cannula to a second Schlenk tube, which contained a solution of 2-amino-2-methylpropanol (0.17 mL, 1.54 mmol) and triethylamine (0.35 mL, 2.5 mmol) in 10 mL of freshly distilled dichloromethane. The resulting mixture was allowed to stir at room temperature overnight and then quenched with 30 mL of distilled water. The organic phase was separated, and the aqueous phase was extracted twice with 15 mL of dichloromethane. After the combined organic phases were dried over $MgSO_4$, the solvent was removed in vacuo. The resulting red solid was dissolved in 20 mL of dry acetonitrile under argon, triphenylphosphine (1.31 g, 5.0 mmol), triethylamine (1.2 mL, 3.4 mmol), and tetrachloromethane (1.16 mL, 12.0 mmol) were added subsequently, and stirring was continued overnight. The deep red solution was worked up with 100 mL of distilled water. This mixture was extracted six times with 100 mL of hexanes, until the organic layer showed no orange color. The combined organic phases were dried over $MgSO_4$, and the solvent was removed into a trap. The resulting orange solid was purified by column chromatography [hexanes/ethyl acetate (70/43)], yielding the product as an orange-red solid. After recrystallization from *n*-hexane, (R_p)-**18** was obtained as orange-brown crystals (224 mg, 71%). Mp: 66−67 °C. $[\alpha]_D = -194.3$ ($c = 0.2$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 6H); 3.96 (d, $J = 8.0$ Hz, 1H); 4.01 (d, $J = 8.0$ Hz, 1H); 4.09−4.24 (m, 2H); 4.14 (s, 5H); 4.28−4.30 (m, 1H); 4.51−4.53 (m, 1H); 4.72−4.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.86 (d); 39.88; 67.88; 70.10 (d); 71.82 (d); 73.05; 73.19; 79.04 (d); 79.39; 163.60. MS (70 eV): *m*/*z* 409 (M, 74%); 209 (100). IR (KBr): 2953; 1655; 1477; 1120 cm^{-1}. Anal. Calcd for $C_{15}H_{16}FeINO$: C, 44.05; H, 3.94; N, 3.42. Found: C, 43.82; H, 3.93; N, 3.34.

(*S*)-2-(2′-Diphenylhydroxymethyl)phenyl-4-*tert*-butyloxazoline (20). A solution of (*S*)-2-(2′-bromophenyl)-4-*tert*-butyloxazoline **19**[35] (1.14 g, 4.03 mmol) in 30 mL of freshly distilled diethyl ether under argon was cooled to −70 °C and treated dropwise with *n*-BuLi (2.9 mL, 4.64 mmol, 1.6 M in *n*-hexane). After being stirred for 1 h at a bath temperature of −40 °C, benzophenone (740 mg, 4.83 mmol) was added directly in one portion, and stirring was continued overnight as the reaction mixture was allowed to warm to room temperature. Standard workup and purification by column chromatography [hexanes/ethyl acetate (75/25)] yielded 1.109 g of **20** (2.88 mmol; 71%) as a white foam. $[\alpha]_D = +19.7$ ($c = 3.0$, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (s, 9H); 3.71−3.75 (m, 1H); 3.81−3.87 (m, 1H); 3.97−4.02 (m, 1H); 7.28−7.40 (m, 10H); 7.45−7.51 (m, 3H); 7.88−7.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.59; 34.76; 64.00; 67.25; 93.42; 124.29; 124.40; 127.40; 127.88; 128.65; 128.69; 128.80; 129.01; 129.34; 130.93; 131.92; 142.95; 143.00; 149.25; 159.31. MS (70 eV): *m*/*z* 385 (M, 13%); 328 (100). IR (KBr): 1677 cm^{-1}. Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01; H, 7.06; N, 3.63. Found: C, 81.03; H, 6.94; N, 3.60.

Acknowledgment. We are grateful to the Volkswagenstiftung, the Fonds der Chemischen Industrie, and the Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (SFB) 380 “Asymmetric Synthesis by Chemical and Biological Methods” for financial support. We thank Degussa AG for its donation of amino acids and Witco for its generous gift of diethylzinc. We also thank Miss Nina Herrmanns for experimental contributions, Professor Kagan and Dr. Riant for sending a manuscript (ref 14b) prior to publication, and Professor Ahn for providing a reprint of ref 25g.

Supporting Information Available: Full spectral characterization (^{1}H and ^{13}C NMR spectra) for all new ferrocenes, HPLC characterization for ferrocene complexes **8** and **14**, experimental details concerning the diethylzinc addition to benzaldehyde, and crystallographic data regarding the X-ray structure of (S,S_p)-**10** (38 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO981098R