

Synthesis of planar chiral ferrocenyl sulfides and evaluation as catalysts for the asymmetric epoxidation of aldehydes

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The paper is dedicated to Prof. S. Swaminathan on the occasion of his 80th birthday
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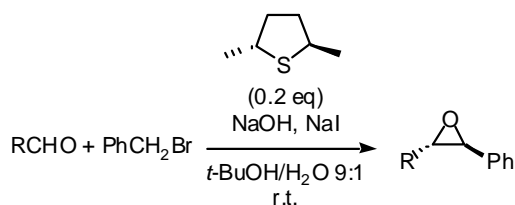
Abstract

New ferrocenyl sulfides, exhibiting planar chirality, have been prepared. They incorporate various heteroatom groups, and in some cases central chirality (sulfur or carbon). They were evaluated as catalysts for the asymmetric epoxidation of aldehydes *via* sulfonium ylides. A one-pot reaction has been achieved, involving addition of benzaldehyde, benzyl bromide, 20% molar equivalent of the ferrocenyl sulfide, sodium iodide in a mixture of *tert*-butanol and water. Good yields of stilbene oxide were obtained, with enantiomeric excesses up to 53%.

Keywords: Ferrocenes, planar chirality, sulfides, sulfur ylides, epoxidation, oxiranes

Introduction

The need for new catalysts and ligands for asymmetric synthesis continues to grow.¹⁻⁷ Organocatalysis^{8,9} brings specific challenges in terms of kinetic rates and efficiency. We are interested in the synthesis of oxiranes by the Johnson-Corey reaction of sulfur ylides with aldehydes.¹⁰⁻¹² We have recently reported¹³⁻¹⁷ an aliphatic C_2 symmetric sulfide, 2,5-dimethylthiolane, as a chiral auxiliary used in a catalytic amount for this reaction, which could be performed easily with yields and enantiomeric excesses around 90% (Scheme 1).



Scheme 1

Despite these achievements, this reaction suffers from some limitations: rates are moderate, and the scope of the substrates is not yet large enough. Therefore, we have wished to explore novel sulfides, which might fulfill these challenges. Among other structures, we have recently investigated ferrocenyl sulfides¹⁸ of two types (Figure 1): compounds **A** bearing an *ortho*-substituent (or their enantiomers), and derivatives **B**, incorporating a ring fused with one of the cyclopentadienyl rings. We have just reported our results¹⁹ with compounds **B** (e.e.'s up to 94%) and wish to report now our investigation of **A** ferrocenyl sulfides. We will discuss first the synthesis of the novel sulfides and we will then describe the evaluation of their activity as catalysts for the asymmetric epoxidation of benzaldehyde.

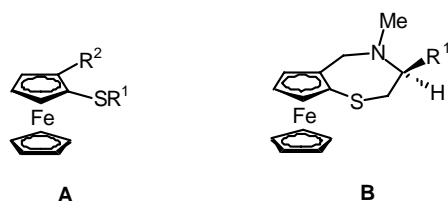


Figure 1

Results and Discussion

Having shown previously¹⁸ with one example of type **A** (its enantiomer bearing $R^1 = t\text{-Bu}$ and $R^2 = \text{NHTs}$) that planar chirality can lead to asymmetric epoxidation (e.e. 67%), we have wished to screen a variety of sulfides (Figure 2), bearing in most cases a *t*-butylsulfanyl group connected directly to one of the cyclopentadienyl ring of ferrocene. In order to investigate steric and electronic factors, we have placed in the *ortho* position, a variety of heteroatomic groups: a trimethylsilyl (**5a**), a methylsulfanyl (**5b**), a stereogenic alkylsulfanyl (**4b**, **4c**), a trialkylstannyl (**5d**, **5e**). In a second series, we have introduced a hindered alkyl chain (**5f**), an aryl group (**5g**), or a chain bearing a stereogenic carbon and a coordinating nitrogen atom (**6a**, **6b**).

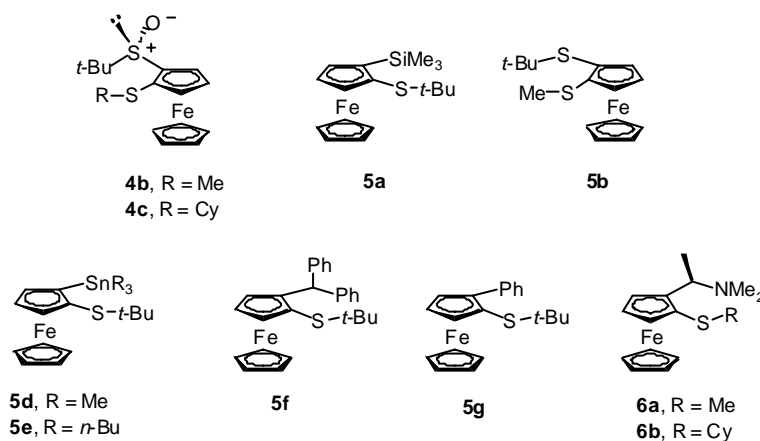


Figure 2

Synthesis of planar chiral ferrocenyl sulfides

Our starting materials were ferrocenes **1**, **2**, and **3** bearing respectively cyclohexylsulfinyl, *t*-butylsulfinyl and 1-(*N,N*-dimethylamino)ethyl groups (Figure 3).

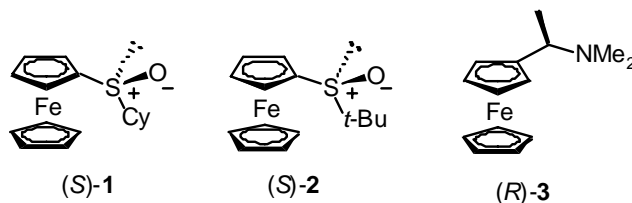
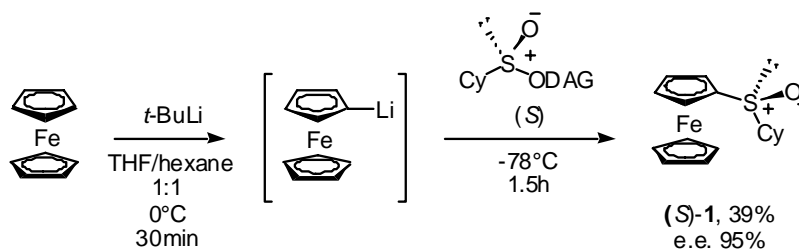


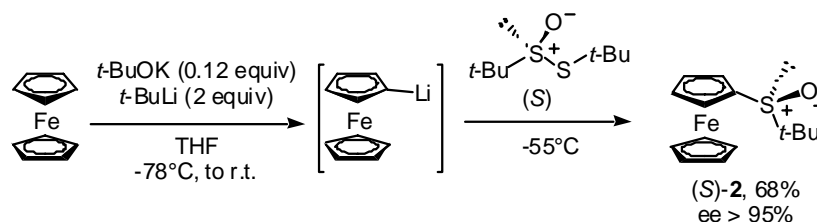
Figure 3

Our synthesis of unreported cyclohexylsulfinylferrocene **1** was motivated by the need of a substituent on sulfur that would be less hindered than a *t*-butyl group. Indeed, we found that the epoxidation reaction can be strongly retarded by steric effects. On the other hand, these effects are also necessary for the asymmetric induction. Therefore, we thought that a good compromise for the group on sulfur would be a cyclohexyl, or alternatively an isopropyl. In order to prepare sulfoxide **1**, we planned to use the Andersen reaction of ferrocenyllithium with (*S*)-DAG-cyclohexanesulfinylate, a reagent, which we have used in another context.^{20,21} It was prepared on a large scale, using the remarkable and efficient Khair-Alcudia dynamic kinetic resolution,^{22,23} based on *D*-glucose as a chiral source and involving the esterification reaction of a racemic alkanesulfinyl chloride. Our first attempts to synthesize (*S*)-**1** were disappointing. As the DAG sulfinylate was less reactive than a disulfide, we carried out the reaction of ferrocenyllithium from 0°C to room temperature. Cyclohexylsulfinylferrocene was isolated in 66% yield, with 29% recovery of ferrocene, but enantioselective HPLC revealed that the product was racemic. This may be explained²⁴ by attack of unreacted ferrocenyllithium with the expected sulfoxide (*S*) configuration, leading to racemization through a hypervalent intermediate. To overcome this undesired process, we have carried out the reaction at -78°C. We obtained sulfoxide **1** in a yield of 39% and an enantiomeric excess of 95% (Scheme 2). This novel sulfoxide is thus available for further studies.



Scheme 2

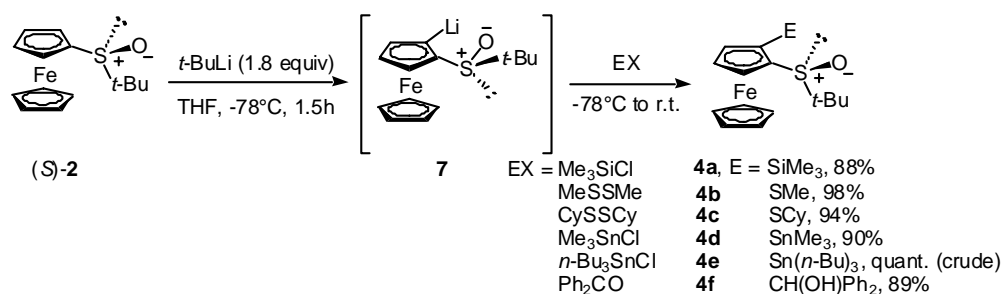
t-Butylsulfoxide **2** can be prepared by enantioselective oxidation of the corresponding sulfide,²⁵ or by the Andersen reaction of ferrocenyllithium with an enantiopure thiosulfinate.^{26,27} We have used the latter method, which was reported by Carretero and his group (Scheme 3). The first step is a facile preparation^{28,29} of (*S*)-*t*-butyl *t*-butanethiosulfinate in 95% enantiomeric excess, according to Ellman *et al.* It involves oxidation of *t*-butyldisulfide by hydrogen peroxide with a catalytic amount (0.5%) of VO(acac)₂ and an hydroxyimine derived from (1*S*,2*R*)-1-amino-2-indanol (0.52%). For the second step, we have preferred to prepare ferrocenyllithium by deprotonation of ferrocene with 2 equiv. of *t*-BuLi and 0.12 equiv. of *t*-BuOK in THF.^{30,31} Subsequent reaction of the cannulated metallated species with the thiosulfinate furnished sulfoxide **2** in 68% yield (e.e. 95-100%).



Scheme 3

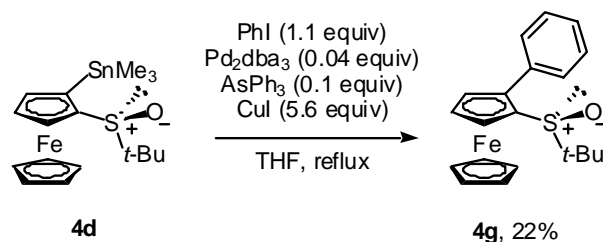
Compound **3** (Figure 3) is commercially available and can also be easily resolved with tartaric acid.^{32,33} Amine **3** and sulfoxide **2** have been reported^{25,32} to undergo *ortho*-deprotonation with high diastereoselectivity in presence of a strong base. We have used this property to synthesize compounds **4** and **6** (Figure 2). Deprotonation of the amine **3** was effected by *n*-BuLi under conditions reported by Ugi and his group.³² The metallated ferrocene was sulfanylated by dimethyl- or dicyclohexyl- disulfides to lead to aminosulfides **6a**³² and **6b**. Very modest yields of pure materials, respectively 21 and 38%, were obtained as a result of the crystallization required for purification.

In the sulfoxide series, *ortho*-deprotonation of **2** was effected by *t*-butyllithium, according to literature.²⁷ A variety of electrophiles were submitted to the resulting lithium *t*-butylsulfinylferrocene **7** (Scheme 4). Introduction of a trialkylsilyl moiety was possible with trimethylchlorosilane from -78°C to ambient temperature, providing ferrocene **4a** in 88% yield. Reaction with dimethyl or dicyclohexyl disulfides, under similar conditions, afforded excellent yields of methyl- and cyclohexylsulfinylferrocenes **4b** and **4c**, respectively 98% and 94%. Stannylation of anion **7** was effective with both tri-*n*-butyl- and trimethylchlorostannane in respective quantitative (crude, unstable to chromatography) and 90% yield. In all cases, a single diastereomer was observed by ¹H NMR. Phosphinoylation with PH₂P(O)Cl was not successful in our hands.



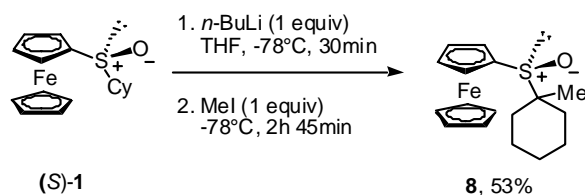
Scheme 4

We have also considered introducing alkyl or aryl groups in the *ortho*-position. An entry to an *ortho*-chain was to treat the sulfinylferrocene anion with a carbonyl compound, such as benzophenone (Scheme 4), affording hydroxyferrocene **4f**. For the introduction of an aryl group, two precedent were reported,^{31,34} including a Negishi type coupling of a zinc metalated *p*-tolylsulfinylferrocene, but we were not able to extend this reaction to *t*-butylsulfinylferrocene **2**. As an alternative, we have examined the Stille coupling of the tin derivative **4d** with phenyl iodide. No coupling was observed with Pd(PPh₃)₄ in toluene or THF at reflux. Catalysis³⁵ of Pd₂dba₃, in the presence of triphenylarsine and CuI, provided phenyl ferrocene **4g**, albeit in modest yield (Scheme 5).



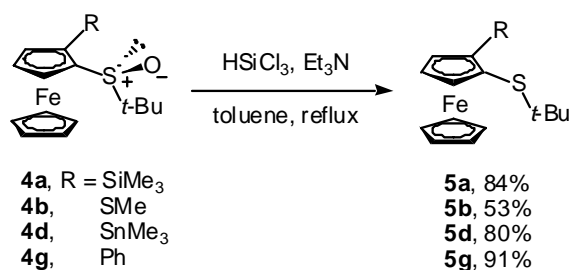
Scheme 5

Our third starting material was cyclohexylsulfinylferrocene **1**, which has not yet been *ortho*-metallated. A further challenge here is the presence of another acidic proton, alpha to the sulfinyl group. Reaction of **1** with one equivalent of *n*-BuLi at -78°C and addition of iodomethane led to the formation of α -methyl sulfoxide **8** (53%), demonstrating higher acidity on the sulfoxide alkyl chain (Scheme 6). Use of an excess (4.2 equiv) of *n*-BuLi in the presence of TMEDA and an excess of MeI (6 equiv) did not produce a bis-alkylated compound, with an *ortho*-methyl. Reaction with 2.2 equiv *n*-BuLi and quench with a single equivalent of TMSCl did not lead either to the selective formation of the desired *ortho*-silyl ferrocene. Further utilization of cyclohexylsulfinyl ferrocene **1** was stopped.



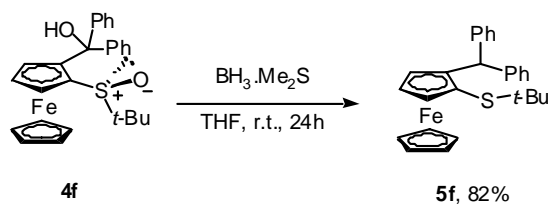
Scheme 6

At this stage, only compounds **4b**, **4c**, **6a**, **6b** were possessing the sulfanyl group requisite for epoxidation through sulfur ylides. It was necessary to reduce the sulfinyl moiety of other compounds: **4a**, **4b**, **4d**, **4g**, **4f**. We have considered two reasonably mild reducing agents: trichlorosilane/triethylamine, or borane. Utilization of HSiCl₃/Et₃N was effective with sulfoxides **4a**, **4b**, **4d**, **4g** (Scheme 7). The corresponding sulfides **5a**, **5b**, **5d**, **5g** were obtained in 53-90% yields.



Scheme 7

For sulfoxide **4f** we desired to reduce also the benzylic hydroxyl group. A literature precedent,³⁶ in the context of a drug process development, has shown that a sulfoxide moiety can assist the reduction of an alkene otherwise sluggish towards borane reaction. We were glad to observe that addition of borane-dimethyl sulfide to hydroxyl sulfinyl ferrocene **4f** provided compound **5f**, with both desired reductions (Scheme 8).



Scheme 8

We propose a mechanism (Figure 4), which involves prior complexation of the borane with the sulfinyl group, internal delivery of a hydride to the benzylic cationic center (with added stabilization due to the adjacent ferrocene), and subsequent reduction of the sulfoxide.

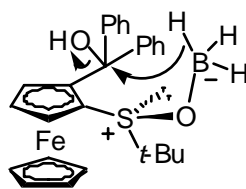
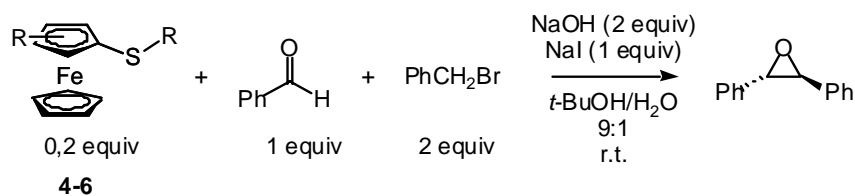


Figure 4

So, our synthetic study has led us to the preparation of 10 new planar chiral sulfides, available for the exploration of their behavior in asymmetric epoxidation.

Evaluation of planar chiral sulfides as source of ylides for asymmetric epoxidation of aldehydes

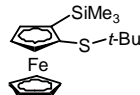
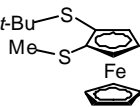
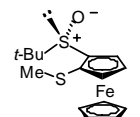
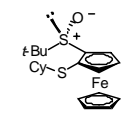
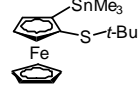
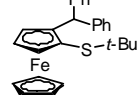
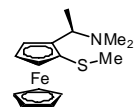
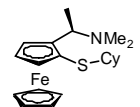
The choice of reaction conditions arose from our previous studies.^{15,19} We had devised a very simple procedure. All reagents are mixed at the start: chiral sulfide, benzyl bromide, sodium iodide, aldehyde, sodium hydroxide and a 9:1 *tert*-butanol/water mixture as solvent. The sulfide is used in a catalytic amount: 0.2 equivalent *versus* the aldehyde. Sodium iodide, or tetra-*n*-butylammonium iodide, has been shown to accelerate the epoxidation, normally slower, probably by halide exchange to provide more reactive benzyl iodide. The nature of the solvent is critical: a polar medium is necessary to bring stabilization of the charged intermediates (sulfonium salt and betaine). *tert*-Butanol and water (roughly optimized at a 9:1 ratio) play a specific role in making the reaction chemo- and enantioselective.^{14,15} Thus, we have chosen the same conditions to explore the epoxidation of the various ferrocenyl sulfides, with benzaldehyde as a model (Scheme 9).



Scheme 9

With the exception of silyl compound **5a**, all sulfides have led to the formation of stilbene oxide (Table 1). Unfortunately, the reactions are sluggish: the *t*-butylsulfanyl compounds required approximately 14 days at room temperature. Only the reactions with methylsulfides **5b** and **6a** were completed in 3 days (entries 2,7).

Table 1

	Sulfide	Time (d)	Yield (%)	Stilbene oxide		Config.	Sulfide recovery %	
				<i>trans/cis</i> ^a	e.e. ^b (%)			
1		5a	14	0	-	-	-	95
2		5b	3	77	80/20	6	(<i>R,R</i>)	0
3		4b	8	84	89/11	2	(<i>S,S</i>)	65
4		4c	14	32	73/27	50	(<i>S,S</i>)	89
5		5d	14	32	73/27	41	(<i>R,R</i>)	0
6		5f	14	85	86/14	0	-	60
7		6a	3.5	91	76/24	40	(<i>R,R</i>)	0
8		6b	14	36	83/17	53	(<i>R,R</i>)	0

^a Measured by GC or ¹H NMR spectroscopy of the crude product. ^b Determined by enantioselective HPLC on Daicel Chiralpak AD-H column.

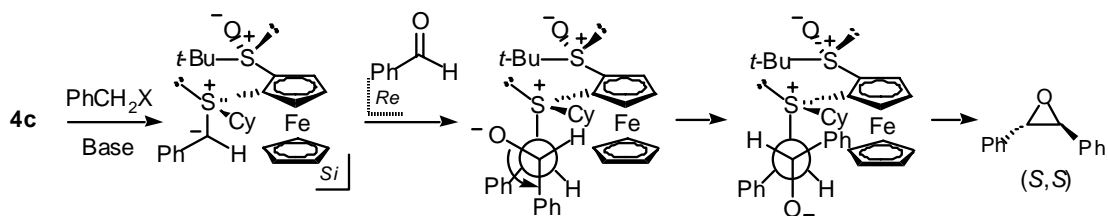
The yields ranged from 32 to 91%. The chiral sulfides could be recovered in 3 examples. The diastereoselectivities vary from 73:27 to 89:11.

A large diversity was observed for enantioselectivities, from a racemic oxirane (entry 6) to e.e.'s up to 53% (entry 8). Both absolute senses of induction were obtained. Although no high stereocontrol was performed, the various examples bring a number of information.

Compound **5b** is a bis(sulfide) with steric differentiation of the two groups. A non-bonding interaction was also hoped between the sulfonium center and the *t*-butyl sulfur atom. The chemical yield is satisfactory (77%, entry 2) but the asymmetric induction is almost absent (6%

e.e.). With a trimethylstannyl group (entry 5) a moderate yield and enantioselectivity (41% e.e.) in favor of the (*R,R*) oxirane are obtained.

Two sulfides bearing a sulfoxide group led to epoxidation. With the methyl sulfide **4b**, an excellent yield is observed for a racemic oxirane (entry 3)! Introduction of steric hindrance by replacement into a cyclohexyl group on the sulfur atom (entry 4) retarded the reaction but gave a 50% e.e. In both cases, the auxiliaries were recovered. We propose the accompanying model to explain the formation of the (*S,S*) oxirane, through favored formation of a diastereomeric sulfonium salt, an *anti* ylide and a backward attack by the aldehyde (Scheme 8).



Scheme 10

A 41% e.e. was observed for sulfide **5d** bearing an *ortho*-trimethylstannyl group.

Three sulfides incorporate a carbon chain in the *ortho*-position. The diphenylmethyl sulfide **5f** gave a good yield (85%) and diastereoselectivity (86:14) but a very disappointing HPLC analysis with a racemic product (entry 6). The *ortho*-phenyl sulfide **5g** (Figure 2) led to significant excesses, which however were not reproducible. With sulfides **6a** and **6b**, we were expecting a stabilizing interaction of the sulfonium moiety with the nucleophilic amine, involving a hypervalent sulfurane intermediate, with trigonal bipyramidal geometry and conformational rigidity.^{37,38} For methylsulfide **6a** (entry 7), the reaction is relatively rapid (3.5 days) and a 40% enantiomeric excess is observed. Replacement of the methyl by a cyclohexyl group (**6b**, entry 8) increased the selectivity (53% e.e., and 83:17 *trans/cis* ratio), but lowered rate and yield.

Discussion

A variety of planar chiral sulfoxides and sulfides have been synthesized for the first time. Standard routes have been explored. The *ortho*-lithiation of *t*-butylsulfinylferrocene and reaction with electrophiles is very efficient (88-100%). Most of the sulfides bear two functional groups and may be used as bidentate ligands for various purposes of asymmetric synthesis, especially as alternative to phosphines with semi-labile metal interactions.³⁹⁻⁴¹

The reaction rates of epoxidation were not improved, as compared to previous results with aliphatic sulfides. The *t*-butyl group was introduced in order to secure differentiation of the sulfur lone pairs. Its steric hindrance is not solely responsible for moderate rates, as shown by the

results with a ring fused sulfide **B**, with much less hindrance around the sulfur atom and epoxidation reactions which are still slow. In 3 cases, the sulfides could be recovered (entries 3,4,6).

Diastereoselectivities¹² range from 73:27 to 86:14. They arise from two competing parameters.¹⁸ The steric hindrance favors *trans* oxirane formation. The aromatic nature of the ferrocenyl substituent favors kinetic control leading to *trans* and *cis* mixtures. This stands in contrast to dialiphatic sulfides for which Aggarwal and co-workers have shown⁴² that the formation of the *syn* betaine, leading to *cis* oxiranes is reversible. The *anti* betaines were formed irreversibly and the *trans* oxiranes were predominantly obtained.

For the absolute stereoselectivity, no major breakthrough has been accomplished here, but we have shown that planar chirality has led to e.e.'s around 50%. The two cases incorporated a complementary central chirality (stereogenic carbon or sulfur atoms). We have not tested the diastereomers (matched or unmatched configurations). The example reported previously with an *ortho*-tosylamino group exhibited only planar chirality and led to a 67% e.e.

Further work, with different structure types, is definitely necessary to increase the rate of the sulfur ylide epoxidation reaction, as well as the scope of the carbonyl compounds and halide substrates.

Conclusions

Nine new planar chiral ferrocenyl sulfides have been prepared in a straightforward manner, often in 3 steps. The evaluation as catalysts for asymmetric epoxidation of benzaldehyde has brought interesting observations. Chemical yields are moderate to excellent. Planar chirality leads to asymmetric induction, with moderate e.e.'s.

Experimental Section

General Procedures. All non-aqueous reactions were carried out in oven-dried, septum-capped flasks, and under an atmospheric pressure of N₂. All liquid reagents were transferred *via* oven-dried syringes. THF was distilled from sodium-benzophenone, Et₂O from LiAlH₄, toluene from Na, or purified on PuresolvTM apparatus developed by Innovative Technology Inc. *n*-Hexane and CH₂Cl₂ were distilled from P₂O₅ and CaH₂ respectively. Et₃N was refluxed with KOH pellets and distilled. All reagents were commercially available and used without further purification unless otherwise noted. Lithium bases were purchased from Aldrich and concentrations were checked before experiments by titration with diphenylacetic acid.

Thin layer chromatography (TLC) was performed on Alugram SIL G/UV₂₅₄ plates and the plates were visualized with UV light and vanillin (600 mg in 100 mL EtOH and 2 mL H₂SO₄) or phosphomolybdic acid (1 g in 100 mL *i*-PrOH). Chromatographic purification of compounds

was achieved with Merck 60 silica gel (40-63 μm) or with Flashmaster Personal apparatus (AIT) and Flashsmart pack silica (BP SUP quality). Petroleum ether refers to the fraction with bp 35-60 $^{\circ}\text{C}$. High pressure liquid chromatography (HPLC) was performed on a Waters apparatus with a diode array M996 detector and a Daicel ChiralPak AD column 250 \times 4.6 mm (L \times I.D.) 5 μm : AS-H, or OD-H, or AD, or AD-H. *t*-Butylbenzene was used as t_0 . GC analyses were carried out on a Varian CP-3800 apparatus with a FID and a JW DB5 capillary column (30 m \times 0.32 mm, L \times I.D.). Melting points were obtained on an Electrothermal IA9000 capillary apparatus and are uncorrected.

Known compound structures were assigned by comparison with the literature spectroscopic data. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 250 or on a Bruker DRX 400. Data appear in the following order: chemical shift in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet), number of protons, coupling constant J and assignment. TMS is the internal standard for the CDCl_3 solutions. IR spectra were recorded on a Perkin-Elmer 16 PC FT-IR spectrophotometer. Wave numbers ν were reported in cm^{-1} . GC/MS analyses were recorded on a Varian 3800 (GC) and Saturn 2000 (MS) instruments. CP-SIL 8CB (Low-Bleed/MS) column (dimensions 30 m \times 0.25 mm), with 5% phenyl/95% dimethylpolysiloxane as the stationary phase, was used for the analysis. Microanalyses were obtained using a ThermoQuest instrument. HRMS were recorded on a Jeol GCmate or by LCMS, on a Xterra MS column.

(*S*)-Cyclohexylsulfinylferrocene (1). A suspension of ferrocene (245 mg, 1.32 mmol) in THF/*n*-hexane (v/v 1/1, 5.00 mL) was stirred at room temperature for 30 min and then cooled to 0 $^{\circ}\text{C}$. *t*-BuLi (750 μL , 1.12 mmol, 1.50 M in pentane) was then added at a rate of approximately 1 mmol.min $^{-1}$. After 30 min, the mixture was cooled to -78 $^{\circ}\text{C}$ and (*S*)-DAG cyclohexylsulfinate (447 mg, 1.14 mmol, ee 95%) was added. After 1.5 h, the mixture was allowed to warm to room temperature. Hydrolysis was performed with saturated aqueous NaCl (5 mL) and the aqueous layer was extracted with dichloromethane (3 \times 5 mL). The organic layer was dried over MgSO_4 and concentrated. Column chromatography using petroleum ether/ethyl acetate (v/v 9/1 to 3/7) afforded 137 mg (0.43 mmol, 39%) of ferrocenyl sulfoxide (*S*)-**1** as an orange solid. ^1H NMR (CDCl_3): 4.69 (m, 1H, Cp ring), 4.41-4.35 (m, 8H, Cp ring), 2.56 (m, 1H, Cy), 2.08-1.19 (m, 10H, Cy). ^{13}C NMR (CDCl_3): 69.9, 69.7, 69.6, 68.8, 64.4, 63.3, 25.7, 25.6, 25.4, 25.2. IR: 3072, 2920, 2850, 1459, 1035. HRMS Calcd for $\text{C}_{16}\text{H}_{20}\text{FeOS}$: 316.0584. Found: 316.0592. HPLC: Daicel Chiralpak AD column 250 \times 4.6 (L \times I.D.), *n*-hexane/*i*-PrOH (v/v: 90/10) at 1 mL.min $^{-1}$, 204 nm, rt. 8.18 min (*S*), 9.96 min (*R*).

(*S*)-*t*-Butylsulfinylferrocene(2). [149094-96-2].^{25,43} To a solution of ferrocene (596 mg, 3.20 mmol) in THF (25 mL) was added *t*-BuOK (385 μL , 1 M in THF, 0.38 mmol). The mixture was cooled to -78 $^{\circ}\text{C}$ and *t*-BuLi (4.30 mL, 6.41 mmol, 1.49 M in hexanes) was added dropwise. The reaction mixture was kept at -78 $^{\circ}\text{C}$ for 1.5 h and 1 h at room temperature. The red solution was then cannulated dropwise into a cold solution (-55 $^{\circ}\text{C}$) of (*S*_S)-(-)-*t*-butyl-*t*-butanethiosulfinate (633 mg, 3.26 mmol) in THF (15 mL). After 1 h at -55 $^{\circ}\text{C}$, water (20 mL)

was added. The aqueous layer was extracted with Et₂O (2 × 20 mL), the combined organic layers were dried over MgSO₄ and evaporated to dryness. Column chromatography using *n*-heptane/ethyl acetate (v/v 7:3) gave **2** (634 mg, 2.18 mmol, 68%) as a cotton-like yellow solid. ¹H NMR (CDCl₃): 4.69 (m, 1H, Cp-H), 4.42-4.35 (m, 8H, Cp-H), 1.12 (s, 9H, *t*-Bu). ¹³C NMR (CDCl₃): 86.4, 70.0, 69.9, 69.6, 69.3, 65.3, 54.9, 22.7. HPLC: Daicel Chiralpak AS-H column 250 × 4.6 (L × I.D.) 5 μm, *n*-hexane/*i*-PrOH (v/v: 98/2) at 1 mL.min⁻¹, 203 nm, 18 °C. 5.64 min (*S*), 7.21 min (*R*)

ortho-Substitution of *t*-butylsulfinylferrocene(2).^{25,43} To a cold solution (−78 °C) of *t*-butylsulfinylferrocene **2** (0.16 mmol) in dry THF (2 mL) was added *t*-BuLi (0.23 mmol). The mixture was stirred for 1.5 h at −78 °C and electrophile (0.25 mmol) was added. The reaction mixture was stirred 0.5 h at −78 °C, then allowed to warm to room temperature. The reaction was monitored by TLC using *n*-heptane/ethyl acetate (v/v 7:3). Hydrolysis was performed with water (2 mL). The aqueous layer was extracted with Et₂O (2 × 3 mL). The combined organic layers were dried over MgSO₄ and then evaporated to dryness. The crude product was purified by column chromatography.

(S_{Fe},S_S)-1-*t*-Butylsulfinyl-2-trimethylsilylferrocene (4a). The general procedure was followed using *t*-butylsulfinylferrocene (*S*)-**2** (47 mg, 0.16 mmol), THF (2 mL), *t*-BuLi (155 μL, 0.23 mmol, 1.49 M in hexanes) and TMSCl (31 μL, 0.24 mmol). Column chromatography using dichloromethane/ethyl acetate (v/v 7:3) afforded **4a** (54 mg, 0.14 mmol, 88%) as an orange solid. mp: 80-81 °C. ¹H NMR (CDCl₃): 4.51 (m, 2H, Cp-H), 4.31 (m, 6H, Cp-H), 1.14 (s, 9H, *t*-Bu), 0.37 (s, 9H, SiMe₃). ¹³C NMR (CDCl₃): 91.3, 76.7, 71.9, 71.1, 70.7, 70.0, 55.8, 23.3, 1.80. IR: 3060, 2952, 1654, 1240, 1172, 1044. HRMS Calcd for [C₁₇H₂₆FeOSSi-H]⁺: 363.0901. Found: 363.0936. Anal. Calcd for C₁₇H₂₆FeOSSi: C, 56.34; H, 7.23; S, 8.85. Found: C, 56.36; H, 7.54; S, 8.23.

(S_{Fe},S_S)-1-*t*-Butylsulfinyl-2-methylsulfanylferrocene(4b). The general procedure was followed using *t*-butylsulfinylferrocene (*S*)-**2** (47 mg, 0.16 mmol), THF (2 mL), *t*-BuLi (165 μL, 0.23 mmol, 1.49 M in hexanes) and dimethyl disulfide (22 μL, 0.25 mmol). Column chromatography using *n*-heptane/ethyl acetate (v/v 7:3) afforded **4b** (56 mg, 0.16 mmol, 98%) as an orange solid. mp: 134-136 °C. ¹H NMR (CDCl₃): 4.45 (m, 1H, Cp-H), 4.41 (s, 5H, Cp-H), 4.36 (m, 1H, Cp-H), 4.33 (m, 1H, Cp-H), 2.40 (s, 3H, S-Me), 1.24 (s, 9H, *t*-Bu). ¹³C NMR(CDCl₃): 87.5, 83.5, 71.6, 70.4, 69.3, 68.6, 56.9, 23.7, 17.7. IR: 3068, 2960, 2916, 1654, 1362, 1180, 1038. HRMS Calcd for [C₁₅H₂₀FeOS₂-H]⁺: 337.0383. Found: 337.0403.

(S_{Fe},S_S)-1-*t*-Butylsulfinyl-2-cyclohexylsulfanylferrocene(4c). The general procedure was followed using *t*-butylsulfinylferrocene (*S*)-**2** (48 mg, 0.16 mmol), THF (2 mL), *t*-BuLi (170 μL, 0.25 mmol, 1.49 M in hexanes) and dicyclohexyl disulfide (54 μL, 0.25 mmol). Column chromatography using dichloromethane/ethyl acetate (v/v 7:3) afforded **4c** (63 mg, 0.16 mmol, 94%) as an orange solid. mp: 152-154 °C. ¹H NMR (CDCl₃): 4.56 (m, 1H, Cp-H), 4.39-4.35 (m, 7H, Cp-H), 2.94 (m, 1H, Cy), 2.11-1.21 (m, 10H, Cy), 1.29 (s, 9H, *t*-Bu). ¹³C NMR (CDCl₃): 84.2, 83.9, 73.1, 72.0, 70.1, 69.2, 56.5, 47.1, 33.9, 33.7, 26.2, 25.8, 24.0. IR: 3072, 2924, 2848, 1654, 1458, 1178, 1040. HRMS Calcd for [C₂₀H₂₈FeOS₂-H]⁺: 405.1009. Found: 405.1007.

(*R*_{Fe},*S*_S)-1-Trimethylstannyl-2-*t*-butylsulfinylferrocene(4d). The general procedure was followed using *t*-butylsulfinylferrocene (*S*)-**2** (206 mg, 0.71 mmol), THF (7 mL), *t*-BuLi (735 μ L, 1.07 mmol, 1.45 M in hexanes) and Me₃SnCl (212 mg, 1.06 mmol) in THF (1 mL). Column chromatography using *n*-heptane/ethyl acetate (v/v 100:0 to 90:10) afforded **4d** (291 mg, 0.64 mmol, 90%) as an orange oily solid. ¹H NMR (CDCl₃): 4.54 (m, 1H, Cp-H), 4.50 (m, 1H, Cp-H), 4.29 (s, 5H, Cp-H), 4.27 (m, 1H, Cp-H), 1.09 (s, 9H, *t*-Bu), 0.32 (s, 9H, SnMe₃). ¹³C NMR(CDCl₃): 90.5, 75.6, 73.2, 69.8, 69.4, 66.8, 55.5, 23.0, -5.6. IR: 2923, 2853, 1637, 1458, 1178, 1084, 1035. HRMS Calcd for [C₁₇H₂₆FeOSSn-H]⁺: 455.0154. Found: 455.0147.

(*R*_{Fe},*S*_S)-1-Tri(*n*-butyl)stannyl-2-*t*-butylsulfinylferrocene(4e). The general procedure was followed using *t*-butylsulfinylferrocene (*S*)-**2** (200 mg, 0.69 mmol), THF (7 mL), *t*-BuLi (715 μ L, 1.04 mmol, 1.45 M in hexanes) and Bu₃SnCl (310 μ L, 1.03 mmol, 90%). The product was obtained in quantitative yield and used as a crude material. Column chromatography using *n*-heptane/ethyl acetate (v/v 1:0 to 0:1) led to decomposition. ¹H NMR (CDCl₃): 4.52 (m, 1H, Cp-H), 4.48 (m, 1H, Cp-H), 4.37 (s, 5H, Cp-H), 4.25 (m, 1H, Cp-H), 1.57-0.90 (m, 36H, *t*-Bu and *n*-Bu).

(*S*_{Fe},*S*_S)-1-*t*-Butylsulfinyl-2-diphenylhydroxymethylferrocene(4f). The general procedure was followed using *t*-butylsulfinylferrocene (*S*)-**2** (50 mg, 0.17 mmol), THF (2 mL), *t*-BuLi (160 μ L, 0.26 mmol, 1.65 M in hexanes) and acetophenone (47 μ L, 0.26 mmol) in THF (1 mL). Column chromatography using *n*-heptane /ethyl acetate (v/v 100:0 to 90:10) afforded **4f** (72 mg, 0.15 mmol, 89%) as an orange solid. mp: 183-184°C. ¹H NMR (CDCl₃): 7.65 (m, 2H, Ph), 7.56 (m, 1H, Ph), 7.34-7.16 (m, 7H, Ph), 4.47 (m, 1H, Cp-H), 4.40 (m, 1H, Cp-H), 4.37 (s, 5H, Cp-H), 3.98 (m, 1H, Cp-H), 0.79 (s, 9H, *t*-Bu). ¹³C NMR(CDCl₃): 149.9, 146.4, 128.1, 127.5, 127.4, 127.1, 126.6, 100.4, 80.2, 77.2, 76.7, 74.6, 71.8, 71.6, 69.5, 57.2, 23.4. IR: 3428 (O-H), 3101, 3063, 2962, 1655, 1466, 1169, 1052, 1003. HRMS Calcd for [C₂₇H₂₈FeO₂S-H]⁺: 473.1238. Found: 473.1259.

(*S*_{Fe},*S*_S)-1-*t*-Butylsulfinyl-2-phenylferrocene (4g). A degassed solution of AsPh₃ (0.01 mmol, 4 g), CuI (0.62 mmol, 118 mg) and Pd₂dba₃ (0.004 mmol, 4 mg) in THF (3 mL) was stirred at room temperature for 30 min. PhI (0.12 mmol, 14 μ L) was then added and the resulting solution was degassed and stirred for another 30 min. Tri-*n*-butylstannyl-*t*-Butylsulfinylferrocene **4d** (0.11 mmol, 50 mg) in THF (2 mL) was then added *via* cannula. After 1 h at room temperature, the mixture was heated for 12 h and then filtrated through Celite. The crude product was purified by column chromatography using *n*-heptane/ethyl acetate (v/v: 9/1), affording compound **4g** (50 mg, 22%). ¹H NMR (CDCl₃): 7.91 (m, 2H, Ph), 7.29-7.24 (m, 3H, Ph), 4.67 (m, 1H, Cp-H), 4.49 (m, 1H, Cp-H), 4.47 (m, 1H, Cp-H), 4.38 (s, 5H, Cp-H), 0.96 (s, 9H, *t*-Bu). ¹³C NMR (CDCl₃): 137.5, 131.1, 127.6, 126.8, 88.9, 85.7, 73.5, 71.4 (2C), 69.1, 56.6, 24.0. IR: 2925, 2855, 1635, 1460, 1400, 1184, 967. HRMS Calcd for [C₂₀H₂₂FeOS-H]⁺: 367.0819. Found: 367.0537.

Reduction of *t*-butylsulfinylferrocenes 4 with HSiCl₃/Et₃N. General procedure.³⁹ To a solution of the sulfinylferrocene (0.05 mmol) in dry toluene (1 mL) was added Et₃N (0.54 mmol) and HSiCl₃ (0.79 mmol). The mixture was refluxed for 15 h and treated with aqueous NaOH (2 mL, 10%). The aqueous layer was extracted with CH₂Cl₂ (2 \times 2 mL). The combined organic

layers were dried over MgSO_4 and then evaporated to dryness. The crude product was purified by column chromatography.

(S)-1-*t*-Butylsulfanyl-2-trimethylsilylferrocene (5a). The general procedure was followed using compound **4a** (20 mg, 0.05 mmol), toluene (1 mL), Et_3N (75 μL , 0.54 mmol) and HSiCl_3 (80 μL , 0.79 mmol). Column chromatography using 100% *n*-heptane afforded **5a** (16 mg, 0.04 mol, 84%) as an orange oil. ^1H NMR (CDCl_3): 4.55 (m, 1H, Cp-H), 4.41 (m, 1H, Cp-H), 4.17 (s, 5H, Cp-H), 4.14 (m, 1H, Cp-H), 1.22 (s, 9H, *t*-Bu), 0.34 (s, 9H, SiMe_3). ^{13}C NMR(CDCl_3): 82.1, 80.2, 75.6, 71.9, 69.7, 45.2, 31.2, 1.1. IR: 2955, 2899, 1406, 1361, 1246, 1177, 1036. HRMS Calcd for $\text{C}_{17}\text{H}_{26}\text{FeSSi}$: 346.0874. Found: 346.0539.

(S)-1-*t*-Butylsulfanyl-2-methylsulfanylferrocene (5b). The general procedure was followed using compound **4b** (20 mg, 0.06 mmol), toluene (1 mL), Et_3N (80 μL , 0.58 mmol) and HSiCl_3 (86 μL , 0.85 mmol). Column chromatography using *n*-heptane/ethyl acetate (v/v 100:0 to 9:1) afforded **5b** (10 mg, 0.03 mmol, 53%) as an orange oil. ^1H NMR (CDCl_3): 4.45 (m, 1H, Cp-H), 4.40 (m, 1H, Cp-H), 4.28 (m, 1H, Cp-H), 4.19 (s, 5H, Cp-H), 2.37 (s, 3H, CH_3), 1.25 (s, 9H, *t*-Bu). ^{13}C NMR(CDCl_3): 77.9, 77.2, 76.7, 70.9, 69.8, 68.5, 46.3, 31.0, 18.6. IR: 2959, 2918, 1659, 1362, 1168, 1029. HRMS Calcd for $\text{C}_{15}\text{H}_{20}\text{FeS}_2$: 320.0356. Found: 320.0401.

(R)-1-Trimethylstannyl-2-*t*-butylsulfanylferrocene (5d). The general procedure was followed using compound **4d** (49 mg, 0.11 mmol), toluene (1.5 mL), Et_3N (150 μL , 1.08 mmol) and HSiCl_3 (165 μL , 1.63 mmol). Column chromatography using *n*-heptane/ethyl acetate (v/v 100:0 then 35:1) afforded **5d** (38 mg, 0.09 mmol, 80%) as an orange oil. ^1H NMR (CDCl_3): 4.52 (m, 1H, Cp-H), 4.42 (m, 1H, Cp-H), 4.13 (s, 5H, Cp-H), 4.10 (m, 1H, Cp-H), 1.19 (s, 9H, *t*-Bu), 0.34 (s, 9H, SnMe_3). ^{13}C NMR (CDCl_3): 79.2, 77.2, 76.2, 72.5, 69.4, 44.9, 31.0, -7.1. IR: 2956, 2922, 2853, 1637, 1449, 1408, 1082. HRMS Calcd for $\text{C}_{17}\text{H}_{26}\text{FeSSn}$: 438.0129. Found: 438.1013.

(S)-1-*t*-Butylsulfanyl-2-diphenylmethylferrocene (5f). To a solution of ferrocene **4f** (5 mg, 0.01 mmol) in dry THF (0.5 mL) was added $\text{BH}_3\cdot\text{Me}_2\text{S}$ (200 μL , 0.20 mmol). The mixture was stirred at room temperature for 24 h and treated with water (0.5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 \times 2 mL). The combined organic layers were dried over MgSO_4 and then evaporated to dryness. Column chromatography on neutral alumina using *n*-heptane/ethyl acetate (v/v 9:1) afforded **5f** (4 mg, 0.01 mmol, 82%) as an orange oil. ^1H NMR (CDCl_3): 7.60 (m, 2H, Ph), 7.53 (m, 1H, Ph), 7.33-7.15 (m, 7H, Ph), 6.04 (s, 1H, CH), 4.51 (m, 1H, Cp-H), 4.27 (m, 1H, Cp-H), 4.14 (s, 5H, Cp-H), 3.93 (m, 1H, Cp-H), 0.84 (s, 9H, *t*-Bu). ^{13}C NMR (CDCl_3): 149.9, 145.5, 127.4 (2C), 127.1, 126.7, 126.5, 97.6, 79.2, 78.4, 72.4, 72.1, 70.9, 68.6, 47.5, 30.0. IR: 2958, 2927, 2862, 1458. HRMS Calcd for $\text{C}_{27}\text{H}_{28}\text{FeS}$: 440.1261. Found: 440.1304.

(S)-1-*t*-Butylsulfanyl-2-phenylferrocene (5g). The general procedure was followed using ferrocene **4g** (8 mg, 0.02 mmol), toluene (1.5 mL), Et_3N (29 μL , 0.21 mmol) and HSiCl_3 (32 μL , 0.32 mmol). Column chromatography using *n*-heptane/ethyl acetate (v/v: 100/0 then 95/5) afforded **5g** (7 mg, 0.02 mmol, 91%) as an orange oil. ^1H NMR (CDCl_3): 7.78 (m, 2H, Ph), 7.31-7.23 (m, 3H, Ph), 4.59 (m, 1H, Cp-H), 4.46 (m, 1H, Cp-H), 4.37 (m, 1H, Cp-H), 4.13 (s, 5H, Cp-H), 0.97 (s, 9H, *t*-Bu). ^{13}C NMR (CDCl_3): 138.1, 129.9, 127.4, 126.3, 92.0, 77.9, 76.7,

70.9, 68.7, 68.5, 46.3, 30.5. IR: 2924, 2852, 1643, 1462. HRMS Calcd for C₂₀H₂₂FeS: 350.0792. Found: 350.1015.

ortho-Lithiation of (R)-(+)-N,N-dimethyl-1-ferrocenylethylamine (3).⁴⁴ To a solution of (R)-(+)-N,N-dimethyl-1-ferrocenylethylamine **3** (0.38 mmol) in dry diethyl ether (1 mL) was added *n*-butyllithium (0.43 mmol). The reaction mixture was heated to reflux for 3 hours before disulfide (0.46 mmol) was added. After 20 hours refluxing, the mixture was cooled to room temperature. Water (1 mL) was added and the organic layer was washed with H₂O (2 × 2 mL) and aqueous H₃PO₄ (3 × 3 mL, 10%). The combined aqueous layers were extracted with Et₂O (3 × 10 mL) before neutralization with aqueous NaOH (2M). After extraction with Et₂O (3 × 20 mL) and drying over MgSO₄, the crude product was concentrated to dryness and purified.

(S_{FC},R)-2-Dimethylaminoethyl-1-methylsulfanyl ferrocene (6a). [100113-94-8].⁴⁴ The general procedure was followed using (R)-(+)-N,N-dimethyl-1-ferrocenylethylamine **3** (98 mg, 0.38 mmol), diethyl ether (1 mL), *n*-BuLi (310 μL, 0.43 mmol, 1.39 M in hexanes) and dimethyl disulfide (41 μL, 0.46 mmol). Crystallization from pentane afforded **6a** (24 mg, 0.08 mmol, 21%) as an orange crystalline solid. ¹H NMR (CDCl₃): 4.32 (m, 1H, Cp-H), 4.18 (m, 1H, Cp-H), 4.16 (m, 1H, Cp-H), 4.11 (m, 5H, Cp-H), 3.93 (q, 1H, *J* = 6.8 Hz, CH), 2.29 (s, 3H, S-Me), 2.13 (s, 6H, N-Me₂), 1.40 (d, 3H, *J* = 6.8 Hz, C-Me). ¹³C NMR (CDCl₃): 91.8, 83.4, 71.1, 70.0, 67.2, 66.5, 56.2, 40.4, 19.8, 13.2.

(S_{FC},R)-1-Cyclohexylsulfanyl-2-dimethylaminoethylferrocene (6b). The general procedure was followed using (R)-(+)-N,N-dimethyl-1-ferrocenylethylamine **3** (98 mg, 0.38 mmol), diethyl ether (1 mL), *n*-BuLi (295 μL, 0.42 mmol, 1.43 M in hexanes) and dicyclohexyl disulfide (110 μL, 0.46 mmol). Column chromatography with Flashmaster Personal apparatus using CH₂Cl₂/NH₄OH (v/v 98:2) afforded **6b** (53 mg, 0.14 mmol, 38%) as an orange solid. mp: 50-55 °C. ¹H NMR (CDCl₃): 4.31 (m, 1H, Cp-H), 4.20 (m, 1H, Cp-H), 4.16 (m, 1H, Cp-H), 4.09 (m, 5H, Cp-H), 3.97 (q, 1H, *J* = 6.9 Hz, CH), 2.97 (m, 1H, Cy), 2.12 (s, 6H, N-Me₂), 1.92-1.11 (m, 10H, Cy), 1.33 (d, 3H, *J* = 6.8 Hz, C-Me). ¹³C NMR (CDCl₃): 94.4, 78.3, 75.1, 70.2, 70.0, 67.8, 66.7, 56.0, 47.8, 40.1, 34.2, 33.0, 26.4, 26.1, 25.9, 11.2. MS (EI) *m/z* (%): 371 (85, M⁺), 326 (53, [M-NMe₂]⁺). IR: 2968, 2850, 2772, 1686, 1654, 1560, 1544, 1362, 1262, 1190, 1096, 1060. HRMS Calcd for C₂₀H₂₉FeNS: 371.1370. Found: 371.1346.

Benzylidene transfer to benzaldehyde. General procedure

To a solution of sulfide (0.05 mmol) in *t*-BuOH/H₂O 9/1 (415 μL) were added benzyl bromide (60 μL, 0.50 mmol), NaI (38 mg, 0.25 mmol), benzaldehyde (25 μL, 0.25 mmol) and NaOH (20 mg, 0.50 mmol). The reaction mixture was stirred at room temperature and monitored by TLC using *n*-heptane/ethyl acetate (v/v 9:1). Water (1 mL) was then added and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The combined organic phases were dried over MgSO₄ and concentrated to dryness. Column chromatography using *n*-heptane/ethyl acetate afforded stilbene oxide **8**. ¹H NMR (CDCl₃): 7.42-7.17 (m, 2 × 10H, Ph, *cis* and *trans*), 4.36 (s, 2H, CHO, *cis*), 3.87 (s, 2H, CHO, *trans*). ¹³C NMR (CDCl₃): 137.0 (*trans*), 134.3 (*cis*), 128.5

(*trans*), 128.3 (*trans*), 127.8 (*cis*), 127.4 (*cis*), 126.9 (*cis*), 125.4 (*trans*), 62.8 (*trans*), 59.8 (*cis*). HPLC: Daicel Chiralpak AD-H column 250 × 4.6 (L × I.D.) 5 μm, *n*-hexane/*i*-PrOH (v/v 90/10) at 1 mL.min⁻¹, 228 nm, 20 °C. 2.45 min (*R,R*), 7.51 min (*S,S*).

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