2-Amino-Substituted 1-Sulfinylferrocenes as Chiral Ligands in the Addition of Diethylzinc to Aromatic Aldehydes

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A simple and modulable access to a structural variety of enantiopure amino-substituted ferrocenyl sulfoxides and their use as chiral catalysts in the asymmetric addition of diethylzinc to aromatic aldehydes is described. Moderate to high enantioselectivities (up to 96% ee) were obtained in the case of the arylsulfonamide ligands (R_{Fc}, R_S)-**4h** and (R_{Fc}, R_S)-**4i**. It has been demonstrated that the planar chirality of the ferrocene unit is the decisive chiral element involved in the reaction.

Introduction

Chiral nonracemic sulfoxides have long been employed as efficient stereochemical controllers in many classical keystone C−C bond-forming reactions,[1] such as Diels−Alder reactions, 1,3-dipolar cycloadditions, 1,2-additions to carbonyls, and conjugate additions, and more recently have also been applied in several transition metal-catalyzed reactions.[2] However, despite the outstanding chemical importance and industrial interest in developing catalytic enantioselective methods,[3] compared to the stoichiometric-based chiral auxiliary approach,[1,2] very few studies on the use of sulfoxides as chiral ligands for asymmetric synthesis have been reported to date, most of them dealing with asymmetric palladium-catalyzed allylic substitutions.[4] Among the plethora of chiral structural motifs used in asymmetric catalysis,[3] enantiopure 1,2-disubstituted ferrocenes have received great attention in recent years.[5] It has been well demonstrated that the planar chirality of this type of compounds can provide an appropriate chiral environment for asymmetric induction, especially when ferrocenes having P,P-, P,N-, or N,O-bidentate metal-coordinating substituents are employed.[5]

In this context, we describe herein the synthesis of enantiopure 2-amino-substituted 1-sulfinylferrocenes[6] as a new family of sterically and electronically modulable ligands, having central (sulfur atom) and planar chirality (ferrocene unit), as well as catalytic effectiveness in the asymmetric addition of diethylzinc to aromatic aldehydes.[7] To the best of our knowledge, there are very few precedents dealing with the use of sulfoxides as chiral ligands in this kind of reaction, the enantioselectivity of the process being very modest (ee in the range 2−55%).[8]

Results and Discussion

Synthesis of Enantiopure *tert*-Butylsulfinylferrocenes. Taking into account that the *tert*-butylsulfinyl group proved to be an excellent chiral auxiliary in our previous studies on asymmetric intramolecular Pauson−Khand reactions of 1-sulfinylenynes,[2f] we considered that this type of sterically encumbered sulfoxide could be a reasonable starting point for the design of chiral ligands

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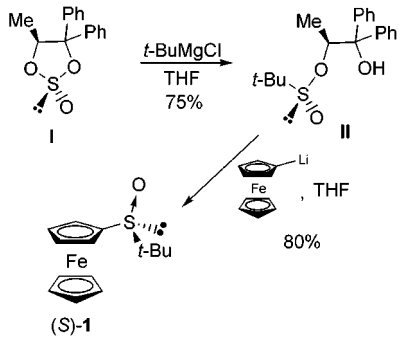
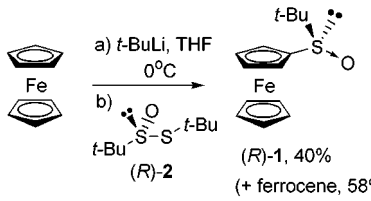
Scheme 1



Scheme 2

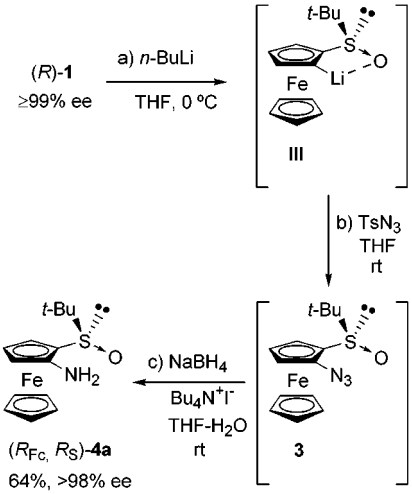


based on sulfinyl-substituted ferrocenes. Optically pure *tert*-butysulfinylferrocene [(*S*)-**1**] was previously prepared by Kagan et al. from the commercially available enantiopure sulfite **I** by two consecutive nucleophilic configurational inversions at the sulfur atom:[9] treatment of **I** with *t*-BuMgCl to give the *tert*-butylsulfinate **II**, followed by further reaction with ferrocenyllithium (Scheme 1). The same group has also reported that (*R*)-**1** can be obtained in high optical purity by asymmetric oxidation of *tert*-butylsulfenylferrocene under appropriate reaction conditions [cumene hydroperoxide, $Ti(O^iPr)_4$, (*R*,*R*)-DET, H_2O, CH_2Cl_2].[10]

As an alternative method, we have developed a simple one-step synthesis of (*R*)-**1** based on the direct sulfinylation of ferrocenyllithium (formed in situ by deprotonation of ferrocene with *t*-BuLi in THF) with (*R*)-*S*-*tert*-butyl 1,1-dimethylethanethiosulfinate **2** (Ellman's reagent).[11] This procedure is experimentally quite simple (THF, 0 °C) and occurs with inversion at the sulfur atom, providing (*R*)-**1** in 40% yield after flash chromatography (58% of starting ferrocene is recovered, Scheme 2). Due to the somewhat tedious preparation of (*R*)-**2** in enantiopure form,[12] we have found that it is experimentally more practical to use (*R*)-**2** with an enantiopurity of about 80%, followed by a single recrystallization (from 1:1 hexane: Et_2O) of the resulting sulfinylferrocene (*R*)-**1**. By this way gram quantities of almost enantiopure (*R*)-**1** (≥99% ee, HPLC, Daicel Chiralcel OD column) have been routinely obtained in a completely reproducible manner.

It is well-known from the work of Kagan[9] and Hua[10a] that the *ortho*-lithiation of *tert*-butylsulfinylferrocene **1** occurs with complete diastereocontrol to generate the *ortho*-lithiated intermediate **III**, in which the sulfinylic

Scheme 3



oxygen coordinates the lithium atom and the large *tert*-butyl group is opposite to the iron atom.[13] Although many examples of trapping of this lithiated species with different electrophiles have been described (>96% de), as far as we know the use of nitrogen electrophiles[14] had not been previously reported. We found that the deprotonation of (*R*)-**1** with *n*-BuLi (THF, 0 °C) and further addition of tosyl azide led to the intermediate ferrocenyl azide **3**. This compound was not isolated and was in situ reduced with $NaBH_4$ under phase-transfer reaction conditions[15] (Bu_4N^+I, H_2O−THF) to provide the aminoferrocene (R_{Fc},R_S)-**4a** as the only isolated diastereomer (64% overall yield after flash chromatography). Starting from enantiopure (*R*)-**1** (≥99% ee), we confirmed that the optical purity of the resulting aminoferrocene **4a** was also very high (>98% ee, HPLC, Chiralpak AS column), proving that the overall procedure occurred without any previous epimerization at the sulfur atom (Scheme 3).

The ready access to different series of ligands with modulable steric and electronic properties around the metal-coordinating atom is of crucial importance in enantioselective catalysis. Thus, having developed a practical procedure for the preparation of enantiopure **4a** in gram quantities from ferrocene, the amino group was transformed into a variety of nitrogen derivatives, such as dialkyl-substituted amines (**4b**), alkyl- and aryl-substituted amides (**4c**−**f**), and alkyl- and aryl-substituted sulfonamides (**4g**−**l**), following straighforward reactions of amine derivatization (Scheme 4). From a practical point of view, it is important to note that all compounds **4** are very stable solids that are readily purified by flash chromatography or recrystallization.

Enantioselective Additions. With this sterically and electronically varied set of enantiopure sulfinylferrocenes in hand, we examined their efficiency as chiral catalysts in the enantioselective addition of diethylzinc to aldehydes. Because of its experimental simplicity and the fact that the reaction is effectively catalyzed by a wide variety of Lewis bases, this type of C−C bond forming transformation is one of the most popular reactions in ligand

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(11) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.

(12) Following the experimental procedure described in ref 11, in our hands, the preparation of (*R*)-**2** with an enantiomeric excess higher than 95% required four or more successive recrystallizations from hexane.

(13) For diastereoselective *ortho*-deprotonation of ferrocenyl sulfoximines, see: Bolm, C.; Kesselgruber, M.; Muñiz, K.; Raabe, G. *Organometallics* **2000**, *19*, 1648.

(14) For a review on electrophilic amination, see: Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947.

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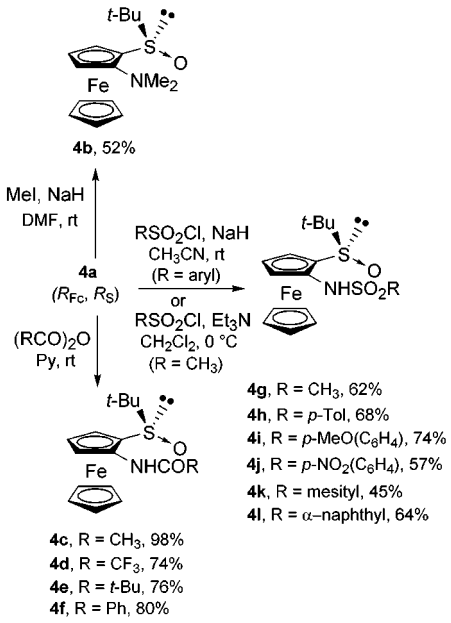
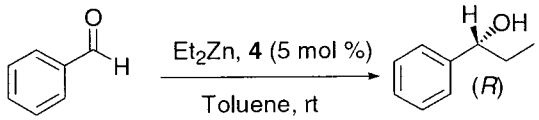
Scheme 4



screening for asymmetric catalysis.[7] Since the discovery of Noyori et al.[16] that aminoisoborneol derivatives are very efficient N,O-bidentate chiral catalysts in this reaction, an extraordinary structural variety of chiral ligands have been reported to date,[7] especially in the case of compounds that possess amino alcohol frameworks.[17]

The results obtained in the addition of diethylzinc to benzaldehyde in the presence of a catalytic amount of ligands **4** are depicted in Table 1. The reactions were performed under standard conditions: 5 mol % of ligand **4**, excess of diethylzinc (200 mol %) in toluene at room temperature. Excepting the ligands having strong electron-withdrawing substitution, ligands **4d** and **4j** (entries 4 and 13), the conversion was complete in 1−4 days, showing that ferrocenes **4** act as catalysts in this reaction. After final flash chromatography, acceptable to good yields in alcohol **5** were obtained in all cases. With the exception of the unsubstituted ligand **4a** (entry 1), all reactions led to the predominant formation of the alcohol (*R*)-**5**, but with very different levels of enantiocontrol. Although a low stereoselectivity was observed in the presence of the amine and amide ligands (entries 2−6), the sulfonamide series provided a significantly higher and more homogeneous enantiocontrol, with ee's ranging from 42% to 82%. The best ligands were found to be the *p*-tolylsulfonamide **4h** (80% ee, entry 8) and the *p*-methoxyphenylsulfonamide **4i** (82% ee, entry 11). The use of bulkier arylsulfonamides (ligands **4k** and **4l,** entries 14 and 15) or the electronically poor *p*-nitrosulfonamide **4j** (entry 13) had a detrimental effect in the enantioselectivity. Interestingly, in the case of the optimal ligands **4h** and **4i** the enantioselectivity was significantly enhanced by performing the reaction at lower temperatures,

Table 1. Diethylzinc Addition to Benzaldehyde Catalyzed by the Ligands (R_{Fc},R_S)-4



5

			5		
entry[a]	ligand	t (h)	config	ee (%)[b]	yield (%)[c]
1	**4a**	48	*S*	28	93
2	**4b**	72	*R*	6	59
3	**4c**	48	*R*	60	76
4	**4d**	96	*R*	6	67[e]
5	**4e**	24	*R*	14	70
6	**4f**	32	*R*	8	74
7	**4g**	72	*R*	74	90
8	**4h**	20	*R*	80	79
9[d]	**4h**	96	*R*	88	80[e]
10[f]	**4h**	24	*R*	4	90
11	**4i**	28	*R*	82	82
12[d]	**4i**	96	*R*	86	76[e]
13	**4j**	96	*R*	58	62[e]
14	**4k**	48	*R*	48	68
15	**4l**	96	*R*	42	51

[a] Reaction conditions: Et_2Zn (200 mol %), ligand (5 mol %), toluene, rt. [b] Determined by HPLC (Daicel Chiralcel OD). [c] In pure alcohol after flash chromatography. [d] Reaction run at −20 °C. [e] Conversion yield. [f] Reaction run in the presence of $Ti(O^iPr)_4$ (120 mol %).

−20 °C instead of room temperature, giving rise to (*R*)-**5** in 88% and 86% ee's, respectively (entries 9 and 12).

Other types of chiral sulfonamides, in particular *C*-2 symmetrical bissulfonamides derived from 1,2-cyclohexanediamine, had been reported as very efficient ligands in the enantioselective titanium-catalyzed addition of dialkylzinc reagents to aldehydes.[18] With this kind of N,N-bidentate ligands the reaction is performed in the presence of a titanium Lewis acid, usually $Ti(O^iPr)_4$, to generate the key chiral titanium bis(sulfonamide) complex. In our case the addition of diethylzinc to benzaldehyde catalyzed by ligand **4h** and $Ti(O^iPr)_4$ occurred in a nearly nonenantioselective manner (4% ee, entry 10). This drastic drop in the enantioselectivity could be ascribed to the inability of the sulfoxide to act as a ligand for the titanium atom, **4h** behaving as an N-coordinating titanium ligand rather than as a more rigid N,O-bidentate ligand.[19]

To explore the scope of the optimal ligands **4h** and **4i** as chiral catalysts in the addition of diethylzinc to aromatic aldehydes, a variety of substrates with quite different steric and electronic substitution on the aromatic ring were tested (Table 2). In all cases the reactions occurred smoothly in toluene at room temperature and, like in the addition to benzaldehyde, the corresponding alcohol of (*R*) configuration was always obtained as the major enantiomer[20] (alcohols **6**−**11**). As in previous cases, the accurate determination of the ee's was always

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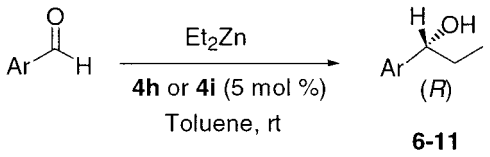
(18) For some very recent references, see for instance: (a) Balsells, J.; Betancort, J. M.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3428. (b) Balsells, J., Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 3250. (c) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1629. (d) Paquette, L. A.; Zhou, R. *J. Org. Chem.* **1999**, *64*, 7929. (e) Fürstner, A.; Muller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (f) Arredondo, V. M.; Tian, S.; McDonald, F. E.; Marks, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 3633. (g) Lutz, C.; Jones, P.; Knochel, P. *Synthesis* **1999**, 312.

(19) A similar very low ee was also observed using TMSCl as additive.

Table 2. Diethylzinc Addition to Aromatic Aldehydes Catalyzed by the Ligands 4h and 4i



entry[a]	Ar	ligand	*t* (h)	prod. (*R*) config	ee (%)	yield[c] (%)
1	*p*-$NO_2C_6H_4$	**4h**	96	**6**	28	73[e]
2	*p*-$NO_2C_6H_4$	**4i**	96	**6**	26	75[e]
3	*p*-$MeOC_6H_4$	**4h**	96	**7**	66[d]	65[e]
4	*p*-$MeOC_6H_4$	**4i**	96	**7**	58[d]	61[e]
5	*p*-MeC_6H_4	**4h**	48	**8**	64[d]	86
6	*p*-MeC_6H_4	**4i**	53	**8**	66[d]	72
7	*p*-$CO_2MeC_6H_4$	**4h**	20	**9**	88	71
8	*p*-$CO_2MeC_6H_4$	**4i**	24	**9**	96	78
9	2-naphthyl	**4h**	31	**10**	82	73
10	2-naphthyl	**4i**	40	**10**	92	79
11	*m*-FC_6H_4	**4h**	48	**11**	80	76
12	*m*-FC_6H_4	**4i**	52	**11**	72	74

[a] Reaction conditions: Et_2Zn (200 mol %), ligand (5 mol %), toluene, rt. [b] Determined by HPLC (Daicel Chiralpak AD). [c] In pure alcohol after flash chromatography. [d] Determined by HPLC (Daicel Chiralcel OD). [e] Conversion yield.

established by HPLC (Daicel Chiralpak AD or Daicel Chiralcel OD). For each aldehyde both ligands **4h** and **4i** afforded rather similar enantioselections and, remarkably, with the exception of *p*-nitrobenzaldehyde (entries 1 and 2), which gave a disappointingly low ee, moderate to relatively high enantioselectivities were obtained with the rest of aldehydes. As the best results, ee's higher than 90% (up to 96% ee) were observed in the addition of diethylzinc to methyl 4-formylbenzoate and 2-naphthaldehyde in the presence of **4i** (entries 8 and 10).

Synthesis of Enantiopure *p*-Tolylsulfinylferrocenes. In our goal in developing a highly tunable family of amino-substituted sulfinylferrocenes for enantioselective catalysis, once the effect of the substitution at the nitrogen atom in enantiopure ferrocenes **4** was explored, it was equally interesting to determine the influence of the substitution at the sulfur atom in the asymmetric induction of the process. Thus, following a reported procedure,[10a,21] (*S*) *p*-tolylsulfinylferrocene [(*S*)-**12**] was prepared by reaction of ferrocenyllithium with (S_S,1*R*) menthyl *p*-toluenesulfinate (40% yield). This sulfinylation reaction was performed at −78 °C in order to avoid a significant degree of racemization at the sulfur atom. Under these conditions (*S*)-**12** was obtained in 97% ee. A further recrystallization from *n*-hexane:Et_2O (1:3) gave enantiomerically pure material (>99% ee, HPLC, Chiralcel OD). By applying the same one-pot method previously developed for the *tert*-butylsulfinylferrocene derivatives, (*S*)-**12** was *ortho*-deprotonated[21b] (LDA, THF, −78 °C) and treated with tosyl azide. The resulting ferrocenyl azide was in situ reduced with $NaBH_4$ ($Bu_4N^+I^-$, THF−H_2O) to furnish the aminoferrocene (S_{Fc},S_S)-**13a** (67% overall yield), whose very high optical purity was confirmed by conversion into its (*S*) Mosher's amide (>99% de). Tosylation of **13a** under usual conditions (NaH, TsCl, CH_3CN) led to the sulfonamide (S_{Fc},S_S)-**13h** (Scheme 5).

Scheme 5

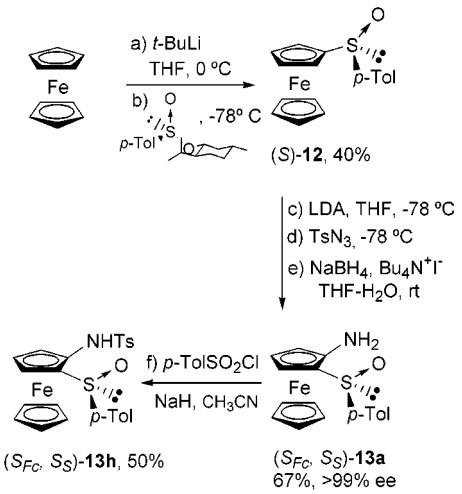
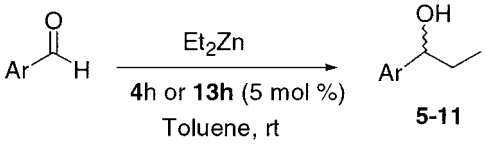


Table 3. Diethylzinc Addition to Aromatic Aldehydes Catalyzed by the Ligands (R_{Fc},R_S)-4h and (S_{Fc},S_S)-13h



entry[a]	Ar	ligand	product	ee (%)[c]	yield[c] (%)
1	Ph	**4h**	(*R*)-**5**	80	79
2	Ph	**13h**	(*S*)-**5**	32	67
3	*p*-$NO_2C_6H_4$	**4h**	(*R*)-**6**	28	73[e]
4	*p*-$NO_2C_6H_4$	**13h**	(*S*)-**6**	9	50[e]
5	*p*-$MeOC_6H_4$	**4h**	(*R*)-**7**	66[d]	65[e]
6	*p*-$MeOC_6H_4$	**13h**	(*S*)-**7**	39[d]	65[e]
7	*p*-MeC_6H_4	**4h**	(*R*)-**8**	64[d]	86
8	*p*-MeC_6H_4	**13h**	(*S*)-**8**	48[d]	80[e]
9	*p*-$CO_2MeC_6H_4$	**4h**	(*R*)-**9**	88	71
10	*p*-$CO_2MeC_6H_4$	**13h**	(*S*)-**9**	69	60
11	2-naphthyl	**4h**	(*R*)-**10**	82	73
12	2-naphthyl	**13h**	(*S*)-**10**	53	62
13	*m*-FC_6H_4	**4h**	(*R*)-**11**	80	76
14	*m*-FC_6H_4	**13h**	(*S*)-**11**	33	75

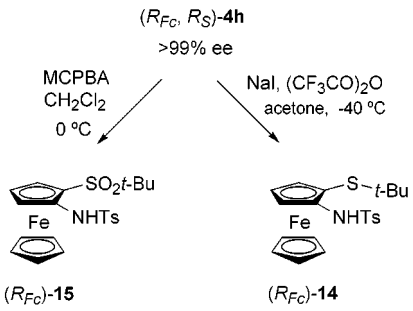
[a] Reaction conditions: Et_2Zn (200 mol %), ligand (5 mol %), toluene, rt, 1−4 days. [b] Determined by HPLC (Daicel Chiralpak AD). [c] In pure alcohol after flash chromatography. [d] Determined by HPLC (Daicel Chiralcel OD). [e] Conversion yield.

Enantioselective Additions. The results obtained in the addition of diethylzinc to several aromatic aldehydes in the presence of a catalytic amount of the enantiopure *p*-tolyl sulfoxide **13h** are shown in Table 3. In all cases satisfactory yields in alcohols **5**−**11** were obtained after reasonable reaction times (1−4 days). For stereochemical comparison purposes, the results obtained from the *tert*-butyl sulfoxide **4h** have been again included (odd entries). According to the fact that ligand (S_{Fc},S_S)-**13h** has opposite configuration to that of (R_{Fc},R_S)-**4h**, the enantioselectivity exerted by both ligands was also opposite [major formation of the (*S*)-alcohol in the case of (S_{Fc},S_S)-**13h**]. However, the most interesting conclusion of this com-

(20) The configurational assignment was established by comparison of the sign of the optical rotation of the enriched enantiomeric mixtures of the final products **6**−**11** with the reported values for the known optically active compounds [all obtained (*R*) alcohols are dextrorotatory]. See, for instance: (a) Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315. (b) Shi, M.; Sui, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3319. (c) Gibson, C. L. *Tetrahedron: Asymmetry* **1999**, *10*, 1551. (d) Jin, M.-J.; Ahn, S.-J.; Lee, K.-S. *Tetrahedron Lett.* **1996**, *37*, 8767.

(21) (a) Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2893. (b) Riant, O.; Argouarch, G.; Guillaneux, D.; Samuel, O.; Kagan, H. B. *J. Org. Chem.* **1998**, *63*, 3511. (c) Rebière, F.; Samuel, O.; Kagan, H. B. *Tetrahedron Lett.* **1990**, *31*, 3121.

Scheme 6

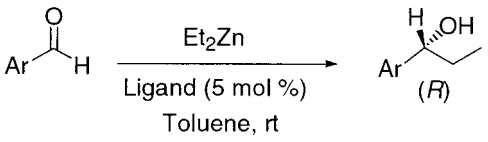


parative study was the very different performances of **4h** and **13h** as chiral inductors: for every tested aldehyde the enantioselectivity of the reaction was much lower from the *p*-tolyl sulfoxide **13h** (69% ee was the best induction, entry 10) than from the *tert*-butyl sulfoxide **4h.** This fact could be due to the higher steric discrimination imposed by the bulky *tert*-butyl group. As previously indicated, a similar trend was observed by us in the diastereoselective intramolecular Pauson−Khand reaction of 1-sulfinyl-1,6-enynes[2f] and in the intermolecular Heck arylations of *β*-sulfinyldihydrofurans.[2g]

Ferrocenes with Only Planar Chirality. Because most of the current methods of synthesis of chiral 1,2-disubstituted ferrocenes require the presence of an *ortho*-directing substituent with stereogenic centers, most of the studies involving ferrocenes as chiral ligands deal with compounds having both planar and central chirality.[5] However, for a more rational design of ferrocene ligands the evaluation of the relative importance of each chirality element is of great importance. Thus, Bolm et al. have recently described[22] that in a series of N,O-bidentate ferrocenes both elements of chirality play a significant role in the enantioselectivity of the addition of dialkylzinc to aldehydes[23] (chiral cooperativity).

From the sulfinylferrocene family **4**, the synthesis of compounds having exclusively planar chirality could be readily achieved by straightforward oxidation/reduction reactions of the sulfinyl group. Thus, the model ligand (R_{Fc},R_S)-**4h** was reduced to the corresponding sulfide (R_{Fc})-**14** by treatment with NaI/$(CF_3CO)_2O$ in acetone[24] (89% yield), while its oxidation with MCPBA in CH_2Cl_2 gave the corresponding sulfone (R_{Fc})-**15** (87% yield, Scheme 6). The results obtained in the addition of diethylzinc to several aldehydes in the presence of this sulfide/sulfoxide/sulfone series of chiral ferrocene ligands under the usual experimental conditions (toluene, rt) are summarized in Table 4.

Table 4. Diethylzinc Addition to Aromatic Aldehydes Catalyzed by the Ligands (R_{Fc},R_S)-4h, (R_{Fc})-14, and (R_{Fc})-15



entry[a]	Ar	ligand	*t* (h)	prod. (*R*) config	ee (%)[b]	yield[c] (%)
1	Ph	**4h**	20	**5**	80[d]	79
2	Ph	**14**	13	**5**	82[d]	85
3	Ph	**15**	24	**5**	82[d]	67
4	*p*-$CO_2MeC_6H_4$	**4h**	20	**9**	88	71
5	*p*-$CO_2MeC_6H_4$	**14**	15	**9**	85	70
6	*p*-$CO_2MeC_6H_4$	**15**	96	**9**	82	84[e]
7	2-naphthyl	**4h**	31	**10**	82	73
8	2-naphthyl	**14**	25	**10**	77	80
9	2-naphthyl	**15**	96	**10**	78	91[e]

[a] Reaction conditions: Et_2Zn (200 mol %), ligand (5 mol %), toluene, rt. [b] Determined by HPLC (Daicel Chiralpak AD). [c] In pure alcohol after flash chromatography. [d] Determined by HPLC (Daicel Chiralcel OD). [e] Conversion yield.

Regarding the stereochemical outcome, outstandingly, both sulfide **14** and sulfone **15** showed a catalysis efficiency very close to that displayed by the model sulfoxide **4h**. In all cases the reactions occurred with very similar enantioselectivities, and in some cases **14** and **15** were even somewhat more effective than the sulfoxide **4h** (entries 2 and 3). These results clearly show that it is the planar chirality of the ferrocene unit, and not the stereogenic sulfur atom, that is the decisive structural element involved in the asymmetric induction. In fact, as can be deduced by comparing entries 1−3, 4−6, and 7−9, the contribution to the asymmetric induction due to the chiral sulfinyl substitution in **4h** appears to be quite small.[25] This surprisingly homogeneous enantiocontrol observed in the sulfide−sulfoxide−sulfone series of ligands (**14**, **4h**, and **15**), with quite different coordinating, steric, and electronic properties around the sulfur atom, leads us to speculate that these kinds of 1,2-disubstituted ferrocenes behave as N-monocoordinating ligands rather than more rigid bidentate N,O- or N,S-chelating ligands, the bulky sulfur substituent likely favoring a suitable steric discrimination in the coordination of diethylzinc with the nitrogen of the sulfonamide moiety.

Conclusions

We have developed a practical three-step synthesis of a novel family of chiral 1,2-heterosubstituted ferrocenes: 2-aminosubstituted 1-sulfinylferrocenes. These compounds are prepared in enantiopure form by sulfinylation of ferrocenyllithium with (*R*)-*S*-*tert*-butyl 1,1-dimethylethanethiosulfinate or (S_S,1*R*) menthyl *p*-toluenesulfinate, *ortho*-diastereoselective electrophilic amination, and amine derivatization. Among all prepared ligands, the (R_{Fc},R_S) *tert*-butylsulfinylferrocenyl sulfonamides **4h** and **4i** behaved as interesting chiral catalysts in the enantioselective addition of diethylzinc to differently substituted aromatic aldehydes, affording the alcohol of (*R*) configuration with ee's usually in the range

(22) (a) Bolm, C.; Muñiz, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem*. **1998**, *63*, 7860. See, also: (b) Deng, W.-P.; You, S.-L.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W.; Sun, J. *J. Am. Chem. Soc.* **2001**, *123*, 6508. (c) Bolm, C.; Muñiz, K. *Chem. Eur. J.* **2000**, *6*, 2309.

(23) For previous studies on ferrocenes as chiral ligands in the addition of diethylzinc to aldehydes, see for instance: (a) Bastin, S.; Agbossou-Niedercorn, F.; Brocard, J.; Pélinski, L. *Tetrahedron: Asymmetry* **2001**, *12*, 2399. (b) Zhang, W.; Yoshinaga, H.; Imai, Y.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *Synlett* **2000**, 1512. (c) Bolm, C.; Muñiz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491. (d) Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1998**, *9*, 2595. (e) Patti, A.; Nicolosi, G.; Howell, J. A. S.; Humphries, K. *Tetrahedron: Asymmetry* **1998**, *9*, 4381. (f) Bolm, C.; Muñiz Fernández, K.; Seger, A.; Raabe, G. *Synlett* **1997**, 1051. (g) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444. (h) Malfait, S.; Pélinski, L.; Brocard, J. *Tetrahedron: Asymmetry* **1996**, *7*, 653. (i) Watanabe, M. *Synlett* **1995**, 1050. (j) Watanabe, M. *Tetrahedron Lett.* **1995**, *36*, 8991. (k) Nicolosi, G.; Patti, A.; Morrone, R.; Piattelli, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1639. (l) Wally, H.; Widholm, M.; Weissensteiner, W.; Schlögl, K. *Tetrahedron: Asymmetry* **1993**, *4*, 285.

(24) Drabowicz, J.; Oae, S. *Synthesis* **1977**, 404.

(25) As an additional example of this behavior, the sulfoxide (R_{Fc},R_S)-**4i** and its corresponding thioether gave also similar ee's in the addition of diethylzinc to benzaldehyde (86% and 74% ee, respectively).

65−96%. The comparison of the results of the sulfoxide (R_{Fc},R_S)-**4h** with those obtained from the corresponding sulfide (R_{Fc})-**14** and sulfone (R_{Fc})-**15** revealed that the planar chirality of the 1,2-disubstituted ferrocene is the key structural element involved in the asymmetric induction.

Experimental Section

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were acquired at 200 or 300 MHz (indicated in each case), and ^{13}C NMR were acquired at 75 MHz. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) was determined at an ionizing voltage of 70 eV. All reactions were carried out in anhydrous solvents. THF and diethyl ether were distilled from sodium−benzophenone under argon. CH_2Cl_2 was distilled from P_2O_5. Flash column chromatography was performed using silica gel Merck-60 (230−400 mesh). Et_2Zn (1 M) solution in hexane was purchased from Sigma-Aldrich Co.

(R_S)-*tert*-Butylsulfinylferrocene[9,10] [(*R*)-1]. To a cold solution (0 °C) of ferrocene (6.17 g, 33.18 mmol) in THF (50 mL) was added *t*-BuLi 1.7 M in pentane (17.0 mL, 28.75 mmol) under argon atmosphere. The reaction mixture was stirred at 0 °C for 2 h, and then a solution of (*R*)-*S*-*tert*-butyl 1,1-dimethylethanethiosulfinate[11] [(*R*)-**2**, 4.30 g, 22.12 mmol; ≥80% ee] in THF (20 mL) was added. The reaction was warmed to room temperature and then kept at this temperature for 2 h. Brine was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 2:1) to afford sulfoxide (*R*)-**1** (2.52 g, 40%), which was recrystallized from diethyl ether and hexane (1:1) to give pure sulfoxide (*R*)-**1** [1.25 g, 99% ee, HPLC: Daicel Chiracel OD, *i*-PrOH/Hexane 2/98, flow rate 0.70 mL/min, t_R: 19.3 min (*R*)-isomer and 24.3 min (*S*)-isomer, detection at 254 nm]. mp 150−151 °C; $[\alpha]^{20}_D$ = −355 (*c* = 0.5, $CHCl_3$), 99% ee; Lit.[10a] $[\alpha]^{20}_D$ = −339 (*c* = 0.5, $CHCl_3$), 95% ee; ^{1}H NMR (200 MHz) δ 4.68 (m, 1H, Cp-H), 4.41 (m, 2H, Cp-H), 4.38 (s, 5H, Cp′-H), 4.35 (m, 1H, Cp-H), 1.12 (s, 9H, *t*-Bu).

(R_{Fc},R_S)-2-Amino-1-(*tert*-butylsulfinyl)ferrocene [(R_{Fc},R_S)-4a]. To a cold solution (0 °C) of sulfoxide **1** (1.38 g, 4.76 mmol) in THF (35 mL) was added *n*-BuLi (1.9 M) in pentane (3.43 mL, 6.19 mmol) under argon. The mixture was stirred at room temperature for 2 h, and then a solution of tosyl azide (1.22 g, 6.19 mmol) was added at 0 °C. The resulting solution was stirred at room temperature for 4 h, and a solution of $Bu_4N^+I^-$ (0.70 g, 1.90 mmol) and $NaBH_4$ (0.72 g, 19 mmol) in H_2O (10 mL) was added. The reaction mixture was stirred at room temperature for 24 h, and then a second solution of $NaBH_4$ (0.36 g, 9.5 mmol) in H_2O (5 mL) was added. After 24 h brine was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−CH_2Cl_2 1:3) to afford the aminosulfoxide **4a** [0.93 g, 64%, >98% ee, HPLC: Daicel Chiralpak AS, *i*-PrOH/Hexane 5/95, flow rate 0.70 mL/min, t_R 9.9 min (*S*)-isomer and 12.2 min (*R*)-isomer, detection at 254 nm]. mp 163−164 °C; $[\alpha]^{20}_D$ = −343 (*c* = 0.1, $CHCl_3$); ^{1}H NMR (200 MHz) δ 4.27 (s, 5H, Cp′-H), 4.09 (t, 1H, *J* = 1.8 Hz, Cp-H), 4.01 (m, 1H, Cp-H), 3.98 (t, 1H, *J* = 2.5 Hz, Cp-H), 3.64 (bs, 2H, NH_2), 1.20 (s, 9H, *t*-Bu); ^{13}C NMR δ 108.5, 70.7, 70.0, 64.6, 64.2, 58.6, 57.0, 23.1; MS (EI) *m*/*z* 305 (M^+, 6), 249 (8), 231 (26), 178 (5), 149 (51), 97 (28), 91 (13), 84 (44), 81 (40), 71 (46), 69 (85), 57 (100). Anal. Calcd for $C_{14}H_{19}FeNOS$: C, 55.09; H, 6.27; N, 4.59; S, 10.50. Found: C, 54.69; H, 6.02; N, 4.28; S, 10.61.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*,*N*-(dimethyl)amino]-ferrocene [(R_{Fc},R_S)-4b]. To a solution of amine **4a** (0.20 g, 0.65 mmol) in DMF (7 mL), at room temperature, NaH (0.10 g, 2.62 mmol) was added. The resulting solution was stirred for 30 min, and MeI (0.92 g, 6.50 mmol) was added. The reaction mixture was stirred for 12 h, and water was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:6) to afford the amine **4b** (0.12 g, 57%). mp 133−134 °C; $[\alpha]^{20}_D$ = −540 (*c* = 0.1, $CHCl_3$); ^{1}H NMR (200 MHz) δ 4.48 (s, 5H, Cp′-H), 4.18 (m, 2H, Cp-H), 4.06 (t, 1H, *J* = 2.6 Hz, Cp-H), 2.73 (s, 6H, 2 Me), 1.17 (s, 9H, *t*-Bu); ^{13}C NMR δ 113.8, 72.2, 70.6, 68.4, 63.5, 63.3, 57.4, 44.8, 24.3; MS (EI) *m*/*z* 333 (M^+, 35), 317 (12), 277 (34), 259 (26), 246 (12), 149 (18), 139 (93), 138 (67), 97 (22), 84 (100), 69 (45), 57 (51); Anal. Calcd for $C_{16}H_{23}FeNOS$: C, 57.66; H, 6.96; N, 4.20; S, 9.62. Found: C, 57.27; H, 6.90; N, 4.09; S, 9.88.

General Procedure for the Synthesis of the Amides 4c−f: (R_{Fc},R_S)-2-(*N*-Acetyl)amino-1-(*tert*-butylsulfinyl)-ferrocene [(R_{Fc},R_S)-4c]. To a solution of amine **4a** (149 mg, 0.49 mmol) in pyridine (1 mL), at 0 °C, was added Ac_2O (100 mg, 0.98 mmol). The reaction mixture was stirred for 2 h at 0 °C and then diluted with water. The pyridine was removed under vacuum, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:3) to afford amide **4c** (166 mg, 98%). mp 138−139 °C; $[\alpha]^{20}_D$ = −1119 (*c* = 0.08, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.06 (s, 1H, NH), 5.50 (m, 1H, Cp-H), 4.31 (s, 5H, Cp′-H), 4.17 (t, 1 H, *J* = 2.5 Hz, Cp-H), 4.08 (dd, 1H, *J* = 2.4, 1.2 Hz, Cp-H), 2.01 (s, 3H, Me), 1.16 (s, 9H, *t*-Bu); ^{13}C NMR δ 168.4, 97.0, 71.2, 70.1, 66.2, 65.4, 64.7, 57.0, 24.3, 22.7; MS (EI) *m*/*z* 347 (M^+, 70), 331 (11), 291 (92), 273 (35), 232 (87), 208 (37), 165 (100), 121 (32), 57(60); Anal. Calcd for $C_{16}H_{21}FeNO_2S$: C, 55.34; H, 6.10; N, 4.03; S, 9.23. Found: C, 55.45; H, 5.98; N, 3.90; S, 9.52.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(trifluoroacetyl)amino]ferrocene [(R_{Fc},R_S)-4d]. Acylating reagent: $(CF_3CO)_2O$; eluent: ethyl acetate−hexane (1:6); yield: 74%; mp 126−128 °C; $[\alpha]^{20}_D$ = −1461 (*c* = 0.08, $CHCl_3$); ^{1}H NMR (300 MHz) δ 10.35 (s, 1H, NH), 5.53 (dd, 1H, *J* = 2.6, 1.4 Hz, Cp-H), 4.39 (s, 5H, Cp′-H), 4.31 (t, 1H, *J* = 2.8 Hz, Cp-H), 4.22 (dd, 1H, *J* = 2.6, 1.4 Hz, Cp-H), 1.20 (s, 9H, *t*-Bu); ^{13}C NMR δ 155.0, 154.4, 117.5, 113.7, 94.6, 71.7, 71.5, 67.0, 65.6, 65.3, 57.4, 22.6; MS (EI) *m*/*z* 401 (M^+, 36), 385 (3), 345 (72), 327 (100), 262 (11), 230 (14), 138 (34), 121 (20), 57 (52). Anal. Calcd for $C_{16}H_{18}F_3FeNO_2S$: C, 47.90; H, 4.52; N, 3.49; S, 7.99. Found: C, 48.11; H, 4.36; N, 3.49; S, 8.12.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(trimethylacetyl)amino]ferrocene [(R_{Fc},R_S)-4e]. Acylating reagent: $(t\text{-BuCO})_2O$; eluent: ethyl acetate−hexane (1:6); yield: 76%; mp 109−111 °C; $[\alpha]^{20}_D$ = −754 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.45 (s, 1H, NH), 5.58 (m, 1H, Cp-H), 4.27 (s, 5H, Cp′-H), 4.17 (t, 1 H, *J* = 2.7 Hz, Cp-H), 4.07 (m, 1H, Cp-H), 1.21 (s, 9H, *t*-Bu); ^{13}C NMR δ 177.3, 97.8, 71.1, 70.0, 66.2, 64.7, 57.0, 39.2, 27.3, 22.7; MS (EI) *m*/*z* 389 (M^+, 43), 333 (57), 268 (50), 232 (70), 165 (44), 121 (17). Anal. Calcd for $C_{19}H_{27}FeNO_2S$: C, 58.60; H, 7.00; N,3.60; S, 8.20. Found: C, 58.49; H, 7.24; N, 3.30; S, 7.83.

(R_{Fc},R_S)-2-(*N*-Benzoyl)amino-1-(*tert*-butylsulfinyl)ferrocene [(R_{Fc},R_S)-4f]. Acylating reagent: $(PhCO)_2O$; eluent: ethyl acetate−hexane (1:6); yield: 80%; mp 135−137 °C; $[\alpha]^{20}_D$ = −853 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (300 MHz) δ 10.24 (s, 1H, NH), 7.92 (m, 2H, Ar), 7.50 (m, 3H, Ar), 5.74 (m, 1H, Cp-H), 4.36 (s, 5H, Cp′-H), 4.28 (t, 1H, *J* = 2.7 Hz, Cp-H), 4.17 (m, 1H, Cp-H), 1.21 (s, 9H, *t*-Bu); ^{13}C NMR δ 164.7, 133.7, 131.6, 128.7, 126.9, 97.5, 71.3, 70.3, 66.4, 65.2, 64.8, 57.1, 22.7, 14.1; MS (EI) *m*/*z* 409 (M^+, 26), 393 (11), 353 (43), 335 (24), 288 (17), 232 (37), 165 (37), 105 (100), 77 (60). Anal. Calcd for $C_{21}H_{23}FeNO_2S$: C, 61.60; H, 5.70; N, 3.40; S, 7.80. Found: C, 61.34; H, 5.85; N, 3.12; S, 7.33.

General Procedure for the Synthesis of Sulfonamides 4g−l: (R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(*p*-tolylsulfonyl)amino]ferrocene [(R_{Fc},R_S)-4h]. To a solution of amine **4a** (101 mg, 0.33 mmol) in CH_3CN (3 mL), at room temperature was added NaH (12 mg, 0.5 mmol). The reaction mixture was stirred for 15 min, and TsCl (189 mg, 0.99 mmol) was added.

The resulting solution was stirred for 6 h, diluted with water, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:4) to afford sulfonamide **4h** (103 mg, 68%): mp 154−155 °C; $[\alpha]^{20}_D = -522$ ($c = 0.1$, $CHCl_3$);^{1}H NMR (300 MHz) δ 8.57 (s, 1H, NH), 7.86 (d, 2H, $J = 8.3$ Hz, Ar), 7.32 (d, 2H, $J = 8.1$ Hz, Ar), 4.84 (dd, 1H, $J = 2.6$, 1.4 Hz, Cp-H), 4.10 (bs, 7H, 5 Cp′-H + 2 Cp-H), 2.42 (s, 3H, Me), 1.10 (s, 9H, *t*-Bu); ^{13}C NMR δ 143.8, 137.5, 129.7, 127.4, 99.0, 71.3, 68.2, 56.6, 64.8, 61.2, 57.0, 22.7, 21.5; MS (EI) *m*/*z* 459 (M^+, 61), 443 (36), 403 (99), 385 (71), 248 (60), 230 (67), 212 (100), 164 (62), 121 (44), 91 (48), 57 (54). Anal. Calcd for $C_{21}H_{25}FeNO_3S_2$: C, 54.90; H, 5.49; N, 3.05; S, 13.96. Found: C, 54.70; H, 5.35; N, 2.99; S, 13.7.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(*p*-methoxyphenylsulfonyl)amino]ferrocene [(R_{Fc},R_S)-4i]. Sulfonyl chloride: *p*-$MeOC_6H_4SO_2Cl$; eluent: ethyl acetate−hexane (1:4); yield: 74%; mp 160−161 °C; $[\alpha]^{20}_D = -476.3$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.51 (s, 1H, NH), 7.87 (d, 2H, $J = 8.9$ Hz, Ar), 6.98 (d, 2H, $J = 8.9$ Hz, Ar), 4.83 (dd, 1H, $J = 2.6$, 1.4 Hz, Cp-H), 4.12 (s, 5H, Cp′-H), 4.10 (m, 1H, Cp-H), 4.07 (dd, 1H, $J = 2.6$, 1.4 Hz, Cp-H), 3.84 (s, 3H, MeO), 1.09 (s, 9H, *t*-Bu); ^{13}C NMR δ 163.0, 132.0, 129.4, 114.2, 99.0, 71.3, 68.1, 65.6, 64.8, 62.0, 56.9, 55.6, 22.7; MS (EI) *m*/*z* 475 (M^+, 63), 459 (62), 419 (89), 403 (63), 401 (59), 272 (24), 248 (69), 232 (91), 228 (100), 166 (75), 121 (40), 77 (24), 57 (62). Anal. Calcd for $C_{21}H_{25}FeNO_4S_2$: C, 53.05; H, 5.30; N, 2.95; S, 13.49. Found: C, 52.72; H, 4.98; N, 2.91; S, 13.19.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(*p*-nitrophenylsulfonyl)amino]ferrocene [(R_{Fc},R_S)-4j]. Sulfonyl chloride: *p*-$NO_2C_6H_4SO_2Cl$; eluent: ethyl acetate−hexane (1:4); yield: 57%; mp 181−182 °C; $[\alpha]^{20}_D = -776$ ($c = 0.05$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.96 (s, 1H, NH), 8.34 (d, 2H, $J = 8.5$ Hz, Ar), 8.11 (d, 2H, $J = 8.5$ Hz, Ar), 4.96 (bs, 1H, Cp-H), 4.23 (s, 5H, Cp′-H), 4.18 (bs, 1H, Cp-H), 4.11 (bs, 1H, Cp-H), 1.03 (s, 9H, *t*-Bu); ^{13}C NMR δ 150.1, 146.2, 128.4, 124.3, 98.1, 71.7, 68.3, 66.1, 65.2, 62.5, 56.7, 22.5; MS (EI) *m*/*z* 490 (M^+, 47), 434 (90), 416 (53), 248 (35), 230 (100), 166 (53), 121 (38), 57 (74). Anal. Calcd for $C_{20}H_{22}FeN_2O_5S_2$: C, 48.99; H, 4.52; N, 5.71; S, 13.08. Found: C, 48.75; H, 4.25; N, 5.55; S, 12.76.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(2,4,6-trimethylphenylsulfonyl)amino]ferrocene [(R_{Fc},R_S)-4k]. Sulfonyl chloride: $(CH_3)_3C_6H_2SO_2Cl$; eluent: ethyl acetate−hexane (1:2); yield: 45%; mp 186−187 °C; $[\alpha]^{20}_D = -440$ ($c = 1$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.77 (s, 1H, NH), 7.03 (s, 2H, Ar), 4.57 (t, 1H, $J = 2.0$ Hz, Cp-H), 4.09 (m, 2H, Cp-H), 4.00 (s, 5H, Cp′-H), 2.78 (s, 6H, 2 Me), 2.31 (s, 3H, Me), 1.21 (s, 9H, *t*-Bu); ^{13}C NMR δ 142.6, 139.3, 134.7, 132.2, 99.6, 70.8, 68.3, 65.5, 64.4, 60.9, 57.4, 23.0, 22.9, 21.0; MS (EI) *m*/*z* 487 (M^+, 53), 431 (61), 248 (100), 240 (71), 230 (63), 165 (43), 119 (35), 57 (36). Anal. Calcd for $C_{23}H_{29}FeNO_3S_2$: C, 56.67; H, 6.00; N, 2.87; S, 13.16. Found: C, 56.33; H, 5.90; N, 2.74; S, 12.99.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(1-naphthalenesulfonyl)amino]ferrocene [(R_{Fc},R_S)-4l]. Sulfonyl chloride: 1-naphthalenesulfonyl chloride; eluent: ethyl acetate−hexane (1:2); yield: 64%; mp 174−175 °C; $[\alpha]_D^{20} = -329$ ($c = 0.2$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 9.05 (s, 1H, NH), 8.70 (dd, 1H, $J = 8.7$, 0.6 Hz, Ar), 8.46 (dd, 1H, $J = 7.5$, 1.2 Hz, Ar), 8.12 (d, 1H, $J = 8.3$ Hz, Ar), 7.95 (d, 1H, $J = 8.1$ Hz, Ar), 7.80 (ddd, 1H, $J = 8.5$, 7.0, 1.4 Hz, Ar), 7.64 (dd, 1H, $J = 8.1$, 7.5 Hz, Ar), 7.62 (ddd,1H, $J = 8.1$, 7.0, 1.1 Hz, Ar), 4.59 (t, 1H, $J = 2.0$ Hz, Cp-H), 4.03 (s, 1H, Cp-H), 4.02 (s, 1H, Cp-H), 3.66 (s, 5H, Cp′-H), 1.18 (s, 9H, *t*-Bu); ^{13}C NMR δ 135.6, 134.6, 134.3, 129.7, 129.1, 128.8, 128.5, 127.3, 124.7, 124.2, 111.4, 110.4, 99.2, 70.6, 68.1, 65.6, 64.6, 57.4, 22.9; MS (EI) *m*/*z* 495 (M^+, 45), 479 (41), 439 (62), 248 (100), 232 (62), 166 (55), 57 (48). Anal. Calcd for $C_{24}H_{25}FeNO_3S_2$: C, 58.18; H, 5.09; N, 2.83; S, 12.94. Found: C, 58.10; H, 5.06; N, 2.71; S, 12.57.

(R_{Fc},R_S)-1-(*tert*-Butylsulfinyl)-2-[*N*-(methanesulfonyl)amino]ferrocene [(R_{Fc},R_S)-4g]. Sulfonyl chloride: CH_3SO_2Cl. In this case Et_3N (1.5 equiv) was used as base in CH_2Cl_2 as solvent; eluent: ethyl acetate−hexane (1:2); yield: 62%; mp 121−123 °C; $[\alpha]^{20}_D = -637$ ($c = 0.1$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.38 (s, 1H, NH), 4.88 (m, 1H, Cp-H), 4.39 (s, 5H, Cp′-H), 4.19 (t, 1H, $J = 2.6$ Hz, Cp-H), 4.16 (m, 1H, Cp-H), 3.07 (s, 3H, Me), 1.22 (s, 9H, *t*-Bu); ^{13}C NMR δ 99.1, 71.6, 68.4, 65.7, 64.9, 61.7, 57.1, 40.6, 22.8; MS (EI) *m*/*z* 383 (M^+, 45), 327 (66), 309 (59), 230 (100), 200 (46), 165 (45), 121(45). Anal. Calcd for $C_{15}H_{21}FeNO_3S_2$: C, 47.00; H, 5.52; N, 3.65; S, 16.73. Found: C, 47.29; H, 5.30; N, 3.41; S, 16.51.

(R_{Fc})-1-(*tert*-Butylsulfenyl)-2-[*N*-(*p*-tolylsulfonyl)amino]ferrocene [(R_{Fc})-14]. To a solution of **4h** (138 mg, 0.30 mmol) and NaI (22 mg, 0.90 mmol) in acetone (4 mL), at −40 °C, $(CF_3CO)_2O$ (252 mg, 1.2 mmol) was added. The reaction mixture was stirred for 2 min, and saturated Na_2SO_3 and saturated $NaHCO_3$ was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:6) to afford the thioether **14** (118 mg, 89%): mp 103−104 °C; $[\alpha]^{20}_D = -451$ ($c = 0.08$, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.82 (d, 2H, $J = 8.3$ Hz, Ar), 7.30 (d, 2H, $J = 8.1$ Hz, Ar), 6.30 (s, 1H, NH), 4.70 (dd, 1H, $J = 2.6$, 1.4 Hz, Cp-H), 4.20 (dd, 1H, $J = 2.4$, 1.4 Hz, Cp-H), 4.06 (t, 1H, $J = 2.6$ Hz, Cp-H), 3.95 (s, 5H, Cp′-H), 2.40 (s, 3H, Me), 1.06 (s, 9H, *t*-Bu); ^{13}C NMR δ 143.9, 136.9, 129.6, 127.4, 98.7, 71.7, 70.7, 65.0, 64.7, 60.4, 46.6, 30.5, 21.5; MS (EI) *m*/*z* 443 (M^+, 72), 387 (74), 232 (100), 166 (57), 121 (19), 91 (16), 57 (32). Anal. Calcd for $C_{21}H_{25}FeNO_2S_2$: C, 56.88; H, 5.68; N, 3.16; S, 14.46. Found: C, 57.28; H, 5.81; N, 3.02; S, 13.98.

(R_{Fc})-1-(*tert*-Butylsulfonyl)-2-[*N*-(*p*-tolylsulfonyl)amino]ferrocene [(R_{Fc})-15]. To a solution of **4h** (50 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) was added MCPBA (50%, 40 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL). The mixture was stirred vigorously at 25 °C. After 4 h saturated Na_2SO_3 (2 mL) and saturated aqueous $NaHCO_3$ (2 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:5) to afford (*R*)-**15** (45 mg, 87%): mp 141−143 °C; $[\alpha]^{20}_D = -238$ ($c = 0.1$,-$CHCl_3$); ^{1}H NMR (300 MHz) δ 7.83 (d, 2H, $J = 8.3$ Hz, Ar), 7.33 (d, 2H, $J = 8.1$ Hz, Ar), 4.95 (dd, 1H, $J = 2.6$, 1.4 Hz, Cp-H), 4.35 (dd, 1H, $J = 2.6$, 1.4 Hz, Cp-H), 4.26 (t, 1H, $J = 2.6$ Hz, Cp-H), 4.19 (s, 5H, Cp′-H), 2.42 (s, 3H, Me), 1.17 (s, 9H, *t*-Bu); ^{13}C NMR δ 144.2, 136.9, 129.8, 127.4, 97.6, 72.0, 70.0, 66.8, 66.5, 63.3, 59.9, 23.0, 21.5; MS (EI) *m*/*z* 475 (M^+, 72), 419 (20), 401 (19), 336 (28), 246 (42), 199 (25), 149 (30), 122 (28), 91 (40), 69 (58), 57 (100). Anal. Calcd for $C_{21}H_{25}FeNO_3S_2$: C, 53.05; H, 5.26; N, 2.95; S, 1347. Found: C, 52.92; H, 5.23; N, 2.84; S, 12.99.

(S_S)-*p*-Tolylsulfinylferrocene[10a,21] [(S_S)-12]. To a solution of ferrocene (9.62 g, 51.7 mmol) in THF (85 mL), was added at 0 °C, *t*-BuLi 1.7 M in pentane (26.0 mL, 44.2 mmol) under argon. The solution was stirred at 0 °C for 2 h and then cooled to −78 °C and transferred slowly to a cold (−78 °C) solution of (S_S,1*R*) menthyl *p*-toluenesulfinate (10.0 g, 34.0 mmol; ≥99% ee) in THF (51 mL). The reaction was stirred at −78 °C for 2 h. Brine was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:1) to afford sulfoxide (*S*)-**12** (4.4 g, 40%, 97% ee). Recrystallization from Et_2O and hexane (3:1) gave pure sulfoxide (*S*)-**12** [2.2 g, >99% ee, HPLC: Daicel Chiracel OD, *i*-PrOH/hexane 10/90, flow rate 0.80 mL/min, t_R: 13.7 min (*R*)-isomer and 15.1 min (*S*)-isomer, detection at 254 nm]. mp 143−144 °C; $[\alpha]^{20}_D = +303$ ($c = 0.5$, $CHCl_3$), >99% ee; Lit.[10b] $[\alpha]^{20}_D = +305$ ($c = 0.5$, $CHCl_3$), 100% ee; ^{1}H NMR (200 MHz) δ 7.52 (d, 2H, $J = 8.3$, Ar), 7.25 (d, 2H, $J = 8.4$ Hz, Ar), 4.61 (dt, 1H, $J = 1.5$, 2.3 Hz, Cp-H), 4.39−4.35 (s+m, 7H, Cp-H+Cp′-H), 4.33−4.31 (m, 1H, Cp-H), 2.37 (s, 3H, Me).

(S_{Fc},S_S)-2-Amino-1-(*p*-tolylsulfinyl)ferrocene [(S_{Fc},S_S)-13a]. To a cold solution of sulfoxide (*S*)-**12** (1.0 g, 3.09 mmol) in THF (20 mL), at −78 °C, was added LDA 0.3 M in THF (13 mL, 4.01 mmol) under argon. The mixture was stirred at −78 °C for 40 min, and then a solution of tosyl azide (1.20 g, 6.08 mmol) was added. The resulting solution was stirred at −78

°C for 4 h. After being warmed to room temperature, and a solution of $Bu_4N^+I^-$ (0.46 g, 1.26 mmol) and $NaBH_4$ (0.45 g, 12.0 mmol) in H_2O (10 mL) was added. The reaction mixture was stirred at room temperature for 24 h. After this time, a second solution of $NaBH_4$ (0.22 g, 6.0 mmol) in H_2O (5 mL) was added, and the reaction was stirred for additional 24 h. Brine was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O. The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:3) to afford the aminosulfoxide **13a** (0.69 g, 67%): mp 114−115 °C; $[\alpha]^{20}_D$ = +453 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 7.50 (d, 2H, *J* = 8.5 Hz, Ar), 7.23 (d, 2H, *J* = 8.1 Hz, Ar), 4.35 (s, 5H, Cp′-H), 4.19 (dd, 1H, *J* = 2.8, 1.2 Hz, Cp-H), 4.09 (dd, 1H, *J* = 2.4, 1.2 Hz, Cp-H), 3.98 (dd, 1H, *J* = 2.8, 2.4 Hz, Cp-H), 3.50 (bs, 2H, NH_2), 2.34 (s, 3H, Me); ^{13}C NMR δ 142.6, 140.8, 129.7, 124.4, 106.3, 77.9, 70.6, 64.0, 63.5, 59.3, 21.3; MS (EI) *m*/*z* 339 (M^+, 58), 323 (M^+-O, 100), 256 (19), 201 (19), 200 (26), 186 (30), 166 (20), 121 (38), 91 (21). Anal. Calcd for $C_{17}H_{17}FeNOS$: C, 60.19; H, 5.05; N, 4.13; S, 9.45. Found: C, 60.11; H, 4.98; N, 4.27; S, 9.23.

(S_{Fc},S_S)-1-(*p*-Tolylsulfinyl)-2-[*N*-(*p*-tolylsulfonyl)amino]-ferrocene [(S_{Fc},S_S)-13h]. To a solution of amine **13a** (100.0 mg, 0.29 mmol) in CH_3CN (3 mL), at 0 °C, was added NaH (8.4 mg, 0.35 mmol). The reaction mixture was stirred for 15 min at room temperature, and a solution of TsCl (110.6 mg, 0.58 mmol) was added. The resulting solution was stirred for 3 h, diluted with water, and extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:1) to afford sulfonamide **13h** (71 mg, 50%): mp 140−141 °C; $[\alpha]^{20}_D$ = +494 (*c* = 0.2, $CHCl_3$); ^{1}H NMR (300 MHz) δ 8.16 (s, 1H, NH), 7.62 (d, 2H, *J* = 8.3 Hz, Ar), 7.25 (d, 2H, *J* = 8.2 Hz, Ar), 7.15 (d, 2H, *J* = 8.5 Hz, Ar), 7.11 (d, 2H, *J* = 8.1 Hz, Ar), 4.92 (dd, 1H, *J* = 2.6, 1.3 Hz, Cp-H), 4.26 (s, 5H, Cp′-H), 4.22 (dd, 1H, *J* = 2.6, 1.3 Hz, Cp-H), 4.11 (t, 1H, *J* = 2.6 Hz, Cp-H), 2.38 (s, 3H, Me), 2.35 (s, 3H, Me); ^{13}C NMR δ 143.4, 141.9, 141.1, 136.8, 129.8, 129.5, 127.2, 124.2, 96.6, 75.8, 71.4, 65.8, 63.8, 63.7, 21.5, 21.4; MS (EI) *m*/*z* 493 (M^+, 10), 477 (M^+ − O, 100), 348 (18), 322 (38), 212 (18), 166 (77), 121 (21), 91 (43). Anal. Calcd for $C_{24}H_{23}FeNO_3S_2$: C, 58.42; H, 4.70; N, 2.84; S, 13.00. Found: C, 58.17; H, 4.71; N, 2.97; S, 13.04.

General Procedure for the Enantioselective Addition of Diethylzinc to Aldehydes. To a solution of ligand **4i** (7.6 mg, 0.02 mmol) in toluene (1 mL) at room temperature under argon atmosphere was added a solution of diethylzinc (1 M) in hexanes (0.80 mL, 0.80 mmol). After stirring for 30 min, benzaldehyde (42 mg, 0.40 mmol) was added, and the reaction mixture was stirred at room temperature for 2 days (the disappearance of the aldehyde was monitored by TLC), the mixture was quenched by addition of 5% HCl, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and evaporated. The resulting mixture was purified by flash chromatography (ethyl acetate−hexane 1:6) to afford (*R*)-**5** [44 mg, 82%, $[\alpha]^{20}_D$ = +39 (*c* = 4.6,$CHCl_3$), 82% ee, HPLC: Daicel Chiracel OD, *i*-PrOH/hexane 5/95, flow rate 1 mL/min, t_R: 14.8 min (*R*)-isomer and 16.3 min (*S*)-isomer, detection at 254 nm].

The same procedure (reaction times of 1−4 days) was applied to the preparation of the known alcohols **6**−**11**.[20]

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