Synthesis and Reactivities of Enantiomerically Pure β-Hydroxyalkyl and β-Aminoalkyl Ferrocenyl Sulfides

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Enantiomerically pure β-hydroxyalkyl and β-aminoalkyl ferrocenyl sulfides have been synthesized in good yields from mercaptoferrocene and amino alcohol derivatives. Primary β-aminoalkyl sulfides allowed the synthesis of tetrahydro-1,4-thiazepines containing the ferrocene moiety with good diastereoselectivity and β-iminoalkyl sulfides. Some of these derivatives have successfully been employed as ligands for palladium-catalyzed allylic substitution, with asymmetric induction of up to 99% *ee*.

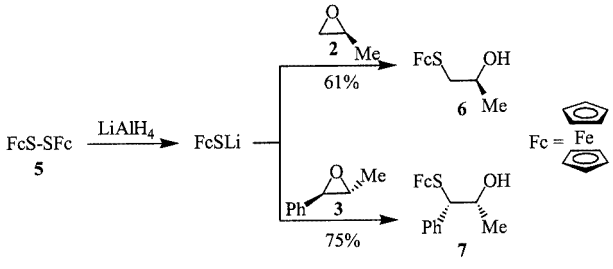
Introduction

Mercaptoferrocene (FcSH, **1**)[1,2] has been known in the literature since 1958, but the use of this compound in synthesis is limited.[3−5] In pursuit of our ongoing interest in sulfur-containing compounds,[6] and in molecules bearing both sulfur and the ferrocene moiety,[7] we focused our attention on the possibility of using mercaptoferrocene as a sulfur-based nucleophile for the synthesis of poly-heterosubstituted ferrocene derivatives with central chirality. Ferrocenes containing atoms with good donor abilities have attracted strong interest, since these complexing moieties are able to act as ligands towards transition metal ions.[2,8] For enantioselective palladium-catalyzed allylic substitution reactions, it has been found that heterobidentate nitrogen-sulfur chiral ligands,[9] which exploit the difference in the electronic character of the two donor atoms, can control the enantioselection in this process. Recently, β-aminoalkyl sulfides prepared by Kellogg[10] by ring-opening of aziridines with thiophenol and used as ligands in palladium-catalyzed alkylation have proven to be quite promising in inducing enantioselectivity, and Anderson[11] synthesized sulfur-imine mixed-donor chiral ligands, obtaining very good enantiomeric excesses in the same reaction. To the best of our knowledge, however, no monosubstituted ferrocene derivatives containing chiral amino-sulfide or hydroxy-sulfide backbones in the side chain have been reported so far. This prompted us to study the reactions between FcSH (**1**) and a series of O- and N-containing electrophiles with the aim of generating new enantiopure ferrocene derivatives with S and N or S and O chelating sites in the side chain. These compounds might merit consideration as building blocks for further synthetic diastereoselective transformations, and as ligands for asymmetric catalysis to be compared to the known families.

Results and Discussion

Synthesis of β-Hydroxyalkyl Sulfides

The oxiranes used for ring-opening reactions with mercaptoferrocene (**1**) were the commercially available (*S*)-(−)-propylene oxide (**2**) and the (2*R*,3*R*)-2-methyl-3-phenyloxirane (**3**),[10] obtained from (1*R*,2*S*)-ephedrine (**4**). Treatment of epoxides **2** and **3** with lithium thiolate, formed in situ by reduction of diferrocenyl disulfide (**5**), afforded β-hydroxyalkyl sulfides **6** and **7** in good yields (Scheme 1).



Scheme 1

The attack of the thiolate occurred at the less substituted carbon atom of the oxirane moiety in **2**, affording an 61% yield of the β-hydroxyalkyl sulfide **6**, the configuration of which has been shown to be (*S*), as in the starting oxirane,

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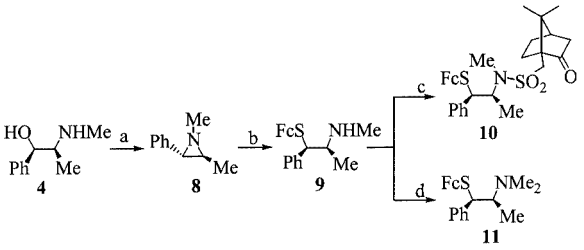
by Mosher's method,[12] and regioselectively at the benzylic center in the *trans*-epoxide **3**, with the formation of the β-hydroxyalkyl sulfide **7** in 75% yield. The stereochemistry of **7** was assigned on the basis of the values of the vicinal coupling constants; furthermore, compound **7** showed only one set of signals in the ^1H and ^{13}C NMR spectra of the crude product, thus ruling out the presence of a second diastereoisomer that could have been formed by partial racemization at the benzylic carbon atom.

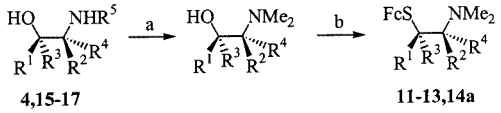
Synthesis of β-Aminoalkyl Sulfides

Several methods were envisioned for the stereoselective synthesis of β-aminoalkyl sulfides. Mercaptoferrocene (**1**) proved very effective in the regio- and stereoselective ring-opening in MeOH of the aziridine **8**[10] (Scheme 2), obtained in turn from (1*R*,2*S*)-ephedrine (**4**). The β-aminoalkyl sulfide **9** was obtained in 77% yield, with the *erythro* stereochemistry assigned on the basis of the value of the vicinal coupling constant of the benzylic proton in the ^1H NMR spectrum. The overall retention of configuration with respect to **4** is due to a double inversion at the benzylic center during the formation of the aziridine and the subsequent ring-opening. The enantiomeric purity of **9** was determined by treatment with (1*S*)-(+)-10-camphorsulfonyl chloride [(1*S*)-(+)-CAS-Cl], affording **10** in quantitative yield and as a single diastereoisomer. *N*-Methylation[13] of **9** gave the β-(dimethylamino)alkyl derivative **11** in 90% yield (Scheme 2).



Scheme 2. a: PPh_3, EtOCO−N=N−COOEt, r.t., 73%; b: **1**, MeOH, r.t. 77%; c: (1*S*)-(+)-10-camphorsulfonyl chloride, DMPA, CH_2Cl_2, r.t., 98%; d: HCO_2H, CH_2O, Δ, 90%

Alternatively, *N*-methylation of (1*R*,2*S*)-ephedrine (**4**), followed by treatment of the β-(dimethylamino)alkyl derivative with mesyl chloride and triethylamine in THF and then with mercaptoferrocene (**1**) in refluxing benzene (Scheme 3), afforded **11** in 68% yield. In this case a regiospecific ring-opening of an intermediate aziridinium ion[14] resulted in a substitution with retention of configuration. By the same procedure, the β-aminoalkyl sulfides **12**, **13**, and **14a** were obtained − in 60, 64, and 58% yields, respectively − from (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**15**), from its enantiomer (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**16**), and from (*S*)-2-phenylglycinol (**17**) (Scheme 3).

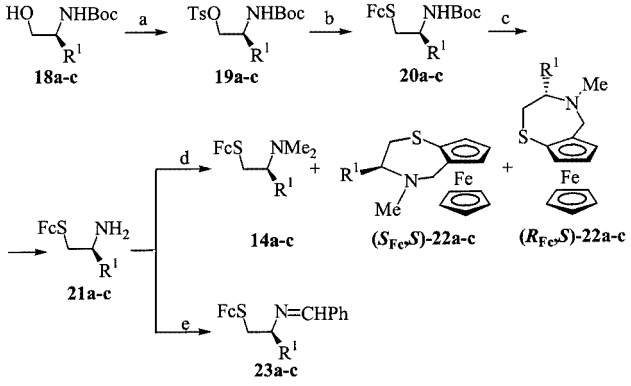


Product	R^1	R^2	R^3	R^4	R^5	Product	Yield [%]
4	Ph	Me	H	H	Me	**11**	68
15	Ph	Ph	H	H	H	**12**	60
16	H	H	Ph	Ph	H	**13**	64
17	H	Ph	H	H	H	**14a**	58

Scheme 3. a: HCO_2H, CH_2O, Δ; b: 1) MsCl, Et_3N, THF, r.t., 2) **1**, C_6H_6, Δ

In both these procedures the regiochemistry depended strongly upon the presence of a phenyl group that directed the attack of the sulfur nucleophile.

A more general route[11b] to β-aminoalkyl sulfides, suitable for application both to aromatic and to aliphatic amino alcohols, afforded as the final products NH_2-containing molecules suitable for use in further synthetic transformations. The *N*-Boc-protected amino alcohols **18a−c** (Scheme 4 and Table 1) were converted into the corresponding tosyl derivatives **19a−c**. The yield of **19c** could be improved by use of *p*-toluenesulfonic anhydride (Ts_2O) instead of TsCl.[15] Subsequent treatment with FcSNa, from **1** and NaH in DMF, gave **20a−c** in very good yields. Deprotection with TFA and triethylsilane provided **21a−c** almost quantitatively. The β-aminoalkyl sulfide **21c** was found to be enantiomerically pure by its reaction with (1*S*)-(+)-CAS-Cl, which gave a single diastereoisomer.



Scheme 4. a: **19a**,**b**: TsCl, Et_3N, CH_2Cl_2, r.t.; **19c**: Ts_2O, Et_3N, CH_2Cl_2, r.t.; b: FcSNa, DMF, r.t.; c: TFA, Et_3SiH, CH_2Cl_2, r.t.; d: HCO_2H, HCHO, Δ; e PhCHO, CH_2Cl_2, $MgSO_4$

Table 1. Synthesis of β-aminoalkyl sulfides and thiazepinoferrocene

	R^1	**20** [%]	**21** [%]	**14** [%]	**22** [%]	*de*
a	Ph	90	98	-	62	75
b	*t*Bu	82	98	-	58	70
c	*i*Pr	91	95	22	75	40

Unexpectedly, the attempted *N*,*N*-dimethylation of **21a−c** with formic acid and formaldehyde at reflux provided the bicyclic compounds **22a−c**, as mixtures of two diastereoisomers, as the major reaction products. The *N*,*N*-dimethylated β-aminoalkyl sulfide **14** was obtained, in 22% yield, only in the case of R = isopropyl (**14c**); no traces of **14a** or **14b** were found in the reaction mixtures when R was *tert*-butyl or phenyl (Scheme 4 and Table 1). The diastereomeric excesses of **22a−c**, determined from the ^1H NMR spectra of the crude products (see Exp. Sect.), suggested

that the selectivity of *ortho* cyclization was governed by a subtle balance between steric and electronic effects: the selectivity increasing as the R group in the β-aminoalkyl sulfide moiety becomes larger, with the phenyl group providing the best result.

In all the reactions examined, the major diastereoisomer of the cyclic product could be isolated by column chromatography. The absolute configuration of the main diastereoisomer of **22b** was determined by single-crystal X-ray analysis, indicating an (S_{Fc},*S*) configuration[16] (Figure 1).

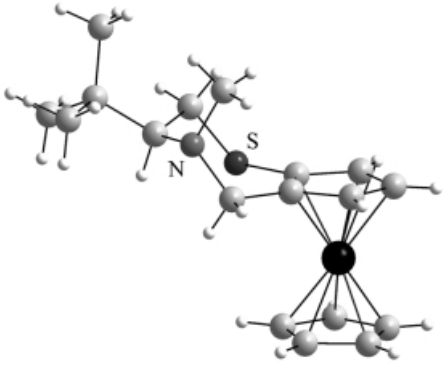
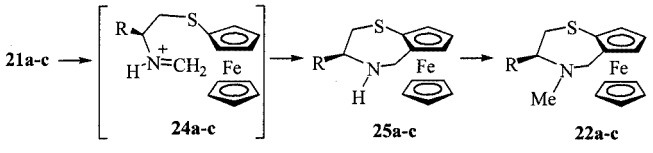


Figure 1. Crystal structure of bicyclic compound **22b**

Various methods for effective asymmetric syntheses of planar chiral ferrocene derivatives have been reported,[17] but only a few examples of planar chirality generated by ring-closure reactions are known.[18] To the best of our knowledge, the use of a chiral chain containing a β-amino sulfide moiety in asymmetric ring-closure reactions as reported here is unprecedented. The formation of the seven-membered rings **22a−c** conforms to a mechanism in which the acid-catalyzed formation of an iminium ion **24** is followed by an intramolecular electrophilic attack at the electronically activated *ortho* position of the substituted ferrocene ring to afford product **25**, which can then be alkylated in situ to provide **22**. Product **25b**, isolated in a reaction performed for a shorter time and fully characterized, was successfully alkylated to afford **22b** in a separate experiment. The formation of the major diastereoisomer is shown in Scheme 5.



Scheme 5

The importance of **22**-type compounds stems from the fact that these systems can be viewed as analogues of tetrahydrobenzothiazepines, in which the aromatic ring is replaced by a ferrocenyl moiety. In virtue of the wide range of pharmacological activities displayed by the benzothiazepine derivatives,[19] the possibility that these new compounds might have potential as biologically active molecules cannot be ruled out.

Finally, β-aminoalkyl sulfides **21a−c** were easily transformed into the corresponding β-iminoalkyl sulfides **23a−c** in quantitative yield by treatment with benzaldehyde in CH_2Cl_2 at room temperature in the presence of magnesium sulfate (Scheme 4).

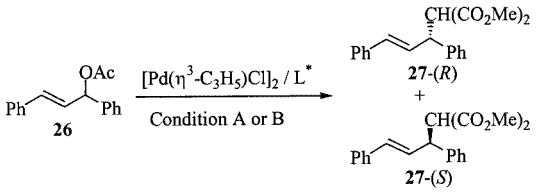
Palladium-Catalyzed Allylic Substitution

With this family of new aminoalkyl sulfides to hand, we examined their effectiveness in one of the most archetypal reactions in chiral ligand screening: the palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate (**26**) with the nucleophile derived from dimethyl malonate. This popular test reaction was performed under two different sets of reaction conditions, and the results are summarized in Table 2.

The reactions were preferentially performed throughout under conditions B, since these provided the alkylation products with faster reaction rates and in higher yields (compare Entries 1 and 2 with 3 and 4) than under conditions A. Table 1 shows that ligands **11−14** successfully catalyzed the substitution reaction. It can readily be seen that the β-(dimethylamino)alkyl derivatives **11** (Entry 4) and **14a** (Entry 7) were by far the most effective in transferring chirality in this reaction (99% *ee*) and that the enantioselectivity was strongly depleted (compare Entries 3 and 4) with ligand **9**, containing only one methyl group at the nitrogen atom. Interestingly, comparison with the *ee* data reported in the literature for a ligand bearing the same aminoalkyl sulfide backbone, but containing a phenyl group bonded to the sulfur atom,[10] emphasizes the beneficial effect due to the presence of the ferrocene moiety in **11**. The effect of increasing the steric bulk of the backbone chiral centers was investigated by the use of ligands **12** and **13** (Entries 5 and 6). The *ee*s obtained with these ligand systems were significantly smaller (79 and 77%, respectively) than those obtained by using ligands **11** and **14a**. A low *ee* value (45%) was obtained with the use of the β-(dimethylamino)alkyl derivative **14c** (Entry 8), prepared starting from (*S*)-valinol. Increased reaction times were necessary when using ligands **23a−c**, containing imino groups (Entry 9−11). Derivatives **23a−c** afforded remarkably high *ee*s (Entries 10 and 11) when R = *tert*-butyl or isopropyl, whereas lower *ee* values were obtained when R = phenyl (Entry 9). The replacement of the phenyl group with the ferrocene moiety in ligands such as **14c** and **23c** did not have any significant effect on the stereochemical outcome.

The origin of the chirality in palladium-catalyzed allylic substitution with mixed nitrogen-sulfur ligands is generally recognized to be due to attack of the nucleophile on the square-planar π-allyl complexes *trans* to the better π-acceptor.[9k,10,11] On these grounds and taking into account the hierarchy of the π-acceptor abilities, we postulate, in agreement with the literature data, that attack of the nucleophile might occur at the carbon atom opposite to the sulfide in the case of aminoalkyl ferrocenyl sulfides, whereas the trajectory of the nucleophile should be *trans* to the imino group when ferrocenyl iminoalkyl sulfides are used as ligands at the palladium center.

Table 2. Palladium-catalyzed allylic substitution reaction



Entry	Ligand	Reaction condition[a]	Time [h][b]	Yield [%][c]	*ee* [%][d]	Absolute configuration[e]
1	**9**	A	80	28	41	(*S*)
2	**11**	A	80	40	86	(*S*)
3	**9**	B	20	87	43	(*S*)
4	**11**	B	20	88	99	(*S*)
5	**12**	B	20	99	79	(*S*)
6	**13**	B	20	96	77	(*R*)
7	**14a**	B	20	96	99	(*S*)
8	**14c**	B	20	87	45	(*S*)
9	**23a**	B	90	90	78	(*R*)
10	**23b**	B	90	85	99	(*R*)
11	**23c**	B	90	90	92	(*R*)

[a] Conditions A: **26** (1 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.02 mmol), ligand (0.03 mmol), $NaCH(CO_2Me)_2$ (1.5 mmol), THF (5 mL). Conditions B: **26** (1 mmol), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.025 mmol), ligand (0.1 mmol), $CH_2(CO_2Me)_2$ (3 mmol), BSA (3 mmol), KOAc (0.03 mmol), CH_2Cl_2 (3 mL). [b] When TLC monitoring indicated complete consumption of the allyl acetate. [c] Isolated yield based on **26**. [d] Determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent. [e] The absolute configuration of **27** was assigned by comparison of the sign of the specific rotation with the literature data.[20]

Furthermore, the assumption that enantioselection might also arise through predisposition of the allyl moiety by the asymmetric steric environment of the ferrocenyl ligand cannot be ruled out.

The sense of the enantioinduction for all reactions was established by comparison of the optical specific rotation of **27** with that reported in the literature.[20] The β-(methylamino) and the β-(dimethylamino) derivatives **9**, **11**, **12**, and **14c**, with the same asymmetric environment, afforded **27** with an *ee* in favor of the (−)-(*S*) enantiomer, whereas ligand **13**, which is the enantiomer of **12**, afforded an excess of the (+)-(*R*) enantiomer. The β-iminoalkyl derivatives **23a**−**c** gave predominantly the (+)-(*R*) enantiomer, in agreement with similar results obtained by Anderson.[11b]

Conclusion

We have outlined an expedient route to monosubstituted ferrocene derivatives with central chirality and which incorporate β-hydroxyalkyl, β-aminoalykl, and β-iminoalkyl sulfide units within their frameworks. An unprecedented ring-closure reaction, affording previously unknown chiral tetrahydrothiazepinoferrocenes and based on the use of a primary amino derivative, has been found. The β-iminoalkyl and β-aminoalkyl ferrocenyl sulfides have been applied to allylic substitution, affording the expected product in good yields and with moderate to good enantioselectivities. The application of this new type of ferrocene ligands to other asymmetric C−C bond-forming reactions is actively under investigation.

Experimental Section

General Remarks: Melting points (uncorrected) were determined with a Büchi melting point apparatus. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were recorded at 300 and 75.46 MHz, respectively, with a Varian Gemini 300. Chemical shifts (δ) are reported in ppm relative to $CHCl_3$ (δ = 7.26 ppm for ^1H and δ = 77.0 ppm for ^{13}C). *J* values are given in Hz. ^{13}C NMR spectral assignments were performed by use of DEPT experiments. IR spectra were recorded with a Perkin−Elmer model 257 grating spectrometer. Mass spectra were obtained with a VG 7070-E spectrometer at an ionizing voltage of 70 eV. $[\alpha]_D^{20}$ values were determined with Perkin−Elmer Polarimeter 341. The originality of all compounds was checked by a CAS online structure search. In the characterization of new compounds, oily products were characterized by accurate mass measurements, because of the small scales used for their preparations. Reactions were conducted in oven-dried (120 °C) glassware under a positive pressure of Ar. Transfer of anhydrous solvents or mixtures was accomplished with oven-dried syringes/septum techniques. THF was distilled from sodium/benzophenone just prior to use and stored under Ar. Et_2O was distilled from phosphorus pentoxide. CH_2Cl_2 was passed through basic alumina and distilled from CaH_2 prior to use. Other solvents were purified by standard procedures. Light petroleum ether refers to the fraction with boiling range 40−60 °C. The reactions were monitored by TLC performed on silica gel plates (Baker-flex IB2-F). Column chromatography was performed on Merck silica gel 60 (70−230 mesh). Preparative thick layer chromatography was carried out on glass plates using a 1-mm layer of Merck 60 P_f 254 silica gel. All chemicals were used as obtained or purified by distillation as needed. (*S*)-(−)-Propylene oxide (**2**), (1*R*,2*S*)-ephedrine (**4**), (1*R*,2*S*)-2-amino-1,2-diphenylethanol (**15**), (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**16**), (*S*)-2-phenylglycinol (**17**), and (+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol were purchased from Fluka. Li-

thium aluminium hydride (1 M in THF) was purchased from Aldrich. *N*-Boc-protected (*S*)-2-phenylglycinol (**18a**), *N*-Boc-protected (*S*)-*tert*-leucinol (**18b**), and *N*-Boc-protected (*S*)-valinol (**18c**) were prepared from (*S*)-2-phenylglycinol (Aldrich), L-*tert*-leucine and L-valine by literature procedures.[21]

(2*S*)-1-(Ferrocenylthio)propan-2-ol (6): $LiAlH_4$ (1 M solution in THF, 3.4 mL, 3.4 mmol) was added to a stirred solution of diferrocenyl disulfide (300 mg, 0.69 mmol) in dry THF. The mixture was heated to reflux for 2 h and then allowed to cool to room temperature. *i*PrOH (4 mL) and (*S*)-(−)-propylene oxide (**2**) (0.15 mL, 2 mmol) were then added, and the mixture was stirred overnight. The mixture was then quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Chromatography (light petroleum ether/ethyl acetate, 10:1) gave **6** (116 mg) as a yellow oil in 61% yield. $[\alpha]_D^{20} = +57.2$ ($c = 0.56$, $CHCl_3$). ^1H NMR: δ = 1.18 (d, $J = 6.3$ Hz, 3 H), 2.48 (dd, $J_1 = 13.5$, $J_2 = 9$ Hz, 1 H), 2.69 (dd, $J_1 = 13.5$, $J_2 = 3.6$ Hz, 1 H), 2.7 (br. s, 1 H), 3.70 (m, 1 H), 4.20 (s, 5 H + m, 2 H), 4.30 (m, 2 H) ppm. ^{13}C NMR: δ = 21.5 (CH_3), 47.1 (CH_2), 65.3, 69.2, 69.45, 73.6, 74.0 (CH), 78.2 (C) ppm. IR (CCl_4): $\tilde{\nu} = 3532$ cm^{-1}. EI-MS: *m*/*z* = 276 [M$^+$], 217, 121, 56. HRMS calcd. for $C_{13}H_{16}FeOS$: 276.0271; found 276.0289.

(1*S*,2*R*)-1-(Ferrocenylthio)-1-phenylpropan-2-ol (7): $LiAlH_4$ (1 M solution in THF, 3.4 mL, 3.4 mmol) was added to a stirred solution of diferrocenyl disulfide (300 mg, 0.69 mmol) in dry THF. The mixture was heated at reflux for 2 h and then allowed to cool to room temperature. *i*PrOH (4 mL) and (2*R*,3*R*)-2-methyl-3-phenyloxirane (**3**)[10] (200 mg, 1.5 mmol) were then added and the mixture was stirred overnight. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and then concentrated in vacuo. Chromatography (light petroleum ether/ethyl acetate, 10:1) gave **7** (148 mg) as a yellow oil in 61% yield. ^1H NMR: δ = 1.15 (d, $J = 6.3$ Hz, 3 H), 2.3 (br. s, 1 H), 3.7 (d, $J = 5.5$ Hz, 1 H), 4.03 (m, 1 H), 4.10−4.30 (m, 9 H), 7.25 (m, 5 H) ppm. ^{13}C NMR: δ = 20.1 (CH_3), 62.9, 68.3, 69.4, 69.5, 69.7 (CH), 73.8 (C), 74.4, 74.7 (CH), 127.4, 128.3, 128.9 (ArCH), 138.3 (ArC) ppm. IR (CCl_4): $\tilde{\nu} = 3580$ cm^{-1}. EI-MS: *m*/*z* = 352 [M$^+$], 218, 121, 56, 43. HRMS calcd. for $C_{19}H_{20}FeOS$: 352.0584; found 352.0573.

(1*R*,2*S*)-1-(Ferrocenylthio)-2-(methylamino)-1-phenylpropane (9): Ferrocenethiol (0.73 g, 3.35 mmol) was added to a solution of *trans*-aziridine **8**[10] (0.5 g, 3.4 mmol) in MeOH (3 mL). The resulting solution was stirred for 24 h at room temperature and concentrated in vacuo. The crude mixture was purified by chromatography (light petroleum ether/ethyl acetate, 5:1) to afford **9** (0.94 g) as a yellow solid in 77% yield. M.p. 58−60 °C (hexane/Et_2O). $[\alpha]_D^{20} = -28.9$ ($c = 1.72$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15 (d, $J = 6.4$ Hz, 3 H), 1.50 (br. s, 1 H), 2.35 (s, 3 H), 2.9 (m, 1 H), 3.75 (d, $J = 6.6$ Hz, 1 H), 3.93 (m, 1 H), 4.08 (m, 1 H), 4.12 (m, 1 H), 4.15 (s, 5 H), 4.17 (m, 1 H), 7.17−7.30 (m, 5 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 17.3, 33.8 (CH_3), 58.0, 61.7, 69.0, 69.2, 69.3, 74.2, 74.5 (CH), 77.6 (C), 126.9, 128.05, 128.7 (ArCH), 140.2 (ArC) ppm. IR (CCl_4): $\tilde{\nu} = 3339$ cm^{-1}. EI-MS: *m*/*z* = 365 [M$^+$], 308, 218, 148, 58. $C_{20}H_{23}FeNS$ (365.09): calcd. C 65.74, H 6.35, N 3.86; found C 65.62, H 6.40, N 3.92.

(1*R*,2*S*)-2-[(Camphylsulfonyl)(methyl)amino]-1-(ferrocenylthio)-1-phenylpropane (10): A solution of **9** (70 mg, 0.19 mmol), (+)-(1*S*)-10-camphorsulfonyl chloride (72 mg, 0.3 mmol), and 4-(dimethylamino)pyridine (DMAP, 36 mg, 0.3 mmol) in CH_2Cl_2 was stirred at room temperature for 5 d (until complete disappearance of the starting product). The mixture was then quenched with water and extracted with CH_2Cl_2. The crude product was analyzed by ^1H and ^{13}C NMR and then purified by preparative TLC (chloroform/methanol, 10:1) to afford **10** (106 mg) as a yellow solid in 96% yield. M.p. 161−162 °C (hexane/Et_2O). $[\alpha]_D^{20} = -39.2$ ($c = 1.18$, $CHCl_3$). ^1H NMR: δ = 0.61 (s, 3 H), 0.95 (s, 3 H), 1.25−1.40 (m, 2 H), 1.55 (d, $J = 6.8$ Hz, 3 H), 1.62 (m, 1 H), 1.85 (d, $J = 17.0$ Hz, 1 H), 1.90−2.00 (2m, 2 H), 2.18−2.40 (4m, 2 H), 2.65 (d, $J = 14.0$ Hz, 1 H), 2.68 (s, 3 H), 3.65 (d, $J = 11.0$ Hz, 1 H), 3.78 (br. s, 1 H), 4.05 (br. s, 1 H), 4.15 (br. s, 7 H), 4.55 (m, 1 H), 7.1−7.3 (m, 5 H) ppm. EI-MS: *m*/*z* = 579 [M$^+$], 272, 218, 120, 58. $C_{30}H_{37}FeNO_3S_2$ (579.16): calcd. C 62.16, H 6.44, N 2.42; found C 62.28, H 6.40, N 2.35.

(1*R*,2*S*)-2-(Dimethylamino)-1-(ferrocenylthio)-1-phenylpropane (11): A solution of **9** (0.86 g, 2.4 mmol) in formic acid (98%, 0.5 mL, 12 mmol) and aqueous formaldehyde (37%, 0.2 mL, 7.2 mmol) was heated to reflux for 6 h. Upon cooling, the mixture was basified with aqueous NaOH (1 M, pH = 10) and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (chloroform/methanol, 10:1) gave **11** (0.64 g) as a yellow solid in 70% yield. M.p. 90−91 °C (hexane/Et_2O). $[\alpha]_D^{20} = -71.3$ ($c = 1.135$, $CHCl_3$). ^1H NMR: δ = 1.21 (d, $J = 6.5$ Hz, 3 H), 2.15 (s, 6 H), 2.93 (m, 1 H), 3.75 (d, $J = 8.1$ Hz, 1 H), 3.78 (m, 1 H), 4.02 (m, 1 H), 4.10 (m, 2 H), 4.12 (s, 5 H), 7.00−7.28 (m, 5 H) ppm. ^{13}C NMR: δ = 10.9, 40.9 (CH_3), 60.2, 62.4, 68.95, 69.1, 69.25, 74.5, 74.8 (CH), 77.4 (C), 126.3, 127.65, 128.5 (ArCH), 142.2 (ArC) ppm. IR (CCl_4): $\tilde{\nu} = 2937$ cm^{-1}. EI-MS: *m*/*z* = 379 [M$^+$], 307, 217, 162, 72. $C_{21}H_{25}FeNS$ (379.11): calcd. C 66.47, H 6.65, N 3.69; found C 66.58, H 6.60, N 3.72.

General Procedure for the *N*,*N*-Dimethylation of 4, 15, 16, and 17: A solution of the amino alcohol (3 mmol) in formic acid (98%, 30 mmol) and aqueous formaldehyde (37%, 18 mmol) was heated to reflux for18 h. Upon cooling, the mixture was basified with aqueous NaOH (1 M, pH = 10) and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford the β-(dimethylamino) alcohols in quantitative yield.

General Procedure for the Synthesis of β-Aminoalkyl Sulfides 11, 12, 13, and 14a: Triethylamine (3 mmol) was added at 0 °C to a solution of the β-(dimethylamino) alcohol (1 mmol) in dry THF (4 mL). Methanesulfonyl chloride (2 mmol) in THF (2 mL) was then added dropwise. A pale yellow precipitate resulted upon the addition. The reaction mixture was stirred for 1 h, and the solvent was removed in vacuo. The solid residue was suspended in dry benzene (5 mL), and triethylamine (2 mmol) and a solution of ferrocenethiol (1.1 mmol) in benzene (5 mL) were added. The resulting mixture was heated to reflux for 12 h under argon. NaOH (1 M) was added after cooling, and the organic layer was extracted, washed with brine, and dried (Na_2SO_4). The resulting mixture was purified by chromatography (light petroleum ether/ethyl acetate, 5:1) to afford the β-aminoalkyl sulfide.

(1*R*,2*S*)-2-(Dimethylamino)-1-(ferrocenylthio)-1-phenylpropane (11): Yield 68% (258 mg).

(1*R*,2*S*)-2-(Dimethylamino)-1-(ferrocenylthio)-1,2-diphenylethane (12): Yield 60% (265 mg). M.p. 127−128 °C (hexane). $[\alpha]_D^{20} = -42.9$ ($c = 1.08$, $CHCl_3$). ^1H NMR: δ = 2.13, (s, 6 H), 3.65 (d, $J = 9.0$ Hz, 1 H), 3.68 (m, 1 H), 3.98 (m, 2 H), 4.06 (s, 5 H + m, 1 H), 4.27 (d, $J = 9.0$ Hz, 1 H), 7.03 (m, 2 H), 7.17 (m, 5 H), 7.34 (m, 3 H) ppm. ^{13}C NMR: δ = 42.15 (CH_3), 58.05, 68.8, 69.0, 69.2, 73.8, 74.4, 74.9 (CH), 78.75 (C), 126.5, 127.3, 127.5, 128.9, 129.5 (ArCH), 135.7, 141.3 (ArC) ppm. IR (CCl_4): $\tilde{\nu} = 1452, 1545$ cm^{-1}.

EI-MS: *m*/*z* = 441 [M$^+$], 307, 241, 217, 134. $C_{26}H_{27}FeNS$ (441.12): calcd. C 70.73, H 6.17, N 3.17; found C 70.24, H 6.11, N 3.28.

(1*S*,2*R*)-2-(Dimethylamino)-1-(ferrocenylthio)-1,2-diphenylethane (13): Yield 64% (283 mg). $[\alpha]_D^{20}$ = +42.0 (*c* = 1.29, $CHCl_3$).

An equimolecular mixture of derivatives **12** and **13** in $CDCl_3$ was analyzed by ^{1}H NMR in the presence of Pirkle's alcohol [(+)-(*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol] and showed two peaks in a 1:1 ratio at δ = 2.03 and 2.08 ppm, corresponding to the NMe_2 protons of the two enantiomers, while the ^{1}H NMR spectra of the single enantiomers showed, in the presence of Pirkle's alcohol, only one of the two signals (δ = 2.03 ppm for derivative **12** and δ = 2.08 ppm for derivative **13**), confirming the enantiomeric purities of the two compounds.

(*S*)-2-(Dimethylamino)-1-(ferrocenylthio)-2-phenylethane (14a): Yield 58% (212 mg). $[\alpha]_D^{20}$ = −38.0 (*c* = 0.85, $CHCl_3$). ^{1}H NMR: δ = 2.23, (s, 6 H), 2.65 (dd, J_1 = 12.6, J_2 = 7.6 Hz, 1 H), 2.79 (dd, J_1 = 12.6, J_2 = 8.3 Hz, 1 H), 3.87 (m, 2 H), 4.06 (m, 1 H), 4.13 (s, 5 H + m, 2 H), 7.06−7.32 (m, 5 H) ppm. ^{13}C NMR: δ = 45.6 (CH_3), 53.0 (CH) 63.9 (CH_2) 69.1, 69.2, 74.7, 75.1 (CH), 77.15 (C), 126.7, 127.9, 128.0 (ArCH), 141.3 (ArC) ppm. IR (CCl_4): $\tilde{\nu}$ = 1451 cm^{-1}. EI-MS: *m*/*z* = 365 [M$^+$], 148, 58. HRMS calcd. for $C_{20}H_{23}FeNS$: 365.0901 found 365.0481.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-phenylethyl *p*-Toluenesulfonate (19a): *p*-Toluenesulfonyl chloride (2.47 g, 10.4 mmol) and triethylamine (2.9 mL, 20.8 mmol) were added to a stirred solution of (*S*)-*N*-*tert*-butoxycarbonyl-2-phenylglycinol (**18a**, 2.5 g, 10.4 mmol) in CH_2Cl_2 (7 mL) at room temperature. The resulting mixture was stirred overnight and then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with citric acid (20%) and dried (Na_2SO_4). The resulting mixture was purified by chromatography (light petroleum ether/ethyl acetate, 5:1 then 1:1) to afford **19a** (3.0 g) in 74% yield. ^{1}H NMR: δ = 1.40, (s, 9 H), 2.40 (s, 3 H), 4.20 (m, 2 H), 4.92 (m, 1 H), 5.11 (br. s, 1 H), 7.15−7.32 (m, 7 H), 7.68 (d, 2 H).

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3,3-dimethylbutyl *p*-Toluenesulfonate (19b): *p*-Toluenesulfonyl chloride (2.94 g, 15.5 mmol) and triethylamine (4.3 mL, 31 mmol) were added to a stirred solution of (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methyl-1-butanol (**18b**, 3.36 g, 15.5 mmol) in CH_2Cl_2 (10 mL) at room temperature. The resulting mixture was stirred overnight and then quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with citric acid (20%) and dried (Na_2SO_4). The resulting mixture was purified by chromatography (light petroleum ether/ethyl acetate, 5:1 then 1:1) to afford **19b**[22] (4.1 g) in 71% yield.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-3-methylbutyl *p*-Toluenesulfonate (19c): *p*-Toluenesulfonic anhydride (6.5 g, 20 mmol) and triethylamine (2.8 mL, 20 mmol) were added at 0 °C to a stirred solution of (*S*)-2-[(*tert*-butoxycarbonyl)amino]-3-methyl-1-butanol (**18c**, 2 g, 10 mmol) in CH_2Cl_2 (200 mL). The resulting mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was suspended in Et_2O and filtered. The filtrate was concentrated and then purified by chromatography (light petroleum ether/ethyl acetate, 3:1) to afford **19c**[15] (2.5 g) in 70% yield.

General Procedure for the Synthesis of *N*-Boc-Protected β-Aminoalkyl Sulfides 20: Ferrocenethiol (2.1 mmol) in DMF (7 mL) was added dropwise at 0 °C to prewashed (hexane, 3 × 10 mL) NaH (2.1 mmol), suspended in DMF (2 mL). After 15 min, a solution of the *p*-toluenesulfonate **19** (2 mmol) in DMF (4 mL) was added, the mixture was stirred for 1 h at 0 °C and 12 h at room temperature, and then aqueous NaOH (1 M, 25 mL) was added. The mixture was extracted with Et_2O, and the combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. Purification by column chromatography (light petroleum ether/ethyl acetate, 15:1 then 10:1) gave the protected amine.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-(ferrocenylthio)-2-phenylethane (20a): Yellow solid (0.79 g, 90%). M.p. 91−93 °C (hexane). $[\alpha]_D^{20}$ = +4.4 (*c* = 0.75, $CHCl_3$). ^{1}H NMR: δ = 1.43 (s, 9 H), 2.91 (m, 2 H), 4.18 (s, 5 H), 4.20 (m, 2 H), 4.26 (m, 1 H), 4.32 (m, 1 H), 4.72 (br. s, 1 H), 5.17 (d, *J* = 7.3 Hz, 1 H) ppm. ^{13}C NMR: δ = 28.25 (CH_3), 44.15 (CH_2), 54.2 (C), 69.2, 69.3, 73.4, 73.7, (CH), 79.3 (C), 126.2, 127.2, 128.35 (CH), 141.5 (C) 155.0 (CO) ppm. IR (CCl_4): $\tilde{\nu}$ = 1486, 1706, 3445 cm^{-1}. EI-MS: *m*/*z* = 437 [M$^+$], 363, 231, 217, 121. $C_{23}H_{27}FeNO_2S$ (437.11): calcd. C 63.14, H 6.23, N 3.20 found C 63.09, H 6.30, N 3.13.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-(ferrocenylthio)-3,3-dimethylbutane (20b): Yellow solid (0.69 g, 82%). M.p. 127−128 °C (hexane). $[\alpha]_D^{20}$ = +42.9 (*c* = 0.64, $CHCl_3$). ^{1}H NMR: δ = 0.82 (s, 9 H), 1.49 (s, 9 H) 2.36 (dd, J_1 = 13.3, J_2 = 11 Hz, 1 H), 2.81 (dd, J_1 = 13.3 J_2 = 3.3 Hz, 1 H), 3.50 (3d, J_1 = 13.3, J_2 = 11, J_3 = 3.3 Hz, 1 H), 4.16 (br. s, 5 H + 1 H), 4.19 (br. s, 1 H), 4.29 (br. s, 1 H), 4.35 (br. d, *J* = 1 0.0 Hz, 1 H), 4.49 (br. s, 1 H) ppm. ^{13}C NMR: δ = 26.3, 28.4 (CH_3), 35.0 (C), 40.1 (CH_2), 58.4, 69.1, 69.3, 69.3, 73.4, 74.5 (CH), 78.8 (C), 156.1 (CO) ppm. IR (CCl_4): $\tilde{\nu}$ = 1503, 1705, 3445 cm^{-1}. EI-MS: *m*/*z* = 417 [M$^+$], 361, 343, 217, 121. $C_{21}H_{31}FeNO_2S$ (417.14): calcd. C 60.41, H 7.49, N 3.36 found C 60.11, H 7.66, N 3.19.

(*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1-(ferrocenylthio)-3-methylbutane (20c): Yellow solid (0.74 g, 91%). M.p. 79−80 °C (hexane). $[\alpha]_D^{20}$ = −6.1 (*c* = 1.00, $CHCl_3$). ^{1}H NMR: δ = 0.80, (d, *J* = 6.6 Hz, 3 H), 0.82 (d, *J* = 6.6 Hz, 3 H), 1.42 (s, 9 H), 1.80 (m, 1 H), 2.70 (d, *J* = 6.1 Hz, 2 H), 3.50 (br. s, 1 H), 4.10 (s, 5 H), 4.28 (br. s, 2 H), 4.38 (br. s, 1 H), 4.5 (br. d, 1 H) ppm. ^{13}C NMR: δ = 17.7, 19.3, 28.3 (CH_3), 30.7 (CH), 40.95 (CH_2), 55.25, 68.9, 69.0, 69.2, 73.2, 73.6 (CH), 79.8 (C), 155.5 (CO) ppm. IR (CCl_4): $\tilde{\nu}$ = 1495, 1719, 3448 cm^{-1}. EI-MS: *m*/*z* = 403 [M$^+$], 347, 232, 218, 121, 57. $C_{20}H_{29}FeNO_2S$ (403.13): calcd. C 59.53, H 7.25, N 3.47 found C 59.48, H 7.18, N 3.39.

General Procedure for the Synthesis of β-Aminoalkyl Sulfides 21: The protected amine **20** (2 mmol) was stirred with trifluoroacetic acid (26 mmol) and Et_3SiH (5 mmol) in CH_2Cl_2 (25 mL) for 1 h at room temperature. Aqueous NaOH (1 M, 120 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography ($CHCl_3$/MeOH, 10:1) gave compounds **21.**

(*S*)-2-Amino-1-(ferrocenylthio)-2-phenylethane (21a): Yellow solid (0.66 g, 98%). M.p. 148−149 °C (hexane). $[\alpha]_D^{20}$ = +5.9 (*c* = 0.63, $CHCl_3$). ^{1}H NMR: δ = 2.89 (dd, J_1 = 14, J_2 = 6.6 Hz, 1 H), 3.07 (dd, J_1 = 14, J_2 = 8.3 Hz, 1 H), 3.99 (br. t, 1 H), 4.18 (s, 5 H), 4.22 (m, 2 H), 4.24 (m, 1 H), 4.28 (m, 1 H), 7.17−7.37 (m, 5 H), 8.28 (br. s, 2 H) ppm. ^{13}C NMR: δ = 41.3 (CH_2), 54.85, 69.5, 69.8, 73.8, 74.0 (CH), 76.8 (C), 127.4, 129.0, 129.4 (CH), 134.9 (C) ppm. IR (CCl_4): $\tilde{\nu}$ = 1674, 3610 cm^{-1}. EI-MS: *m*/*z* = 337 [M$^+$], 232, 106. $C_{18}H_{19}FeNS$ (337.06): calcd. C 64.08, H 5.68, N 4.15; found C 63.98, H 5.39, N 4.25.

(*S*)-2-Amino-1-(ferrocenylthio)-3,3-dimethylbutane (21b): Yellow solid (0.63 g, 98%). M.p. 108−110 °C (hexane). $[\alpha]_D^{20}$ = +87.7 (*c* = 0.7, $CHCl_3$). ^{1}H NMR: δ = 0.97 (s, 9 H), 2.61, (dd, J_1 = 13.8,

J_2 = 11.4 Hz, 1 H), 2.88 (br. d, J = 4.0 Hz, 1 H + m, 1 H), 4.26 (s, 5 H), 4.32 (br. s, 2 H), 4.39 (br. s, 2 H), 7.7 (br. s, 2 H) ppm. ^{13}C NMR: δ = 25.85 (CH_3), 32.9 (C), 37.1 (CH_2) 60.15, 69.9, 70.2, 70.6, 73.75, 74.2 (CH), 76.2 (C) ppm. IR (CCl_4): ṽ = 1519, 3450 cm^{-1}. EI-MS: *m*/*z*: 317 [M$^+$], 232, 218, 121, 86. $C_{16}H_{23}FeNS$ (317.09): calcd. C 60.55, H 7.31, N 4.42 found C 60.31, H 7.58, N 4.28.

(*S*)-2-Amino-1-(ferrocenylthio)-3-methylbutane (21c): Light brown oil that crystallized at below 0 °C (0.57 g, 95%). $[\alpha]_D^{20}$ = +69.7 (*c* = 1.58, $CHCl_3$). ^{1}H NMR: δ = 0.85, (d, J = 6.7 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 1.61 (br. s, 2 H), 1.65 (m, 1 H), 2.42 (dd, J_1 = 9.4, J_2 = 12.8 Hz, 1 H), 2.58 (m, 1 H), 2.75 (dd, J_1 = 12.8, J_2 = 16.0 Hz, 1 H), 4.11 (m, 2 H + s, 5 H), 4.25 (m, 2 H) ppm. ^{13}C NMR: δ = 17.4, 19.1 (CH_3), 32.5 (CH), 43.95 (CH_2), 55.4, 68.85, 69.0, 69.3, 73.3, 73.5 (CH), 79.4 (C) ppm. IR (CCl_4): ṽ = 3388 cm^{-1}. EI-MS: *m*/*z* = 303 [M$^+$], 232, 218, 72. HRMS calcd. for $C_{15}H_{21}FeNS$: 303.0744 found 303.0732.

General Procedure for the Reaction with HCO_2H/HCHO: A solution of **21** (2 mmol) in formic acid (98%, 20 mmol) and aqueous formaldehyde (37%, 12 mmol) was heated at reflux for 2 h. Upon cooling, the mixture was basified with aqueous NaOH (1 M, pH = 10) and extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo.

Phenyl Derivatives: The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the bicyclic product **22a** as a mixture of two diastereoisomers in a 7:1 ratio (*de* = 75%) and the absence of the *N*,*N*-dimethylated product. Purification by column chromatography (light petroleum ether/ethyl acetate, 2:1) of the crude product gave, as the first R_f fraction, the minor diastereoisomer **(*R*$_{Fc}$,*S*)-22a** as a yellow/orange solid and, as the second R_f fraction, the major diastereoisomer **(*S*$_{Fc}$,*S*)-22a** as a yellow/orange solid with a total yield of 62% (0.45 g). **(*S*$_{Fc}$,*S*)-22a:** M.p. 70−71 °C (ethanol). $[\alpha]_D^{20}$ = +233.3 (*c* = 0.925, $CHCl_3$). ^{1}H NMR: δ = 1.86 (s, 3 H), 2.66 (dd, J_1 = 14.6, J_2 = 1.8 Hz, 1 H), 2.98 (dd, J_1 = 14.6, J_2 = 10 Hz, 1 H), 3.78 (d, J = 14.4 Hz, 1 H), 4.03 (br. t, 1 H), 4.10 (m, 1 H), 4.14 (m, 1 H), 4.16 (s, 5 H), 4.20 (m, 1 H), 4.48 (d, J = 14.4 Hz, 1 H) 7.19−7.36 (m, 5 H) ppm. ^{13}C NMR: δ = 33.6 (CH_2), 35.6 (CH_3), 57.0 (CH_2), 65.3, 69.4, 69.85, 70.5, 74.3 (CH), 83.15, 91.4 (C), 127.0, 127.7, 128.2 (CH), 143.5 (C) ppm. IR (CCl_4): ṽ = 1475, 3390 cm^{-1}. EI-MS: *m*/*z* = 363 [M$^+$], 348, 244, 121, 91, 56. $C_{20}H_{21}FeNS$ (363.07) calcd. C 66.10, H 5.83, N 3.86; found C 65.89, H 5.99, N 3.46. **(*R*$_{Fc}$,*S*)-22a:** ^{1}H NMR: δ = 2.26 (s, 3 H), 3.01−3.21 (m, 2 H), 3.48 (d, J = 15.2 Hz, 1 H), 4.03 (br. t, 1 H), 4.09 (br. t, 1 H), 4.14 (m, 2 H), 4.15 (s, 5 H), 4.20 (m, 1 H), 7.22−7.54 (m, 5 H) ppm. EI-MS: *m*/*z* = 363 [M$^+$], 348, 244, 121, 91, 56.

***tert*-Butyl Derivatives:** The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the bicyclic product **22b** as a mixture of two diastereoisomers in a 5.7:1 ratio (*de* = 70%) and the absence of the *N*,*N*-dimethylated product. Purification by column chromatography (ethyl acetate/light petroleum ether, 2:1) of the crude product gave, as the first fraction, the minor diastereoisomer **(*R*$_{Fc}$,*S*)-22b** as an orange solid and, as the second fraction, the major diastereoisomer **(*S*$_{Fc}$,*S*)-22b** as an orange solid and with a total yield of 58% (0.40 g). **(*S*$_{Fc}$,*S*)-22b:** M.p. 68−70 °C (ethanol). $[\alpha]_D^{20}$ = +208.4 (*c* = 0.80, $CHCl_3$). ^{1}H NMR: δ = 0.94 (s, 9 H), 1.93 (s, 3 H), 2.3 (d, J = 14.5 Hz, 1 H), 2.58 (dd, J_1 = 14.5, J_2 = 10.5 Hz, 1 H), 2.89 (d, J = 10.5 Hz, 1 H), 3.74 (d, J = 1 5.0 Hz, 1 H), 3.97 (br. t, 1 H), 4.07 (m, 1 H), 4.10 (s, 5 H), 4.14 (m, 1 H), 4.26 (d, J = 15.0 Hz, 1 H) ppm. ^{13}C NMR: δ = 26.9 (CH_2), 28.4 33.1 (CH_3), 36.1 (C), 58.8 (CH_2), 65.0, 69.6, 69.8, 70.6, 79.3 (CH), 76.2, 82.3 (C) ppm. IR (CCl_4): ṽ = 1475, 3390 cm^{-1}. EI-MS: *m*/*z* = 343 [M$^+$], 286, 244, 132, 91, 56. $C_{18}H_{25}FeNS$ (343.11) calcd. C 62.95, H 7.34, N 4.08; found C 62.68, H 7.44, N 4.19. A suitable crystal for X-ray analysis was obtained by crystallization from ethanol. **(*R*$_{Fc}$,*S*)-22b:** M.p. 58−60 °C (ethanol). $[\alpha]_D^{20}$ = −201.4 (*c* = 0.78, $CHCl_3$). ^{1}H NMR: δ = 0.95 (s, 9 H), 2.50 (s, 3 H), 2.63 (dd, J_1 = 12, J_2 = 3.2 Hz, 1 H), 2.95 (dd, J_1 = 15, J_2 = 3.2 Hz, 1 H), 3.42 (d, J = 16.4 Hz, 1 H), 3.54 (br. t, 1 H), 3.96 (br. s, 1 H), 4.03 (br. s, 1 H), 4.15 (s, 5 H), 4.19 (d, J = 16.4 Hz, 1 H), 4.24 (br. s, 1 H) ppm. EI-MS: *m*/*z* = 343 [M$^+$], 286, 244, 132, 56.

In a separate experiment, performed for a shorter reaction time (1 h), it was possible to isolate (beside the two diastereoisomers of **22b**) product **(*S*$_{Fc}$,*S*)-25b** as a single diastereoisomer in 23% yield. **25b:** ^{1}H NMR: δ = 0.89 (s, 9 H), 2.12 (dd, J_1 = 14, J_2 = 10 Hz, 1 H), 2.64 (dd, J_1 = 10 J_2 = 1.5 Hz, 1 H), 2.84 (dd, J_1 = 14 J_2 = 1.5 Hz, 1 H), 3.85 (d, J = 14.8 Hz, 1 H), 3.94 (br. t, 1 H), 4.01 (d, J = 14.8 Hz, 1 H), 4.10 (s, 5 H), 4.13 (br. s, 1 H), 4.14 (br. s, 1 H) ppm. ^{13}C NMR: δ = 27.05 (CH_3), 35.5 (C), 36.9, 49.2 (CH_2), 64.9, 68.9, 69.5, 69.8, 75.4 (CH), 83.1, 95.8 (C) ppm. EI-MS: *m*/*z* = 329 [M$^+$], 245, 91, 56. This product was subsequently methylated by the standard procedure to provide **(*S*$_{Fc}$,*S*)-22b** in 85% yield.

Isopropyl Derivatives: The ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the bicyclic product **22c** as a mixture of two diastereoisomers in a 2.4:1 ratio (*de* = 40%), and also the presence of the *N*,*N*-dimethylated product. Purification of the crude reaction mixture by column chromatography (ethyl acetate/light petroleum ether, 10:1 and then 3:1) gave as the first fraction the cyclic product **22c** (500 mg) as a brown solid in 75% yield as a mixture of two diastereoisomers and as the second fraction product **14c** as an orange solid (125 mg, 22%). The two isomers of **22c** were isolated by a second chromatography column (light petroleum ether/ethyl acetate, 10:1). **(*S*$_{Fc}$,*S*)-22c:** M.p. 93−94 °C (ethanol). $[\alpha]_D^{20}$ = +119.2 (*c* = 0.775, $CHCl_3$).^{1}H NMR (400 MHz): δ = 0.92 (d, J = 6.6 Hz, 3 H), 0.96 (d, J = 6.6 Hz, 3 H), 1.51 (m, 1 H), 1.80 (s, 3 H), 2.38 (dd, J_1 = J_2 = 14.4 Hz, 1 H), 2.39 (dd, 1 H, J_1 = J_2 = 14.7 Hz), 2.69 (br. t, J = 8.7 Hz, 1 H) 3.74 (d, J = 14.8 Hz, 1 H), 3.96 (br. t, 1 H), 4.08 (m, 1 H). 4.10 (s, 5 H), 4.14 (m, 1 H), 4.31 (d, J = 14.8 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 20.65, 20.8 (CH_3), 28.25 (CH_2), 30.6 (CH_3), 31.0 (CH), 56.9 (CH_2), 64.9, 69.5, 69.7, 70.5 (FcCH), 76.75 (CH), 82.2, 92.2 (FcC) ppm. IR (CCl_4): ṽ = 1480, 3399 cm^{-1} . EI-MS: *m*/*z* = 329 [M$^+$], 286, 244, 91, 56. $C_{17}H_{23}FeNS$ (329.09) calcd. C 61.99, H 7.04, N 4.26; found C 61.52, H 7.37, N 4.09. **(*R*$_{Fc}$,*S*)22c:** ^{1}H NMR (400 MHz): δ = 0.90 (d, J = 6.5 Hz, 3 H), 1.07 (d, J = 6.5 Hz, 3 H), 2.14 (s, 3 H), 2.34−2.55 (m, 2 H) 2.59 (m, 1 H), 2.77 (dd, J_1 = J_2 = 14.7 Hz, 1 H), 3.29 (d, J = 14.9 Hz, 1 H), 3.96 (br. t, 1 H), 4.06 (m, 1 H). 4.11 (s, 5 H + m, 1 H), 4.42 (d, J = 14.9 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 20.5 (CH_3), 27.1 (CH), 29.9 (CH_2), 40.3 (CH_3), 48.0 (CH_2), 65.3, 69.5, 70.0 (FCH), 70.4 (CH), 70.9 (FcCH) ppm. IR (CCl_4): ṽ = 1480, 3399 cm^{-1} . EI-MS: *m*/*z* = 329 [M$^+$], 286, 244, 91, 56. **(*S*)-2-(Dimethylamino)-1-(ferrocenylthio)-3-methylbutane (14c):** M.p. 39−41 °C (Et_2O). $[\alpha]_D^{20}$ = +22.4 (*c* = 1.04, $CHCl_3$). ^{1}H NMR: δ = 0.92, (d, J = 6.5 Hz, 6 H), 1.82 (m, 1 H), 2.25 (s, 6 H), 2.30 (m, 1 H), 2.55 (dd, J_1 = 4.7, J_2 = 13 Hz, 1 H), 2.77 (dd, J_1 = 6.5, J_2 = 13 Hz, 1 H), 4.18 (m, 2 H), 4.19 (s, 5 H), 4.30 (m, 2 H) ppm. ^{13}C NMR: δ = 19.9, 21.2 (CH_3), 29.7 (CH), 36.3 (CH_2), 41.4, 68.9, 68.9, 69.4, 69.7, 73.3, 73.35 (CH), 78.6 (C) ppm. IR (CCl_4): ṽ = 1480, 2780 cm^{-1}. EI-MS: *m*/*z* = 331 [M$^+$], 217, 100, 58. $C_{17}H_{25}FeNS$ (331.11) calcd. C 61.61, H 7.61, N 4.23; found C 61.58, H 7.64, N 4.28.

General Procedure for the Synthesis of β-Iminoalkyl Sulfides 23: A mixture of **21** (1 mmol) and freshly distilled benzaldehyde

(0.95 mmol) with $MgSO_4$ (100 mg) was stirred in CH_2Cl_2 (2 mL) until disappearance of the starting aminoalkyl sulfides. Filtration and concentration in vacuo gave the imines **23** as orange liquids. The imines were found to be unstable to chromatography, but were judged to be > 95% pure by ^1H NMR.

(*S*)-2-(Benzylideneamino)-1-(ferrocenylthio)-2-phenylethane (23a): Yield 90% (0.4 g). ^1H NMR: δ = 3.20 (br. d, 1 H), 3.48 (br. d, 1 H), 4.19 (s, 5 H), 4.23 (m, 2 H), 4.33 (m, 2 H), 4.66 (br. s, 1 H), 7.12−8.19 (m, 10 H), 8.45 (br. s, 1 H) ppm. ^{13}C NMR: δ = 43.3 (CH_2), 69.4, 69.4, 71.9, 73.5, 73.5 (CH), 127.3, 128.2, 128.8, 129.55, 130.6, 133.9, (ArCH), 127.95, 131.5 (ArC), 165.6 (CN) ppm. IR (CCl_4): $\tilde{\nu}$ = 1202, 1664 cm^{-1}. EI-MS: *m/z* = 425 [M^+], 317, 218, 69. HRMS calcd. for $C_{25}H_{23}FeNS$: 425.0901; found 425.0915. It was not possible to measure the optical rotation of **23a** because of the very intense red color of the solution.

(*S*)-2-(Benzylideneamino)-1-(ferrocenylthio)-3,3-dimethylbutane (23b): Yield 92% (0.38 g). ^1H NMR: δ = 0.95, (s, 9 H), 2.97 (br. d, 1 H), 3.26 (br. t, 1 H), 3.36 (br. d, 1 H), 4.14 (s, 5 H), 4.18 (m, 2 H), 4.23 (br. s, 1 H), 4.30 (br. s, 1 H), 7.45−7.94 (3m, 5 H), 8.26 (s, 1 H) ppm. ^{13}C NMR: δ = 26.4 (CH_3), 35.0 (C), 36.2 (CH_2), 69.5, 69.6, 69.9, 73.4, 73.55, 77.3 (CH), 129.6, 132.5, 136.5 (ArCH), 136.3 (ArC), 169.9 (CN) ppm. IR (CCl_4): $\tilde{\nu}$ = 1652 cm^{-1}. EI-MS: *m/z*: 405 [M^+], 317, 217, 121, 86. HRMS calcd. for $C_{23}H_{27}FeNS$: 405.1214; found 405.1245. It was not possible to measure the optical rotation of **23b** because of the very intense red color of the solution.

(*S*)-2-(Benzylideneamino)-1-(ferrocenylthio)-3-methylbutane (23c): Yield 95% (0.38 g). $[\alpha]_D^{20}$ = +138.8 (*c* = 1.52, $CHCl_3$). ^1H NMR: δ = 0.86, (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 1.95 (m, 1 H), 2.85−3.05 (m, 3 H), 4.15 (s, 5 H), 4.15 (m, 2 H), 4.28 (m, 2 H), 7.43 (m, 3 H,), 7.78 (m, 2 H), 8.20 (s, 1 H) ppm. ^{13}C NMR: δ = 18.3, 19.8 (CH_3), 32.5 (CH), 42.0 (CH_2), 68.7, 68.9, 69.4, 69.4, 73.2, 73.3, 76.3 (CH), 128.3, 128.45, 130.4 (ArCH), 136.3 (ArC), 160.1 (CN) ppm. IR (CCl_4): $\tilde{\nu}$ = 1648 cm^{-1}. EI-MS: *m/z* = 391 [M^+], 326, 217, 160. HRMS calcd. for $C_{22}H_{25}FeNS$: 391.1057; found 391.1048.

General Procedure for the Palladium-Catalyzed Allylic Substitution (Conditions A): A solution of allylpalladium chloride dimer (9.1 mg, 0.025 mmol) and ligand (0.025 mmol) in THF (2 mL) was degassed by three freeze-evacuate-thaw cycles and then stirred at room temperature for 30 min. The acetate **26** (252 mg, 1.0 mmol) and the sodium dimethyl malonate [prepared by addition of dimethyl malonate (198 mg, 1.5 mmol) to prewashed (hexane, 3 × 10 mL) NaH (60% dispersion in mineral oil, 1.6 mmol)] were then added and the resulting mixture was again degassed by three freeze-evacuate-thaw cycles. The stirring was maintained for 80 h, aqueous NH_4Cl was then added, and the mixture was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (ethyl acetate/light petroleum ether, 5:1) gave **27**[20,23] as clear oil that solidified on standing. The ligand could be recovered in almost quantitative yield. The *ee* was determined by ^1H NMR with $Eu(hfc)_3$ (10^{-3} M in $CDCl_3$) as chiral shift reagent.

General Procedure for the Palladium-Catalyzed Allylic Substitution (Conditions B): A solution of the acetate **26** (252 mg, 1.0 mmol), allylpalladium chloride dimer (9.1 mg, 0.025 mmol), and ligand (0.1 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 15 min, and a solution of dimethyl malonate (396 mg, 3.0 mmol) and *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 0.74 mL, 3.0 mmol) in CH_2Cl_2 (1 mL) was then added dropwise, followed by potassium acetate (2.5 mg, 0.03 mmol). The reaction mixture was degassed by three freeze-evacuate-thaw cycles and stirred at room temperature for the time reported in Table 1 (until disappearance of the starting acetate **26**). Aqueous NH_4Cl was added, and the mixture was extracted with Et_2O. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (ethyl acetate/light petroleum ether, 5:1) gave compounds **27**[20,23] as clear oils that solidified on standing. The ligand could be recovered in almost quantitative yield except in the case of the imine derivatives **23**. The *ee*s were determined by ^1H NMR with $Eu(hfc)_3$ as chiral shift reagent (10^{-3} M in $CDCl_3$).

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[16] X-ray crystallography data for **20b**: $C_{18}H_{25}FeNS$, M_r = 343.30, orange prismatic crystal, 0.80 × 0.15 × 0.10 mm, orthorhombic, space group $P2(1)2(1)2(1)$, a = 7.0602(4), b = 10.9158(7), c = 22.4177(14) Å, d = 1.320 g/cm^3, V = 1727.68(18) Å^3, Z = 4, 23255 reflections collected, 5047 unique (R_{int} = 0.0432), $R1$ = 0.0553 [$I > 2\sigma(I)$], $wR2$ = 0.1563 for all data. All crystal data were collected with a Bruker SMART 2000 diffractometer at 293 K with graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined with full-matrix, least squares (G. M. Sheldrick, SHELX97, Crystal structure determination program, Göttingen, **1997**). Non-hydrogen atoms were refined anisotropically, with the exception of the carbon atoms on the free Fc ring, which were disordered and split in two positions, using distance and anisotropic displacement parameter restraints. Hydrogen atoms were set geometrically. CCDC-179909 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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