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Enantiocontrolled Preparation of the First Stable α-Ferrocenylalanine Derivatives

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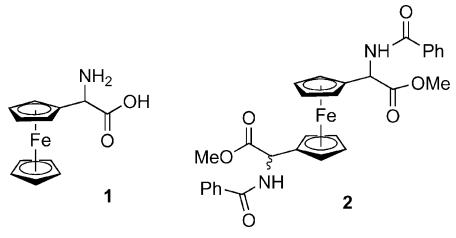
An enantiocontrolled synthesis of α-ferrocenylalanine methyl ester (*S*)-**24** and of the corresponding *N*-Boc derivative (*S*)-**25** is presented. We have found that an important source of instability for α-ferrocenyl-α-amino acid derivatives is the high reactivity of the α-hydrogen, and its replacement by a methyl group has proven to be essential for the stability of these compounds. The synthesis of (*S*)-**24** requires only six steps from the readily available 2-propenylferrocene which is converted into the diol (*S*)-**16** by Sharpless catalytic dihydroxylation. Regio- and stereoselective azide substitution of the tertiary hydroxy group affords the azido diol (*S*)-**17**. Swern oxidation gives the corresponding aldehyde which is smoothly oxidized to the carboxylic ester by means of the Smith–Kozlowski protocol. Transesterification and azide reduction lead to the α-amino ester (*S*)-**24** in a good overall yield and enantiomeric purity. A cyclic voltammetric study of this compound showed that oxidation takes place by a simple reversible one-electron-transfer process. Half a century after the initial unsuccessful attempts to obtain ferrocenylglycine, this is the first synthesis of a stable α-amino acid derivative incorporating a ferrocene unit at the α-position.

Introduction

The bioorganometallic chemistry of ferrocene is nowadays a very active field of research.[1] The chemical stability in aqueous and oxygenated media, the ready availability, and the electrochemical properties characteristic of ferrocene derivatives have fostered an increasing number of applications in biology, medicinal chemistry, and molecular biotechnology.[2] In this context, the incorporation of the ferrocenyl moiety into amino acids, peptides, and proteins occupies a preeminent position and in fact the starting point for the bioorganic chemistry of ferrocene can be traced to the preparation of racemic β-ferrocenylalanine in 1957,[3] only a few years after the seminal discovery of ferrocene.[4] Since then, a number of ferrocenyl-based amino acids have been prepared, both in racemic and in highly enantiopure form, and have been incorporated into peptidic chains.[1a,2i,5] It is worth noting, however, that the simplest α-amino acid with a metallocene side-chain, ferrocenylglycine (**1**), is still an unknown compound. Its preparation was attempted independently in 1957, both by Schlögl[3a] and by Graham et al.,[6] but attempted hydrolysis of the already unstable ferrocenylhydantoin to **1** led only to decomposition products. The instability associated with the α-ferrocenyl-α-amino acid subunit was again showcased more than four decades later when Beck and co-workers[7] found that the 1,1′-ferrocenylenebis(glycine) derivative **2**, obtained as a 1:1 diastereomeric mixture, was very air- and light-sensitive and could only be purified by column chromatography under argon and by the exclusion of light. The authors attributed this instability to photoinduced coordination of the ester groups to the metal center followed by a η^5-to-η^4 rearrangement.[7] No other reports can be found in the chemical literature, to the best of our knowledge, concerning the preparation of **1** or its derivatives, or of an α-amino acid incorporating a ferrocenyl substituent at the α-position. In summary, half a century after the first unsuccessful assays devoted to the synthesis of ferrocenylglycine, serious doubts remain concerning the intrinsic stability of the α-ferrocenyl-α-amino acid structural motif.



In the course of our research into the scope and applications of the catalytic asymmetric dihydroxylation of vinylferrocenes,[8] we have developed efficient, enantioselective

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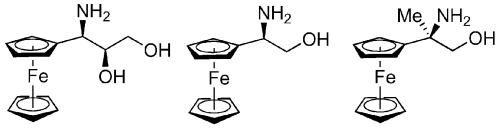
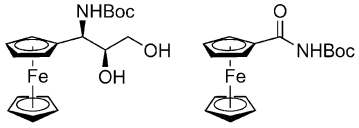
routes to the previously unknown 2-amino-2-ferrocenylalkanols **3**–**5**.[8a,8e] It appeared to us that these compounds, or some of their derivatives, could be suitable precursors of the α-ferrocenyl-α-amino acid structure upon application of well-known oxidative protocols. We disclose in this paper the full details of this approach which has resulted in the preparation of the first stable, totally characterized α-ferrocenylalanine derivatives.



(2*S*,3*S*)-**3** (*S*)-**4** (*S*)-**5**

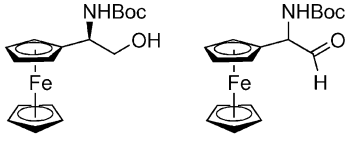
Results and Discussion

In our first attempts to obtain an α-ferrocenyl-α-amino acid, the *N*-protected amino diol **6**[8a] was submitted to several standard oxidative protocols ($NaIO_4$/cat. $RuCl_3$, $NaIO_4$/cat. $KMnO_4$, $NaIO_4/NaClO_2$),[9] but the formation of very complex product mixtures was observed. In some of these reactions, the formation of a ferrocenyl carboxamide derivative **7** was inferred from spectroscopic data.



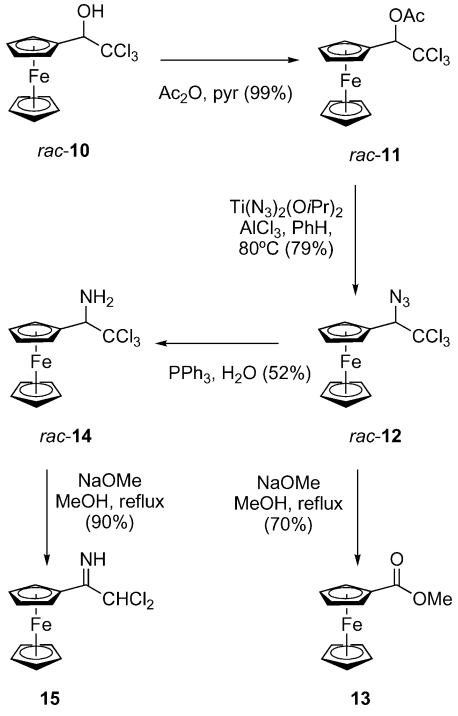
(2*S*,3*S*)-**6** **7**

The sensitivity of the β-amino-β-ferrocenyl alcohol moiety to oxidative conditions was evinced when, upon attempted Swern oxidation[10] of *N*-Boc-2-amino-2-ferrocenylethanol [(*S*)-**8**], a complex mixture of products was also obtained in which the expected aldehyde **9** could not be detected.[11]



(*S*)-**8** **9**

In the light of these unwelcome results, we decided to explore the feasibility of a nonoxidative approach, such as the Corey–Link procedure,[12] to ferrocenylglycine (**1**). To this end, racemic 1-ferrocenyl-2,2,2-trichloroethanol (**10**), easily obtained from ferrocenecarbaldehyde,[13] was treated with 2 mol equiv. of sodium azide in an aqueous sodium hydroxide solution,[12] a protocol that resulted in extensive decomposition of the starting material. A stepwise approach (Scheme 1) was next investigated. The acetylation of **10** afforded the ester **11** in quantitative yield, but this compound was recovered unchanged when submitted to standard azide nucleophilic substitution conditions.[8a] After considerable experimentation, we found that the trichloro azide **12** could be obtained in good yield upon treatment of **11** with titanium diazido(diisopropoxide)[14] and aluminium trichloride in refluxing benzene.[15] All of our attempts to convert the trichloromethyl group in **12** into a methoxycarbonyl moiety by treatment with methanol under acidic[16] or basic[17] conditions were unsuccessful, leading either to the recovery of the starting reagent or to the formation of methyl ferrocenecarboxylate (**13**). A change in the order of the alcoholysis and reduction steps was to no avail as the reaction of the 2,2,2-trichloroethylamine **14** (obtained in 52% yield by triphenylphosphane-mediated reduction of the azide **12**) with sodium methoxide in refluxing methanol afforded a relatively stable compound to which, in accord with spectral evidence, we assigned the structure of the imine **15** instead of the expected ferrocenylglycine methyl ester.



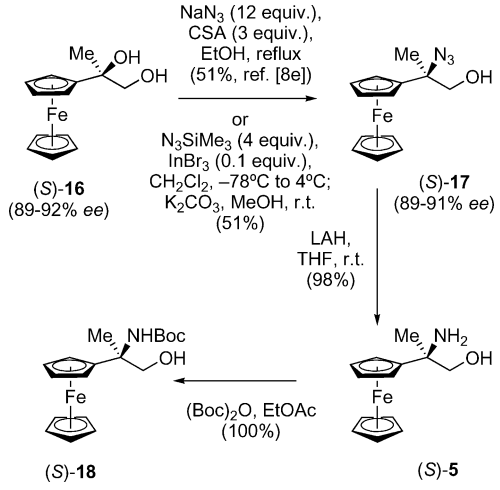
rac-**10** *rac*-**11** *rac*-**12** *rac*-**14** **15** **13**

Scheme 1. Attempted synthesis of methyl ferrocenylglycinate from 1-ferrocenyl-2,2,2-trichloroethanol (**10**).

At this point we reasoned that our efforts to access an α-ferrocenyl-α-amino acid had been thwarted by the high reactivity of the α-ferrocenyl CH bond, due in turn to the well-known ability of ferrocene to stabilize an adjacent positive charge or an unpaired electron,[18] which had led to the formation of the α-unsaturated derivatives **7**, **13**, and **15**.

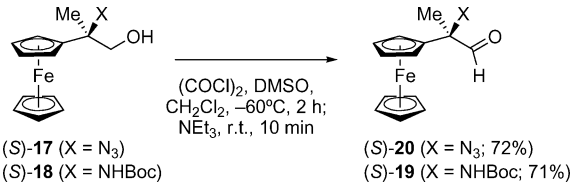
Our next goal was therefore the suppression of this source of instability, and we turned our attention to the synthesis of α-methyl-α-ferrocenyl glycine derivatives from 2-amino-2-ferrocenylpropanol (**5**). As we have previously described,[8e] the efficient enantioselective preparation of this compound relies on the direct azide substitution of the

tertiary hydroxy in (*S*)-2-ferrocenyl-1,2-propanediol (**16**; obtained in 89–92% *ee* by the catalytic asymmetric dihydroxylation[19] of 2-ferrocenylpropene) to give the corresponding azido alcohol (*S*)-**17** with minimum racemization. This can be achieved by treatment of **16** with a large excess (12 mol-equiv.) of sodium azide in refluxing ethanol in the presence of camphorsulfonic acid (CSA, 3 mol-equiv.). We have now found that this transformation can also be achieved by the reaction of **16** with azidotrimethylsilane (4 mol-equiv.) in dichloromethane at –78 °C under catalysis by indium tribromide[20] followed by methanolysis of the intermediate silyl ether (Scheme 2). In this way, highly enantiopure (89–91% *ee*) azido alcohol (*S*)-**17** can be reproducibly obtained in a moderate yield (51%). The reduction of (*S*)-**17** with lithium aluminium hydride afforded in essentially quantitative yield the amino alcohol (*S*)-**5**[8e] which was uneventfully converted into the *N*-Boc derivative (*S*)-**18** (Scheme 2).



Scheme 2. Synthesis of amino alcohol (*S*)-**5**.

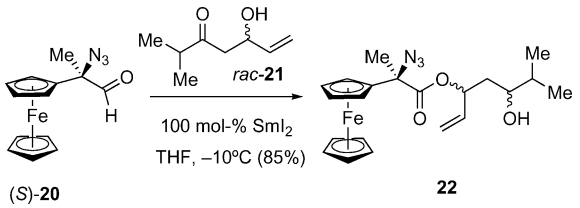
With this compound in our hands, we could perform a first test of our hypothesis that the substitution of the α-ferrocenyl hydrogen by a methyl group would lead to enhanced stability of the compounds towards oxidative conditions. We were pleased to find that the Swern oxidation of (*S*)-**18**, contrary to what we had observed in the case of (*S*)-**8**, and following the protocol described by Hakateyama et al.,[21] led to the isolation of the relatively unstable aldehyde (*S*)-**19** in good yield (71%). In a similar way, the oxidation of (*S*)-**17** afforded the more stable aldehyde (*S*)-**20** with comparable efficiency (Scheme 3).



Scheme 3. Preparation of aldehydes (*S*)-**19** and (*S*)-**20**.

These encouraging results impelled us to assay the oxidation of aldehydes (*S*)-**19** and (*S*)-**20** to the corresponding carboxylic acids. However, when both compounds were submitted to a variety of selective, reliable procedures for their conversion into carboxylic acids ($KMnO_4$/phosphate buffer,[22] $NaClO_2$/2-methyl-2-butene,[23] MCPBA/CH_2Cl_2,[24] NBS/AIBN/refluxing CCl_4[25]) or to methyl carboxylates (I_2/methanolic KOH),[26] we observed no reaction in the latter case and oxidative decarbonylation leading to acetylferrocene and other degradation products in the former case.

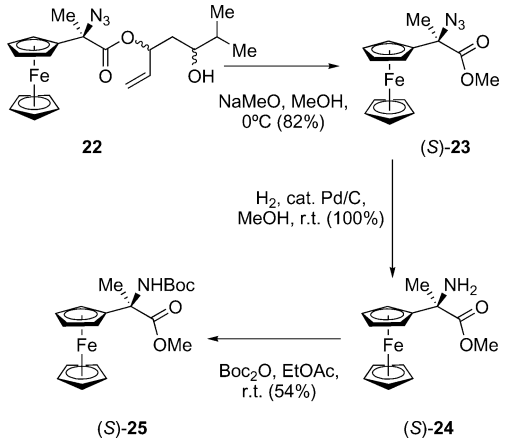
In view of the extreme lability of our substrates, we reasoned that the method of choice should involve an intramolecular hydride transfer so we turned our attention to a procedure disclosed by Smith and Kozlowski and co-workers for the oxidation of aldehydes containing electron-rich heteroatoms.[27] This methodology relies on the use of the Evans–Tishchenko reaction[28] in which a samarium species catalyzes the oxidation of aldehydes by hydride transfer to a sacrificial hydroxy ketone in an intermediate hemiacetal. To our delight, when a solution of aldehyde (*S*)-**20** and ketone *rac*-**21** (prepared by aldol addition of 3-methyl-2-butanone to propenal)[27] in dry tetrahydrofuran was treated at –10 °C with a 20% molar amount of samarium diiodide, the desired ester **22** (ca. 2:1 diastereomeric mixture) was isolated in 16% yield after chromatographic purification. We verified that the yield of **22** was proportional to the quantity of samarium promoter and in fact a mixture of hydroxy esters **22** was obtained in 85% yield when using a molar equivalent of samarium diiodide [or triiodide; we found that similar results could be obtained with oxidized, yellow-colored solutions containing mainly samarium(III) species; Scheme 4]. On the other hand, no reaction was observed when aldehyde (*S*)-**19** was submitted to the same conditions, probably as a result of the preferential coordination of samarium cations to the carbamate moiety which prevents the formation of the samarium-bonded reactive hemiacetal intermediate.[28]



Scheme 4. Smith–Kozlowski oxidation of aldehyde (*S*)-**20**.

When the mixture of esters **22** was treated with sodium methoxide in cold methanol, the methyl ester (*S*)-**23** was obtained in 82% yield. This compound was quantitatively hydrogenated to the α-amino ester (*S*)-**24** which was subsequently converted into the *N*-protected derivative (*S*)-**25** (Scheme 5).

Compounds (*S*)-**23**–(*S*)-**25** were isolated as orange-colored oils which showed no decomposition when stored in the refrigerator for prolonged periods of time and gave sat-



Scheme 5. Preparation of esters (*S*)-**23**–(*S*)-**25**.

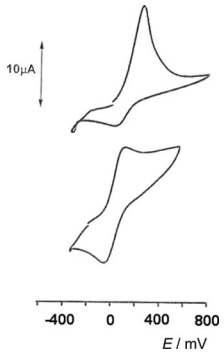
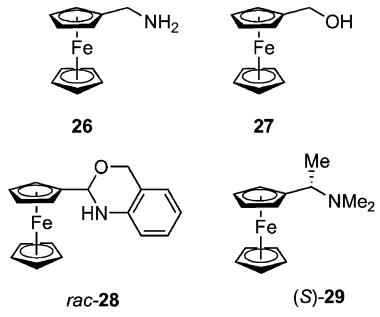


Figure 1. Cyclic voltammograms of compounds (*S*)-**24** (bottom) and (*S*)-**25** (top) at 298 K in acetonitrile at a scan rate v = 100 mV s^{-1}.

isfactory IR, NMR, MS, and HMRS data. All our attempts to isolate the corresponding carboxylic acids from these compounds (by saponification with LiOH/aqueous methanol)[27] met with failure as instantaneous decomposition of the reaction product to acetylferrocene was observed in all instances. Thus, it appears that although the α-amino- or α-azido-ferrocenylacetic acids show an intrinsic instability, the corresponding esters are perfectly stable and both (*S*)-**24** and (*S*)-**25** are the first derivatives of an α-ferrocenyl-α-amino acid that have been isolated in a pure state and adequately characterized. They also represent the sole examples of α-methyl-α-amino acid derivatives (a class of unnatural amino acid analogues that have received considerable interest due to their unique conformational and biological properties)[29] that incorporate a metallocenyl sidechain.

Electrochemical data for compounds (*S*)-**24** and (*S*)-**25** were obtained by cyclic voltammetric studies of freshly prepared solutions (10^{-3} M) in acetonitrile using [Bu_4N^+][PF_6^-] as the supporting electrolyte. The cyclic voltammogram of (*S*)-**25** (Figure 1, top) showed an anodic peak at 259 mV; the peak due to the reduction process was not clearly defined and its intensity was smaller than that of the anodic peak. According to the literature,[30] these findings indicate that the oxidation of this compound proceeds through an irreversible electrochemical process. After several runs even the anodic peak became broader and less intense which suggests that decomposition of the product takes place after the oxidation process. The electrochemical behavior of (*S*)-**24** is markedly different to that of (*S*)-**25**. The cyclic voltammogram (Figure 1, bottom) showed an anodic peak with a directly associated reduction in the reverse scan. The experiments were carried out at different scan rates v (from 10 to 100 V s^{-1}) and a linear relationship between I_{pa} and $v^{1/2}$ was obtained. These observations are consistent with those expected for a simple reversible one-electron-transfer process.[30] For (*S*)-**24**, the ΔE value departs appreciably from the constant value of 59 mV (theoretically expected for an electrochemical reversible one-electron oxidation–reduction process[30]) which suggests that structural reorganization takes place on oxidation.

In order to elucidate the effect induced by substituents on the α-carbon upon the proclivity of the ferrocenyl moiety to oxidize, we also compared the electrochemical behavior of (*S*)-**24** and (*S*)-**25** with that reported for ferrocenylmethanamine (**26**),[31] ferrocenylmethanol (**27**),[32] and *rac*-2-ferrocenyl-2,4-dihydro-1*H*-1,3-benzoxazine (**28**).[33] For comparison purposes, an electrochemical study based on the cyclic voltammetry of the commercially available (*S*)-Ugi's amine[34] [(*S*)-(**29**)] was also carried out.



Except for compound **27**, which associates to form dimeric species in acetonitrile,[32] for the remaining products, the data presented in Table 1 reveal that the E_{pa} values increase according to the sequence **29** < **26** < **28** < **24** < **25**. Previous electrochemical studies of ferrocene derivatives have shown that the proclivity of iron(II) to undergo oxidation depends on the electronic nature of the α-substituents;[35] whereas electron-withdrawing groups produce an increase in the E_{pa} value relative to that of ferrocene, electron-donating groups have the opposite effect. Consequently the sequence presented above reflects an increase in the electron-withdrawing character of the substituents on the α-carbon atom.

Thus, the differences detected in the positions of the anodic peaks for (*S*)-**24** and (*S*)-**25** (Table 1, entries 1 and 2) indicate that the ferrocenyl moiety is less prone to oxidation in the latter compound, in accordance with the diminished electron-releasing capability of a carbamate with respect to that of an amino group. On the other hand, the differences detected in the E_{pa} values of (*S*)-**24** and ferrocenylmethanamine[31] (**26**) under identical experimental conditions

Table 1. Summary of electrochemical data (anodic and cathodic potentials referenced to the ferrocene/ferricinium couple and separation of the peaks, in mV) for the compounds under study and related derivatives obtained under identical experimental conditions.

Entry	Compound	E_{pa} [mV][a]	E_{pc} [mV] [b]	ΔE [mV] [c]	$E^1/_2$ [mV][d]	Ref.
1	(*S*)-**24**	110	–8	118	59	this work
2	(*S*)-**25**	259	_[e]	_[e]	_[e]	this work
3	**26**	10	–60	70	–25	[31]
4	**27**	–0.017, 0.093[f]	_[f,g]	_[f,g]	_	[32]
5	*rac*-**28**	102	23	79	63	[33]
6	(*S*)-**29**	–5	–91	86	48	this work

[a] Anodic potential referenced to the ferrocene/ferricinium couple. [b] Cathodic potential referenced to the ferrocene/ferricinium couple. [c] Peak separation. [d] Half-wave potentials. [e] The process is electrochemically irreversible and the position of the cathodic peak in the reverse scan (see Figure 1, top) was not clearly defined. [f] In this case, two poorly resolved ferrocene-based waves were obtained in acetonitrile. This finding has been attributed to the formation of dimeric species in this solvent.[32] [g] The corresponding peaks were not observed.

(entries 1 and 3, respectively) are consistent, according to the literature, with the strong electron-withdrawing ability of the methoxycarbonyl group, whereas the negative E_{pa} value of (*S*)-**29** (entry 6) reflects the weak electron-releasing character of the methyl substituent. Finally, the similarity between the electrochemical behavior of (*S*)-**24** and *rac*-**28** (entry 5) suggests that the combined effect produced simultaneously by the three substituents on the stereogenic carbon atom of **24** (methyl, amino, and methoxycarbonyl) is clearly electron-withdrawing and roughly comparable to that of the dihydrobenzoxazine group in **28**.

Conclusions

In summary, after exploring a variety of synthetic approaches, we have shown that an important source of instability for α-ferrocenyl-α-amino acid derivatives is the high reactivity of the α-hydrogen atom, and that the application of very mild oxidation protocols (Swern and Smith–Kozlowski) to (*S*)-2-ferrocenyl-2-azidopropanol has allowed the isolation and characterization of an α-ferrocenylalanine ester for the first time. The corresponding carboxylic acid, however, appears to be intrinsically unstable. The synthetic route involves six steps starting from the readily available 2-ferrocenylpropene and leads to the (*S*) enantiomer of methyl α-ferrocenylalaninate in around 90% *ee*. Given that the source of chirality is the Sharpless asymmetric dihydroxylation process, the (*R*) enantiomer of the same compound should be easily accessible by this procedure. These results pave the way for the conjugation of the α-ferrocenyl-α-amino acid structural unit with biologically important compounds.

Experimental Section

General: Melting points were recorded with a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet 510 FT spectrometer as NaCl films or in KBr pellets. Only the most representative wavenumbers are reported. NMR spectra were recorded in $CDCl_3$ solution, unless otherwise specified. ^1H (200, 300, and 400 MHz) and ^{13}C NMR (50.3, 75.5, and 100.6 MHz) were obtained with a Varian Gemini, Varian Unity and Mercury 400 spectrometers, respectively. Chemical shifts δ are quoted in ppm and referenced to internal TMS for ^1H NMR and to $CDCl_3$ (δ = 77.0 ppm) for ^{13}C NMR. Coupling constants J are quoted in Hertz [Hz]. The data are reported as follows: s singlet, d doublet, t triplet, m multiplet, br. broad. Low-resolution chemical ionization (CI) mass spectra were recorded with an HP-5988A or a VG-Platform spectrometer. High-resolution mass spectra (HRMS) were recorded at the "Unidad de Espectrometría de Masas de la Universidad de Santiago de Compostela". Elemental analyses were performed by the "Servicios Xerais de Apoio á Investigación" (Universidad de La Coruña, Coruña, Spain). Reactions were run in flame- or oven-dried glassware under N_2 or Ar. Commercially available reagents were used as received. Solvents were dried by standard techniques: benzene was distilled from sodium; tetrahydrofuran was distilled from sodium/benzophenone ketyl; dichloromethane was distilled from calcium hydride. Silica gel (0.063–0.200 mm) was used for chromatography.

1-Ferrocenyl-2,2,2-trichloroethyl Acetate (11): A solution of 1-ferrocenyl-2,2,2-trichloroethanol (**10**)[12] (282 mg, 0.85 mmol) and acetic anhydride (0.40 mL, 4.2 mmol) in anhydrous pyridine (1 mL) was stirred overnight at room temp. under nitrogen. The volatiles were eliminated in vacuo (1 Torr, 5 h, room temp.) to afford the expected acetate **11** (316 mg, 99% yield) as an orange-colored solid, m.p. 106.5–107.5 °C. IR (KBr): $\tilde{\nu}$ = 3102, 2952, 1762, 1374, 1218, 1050, 801 cm^{-1}. ^1H NMR (200 MHz): δ = 2.33 (s, 3 H, $COCH_3$), 4.15 (s, 5 H, 5 CH Cp2), 4.26 (m, 2 H, CH Cp1), 4.46 (d, J = 1.6 Hz, 1 H, CH Cp1), 4.51 (d, J = 2.2 Hz, 1 H, CH Cp1), 6.34 (s, 1 H, C*H*OAc) ppm. ^{13}C NMR (50.3 MHz): δ = 21.0 (CH_3), 67.6 (CH), 68.3 (CH), 68.5 (CH), 69.0 (CH), 71.0 (CH), 79.9 (CHO), 81.0 (C Fc), 99.5 (CCl_3), 169.0 (CO) ppm. MS (CI, NH_3): *m*/*z* (%) = 374/376/378 (4/3/1) $[M]^+$, 315/317/319/321 (100/93/33/4) $[M - OAc]^+$. HRMS (CI, NH_3): calcd. for $C_{14}H_{13}{}^{35}Cl_3FeO_2$ $[M]^+$ 373.9331; found 373.9329. $C_{14}H_{13}Cl_3FeO_2$ (375.46): calcd. C 44.79, H 3.49; found C 44.87, H 3.52.

(1-Azido-2,2,2-trichloroethyl)ferrocene (12): A solution of trichloroethyl acetate (**11**) (400 mg, 1.10 mmol) in dry benzene (6 mL) was added with the aid of a cannula to a stirred suspension of diazido(diisopropoxido)titanium[14] (1.60 g, 6.4 mmol) in refluxing anhydrous benzene (10 mL) under argon. To the resulting mixture, under a flow of argon, aluminium trichloride (0.57 g, 4.25 mmol) was added in one portion. The color of the solution changed immediately from orange to dark-green, indicative of the formation of a ferrocenylmethyl cation; this color remained for several hours. Reflux was maintained for 16 h before the mixture was cooled to room temp. and the contents of the reaction flask were poured over a stirred mixture of 5% aqueous sulfuric acid (40 mL) and dichloromethane (80 mL). Stirring was maintained for 1 h, until a clear orange-colored organic phase was observed. The aqueous phase was separated and washed with dichloromethane (3 × 20 mL). The combined organic phase was dried with sodium sulfate and the solvents were removed under reduced pressure to afford 302 mg (79% yield) of the azide **12** (orange-colored oil) which decomposed extensively upon attempted chromatographic purification. IR (film): $\tilde{\nu}$ = 2925, 2113, 1656, 1304, 801 cm^{-1}. ^1H NMR (300 MHz): δ = 4.28 (s, 5 H, 5 CH Cp2), 4.29 (m, 2 H, CH Cp1), 4.48 (m, 2 H, CH Cp1), 4.85 (s, 1 H, CHN) ppm. ^{13}C NMR (75.5 MHz): δ = 68.1 (CH), 68.2 (CH), 69.1 (CH), 71.3 (CH), 77.4 (CHN), 82.2 (C Fc), 101.3 (CCl_3) ppm. MS (CI, NH_3): *m*/*z* (%) = 357/359/361/363

(20/18/6/1) $[M]^+$, 315/317/319/321 (100/95/35/5) $[M - 27]^+$. HRMS (CI, NH_3): calcd. for $C_{12}H_{10}{}^{35}Cl_3FeN_3$ $[M]^+$ 356.9290; found 356.9298. $C_{12}H_{10}Cl_3FeN_3$ (358.44): calcd. C 40.21, H 2.81, N 11.72; found C 40.01, H 2.97, N 11.65.

1-Ferrocenyl-2,2,2-trichloroethylamine (14): Triphenylphosphane (239 mg, 0.91 mmol) and water (16.5 mL, 0.91 mmol) were added sequentially to a stirred solution of trichloroethyl azide **12** (326 mg, 0.91 mmol) in tetrahydrofuran (4.5 mL) and the resulting mixture was stirred at room temp. under nitrogen for 19 h. After diluting with water (3 mL), the solution was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were dried with sodium sulfate and evaporated under reduced pressure to give a crude product which, upon chromatographic purification (2.5% v/v SiO_2/NEt_3, hexanes/ethyl acetate mixtures as eluent), gave 128 mg (52% yield) of the trichloroethylamine **14** as an orange-colored solid, m.p. 65.0–67.5 °C. IR (KBr): $\tilde{\nu}$ = 3380, 3100, 1305, 1220, 1060, 1005 cm^{-1}. ^1H NMR (300 MHz): δ = 2.28 (br. s, 2 H, NH_2), 4.22 (s, 5 H, 5 CH Cp2), 4.23 (m, 2 H, CH Cp1), 4.36 (m, 2 H, CH Cp1), 4.47 (s, 1 H, CHN) ppm. ^{13}C NMR (75.5 MHz): δ = 66.8 (CH), 67.8 (CH), 68.1 (CH), 68.3 (CH), 69.0 (CH), 71.4 (CHN), 84.9 (C Fc), 104.9 (CCl_3) ppm. MS (CI, NH_3): *m*/*z* (%) = 349/351/353/355 (16/15/5/1) $[M + 18]^+$, 332/334/336/338 (100/89/29/3) $[M + 1]^+$, 315/317/319/321 (47/89/29/3) $[M - NH_2]^+$. HRMS (CI, NH_3): calcd. for $C_{12}H_{12}{}^{35}Cl_3FeN$ $[M]^+$ 330.9385; found 330.9378. $C_{12}H_{12}Cl_3FeN$ (332.44): calcd. C 43.36, H 3.64, N 4.21; found C 43.20, H 3.62, N 3.65.

2,2-Dichloro-1-ferrocenylethylideneamine (15): A freshly prepared 1.7 M solution of sodium methoxide in methanol (0.34 mL, 0.57 mmol) was added with the aid of a syringe to a stirred solution of the trichloroethylamine **14** (44 mg, 0.13 mmol) in anhydrous methanol (0.6 mL) under argon. The resulting mixture was heated at reflux for 3.5 h (TLC monitoring). After cooling to room temp., the mixture was diluted with ethyl acetate (1 mL) and washed with brine (2 × 1 mL). The organic layer was dried with sodium sulfate and the solvents evaporated in vacuo to afford 35 mg (90% yield) of a dense brown-orange oil that decomposed upon attempted chromatographic purification and to which we assigned the structure of 2,2-dichloro-1-ferrocenylethylideneamine. IR (film): $\tilde{\nu}$ = 3097, 2927, 1619, 1459, 1108, 1054 cm^{-1}. ^1H NMR (200 MHz): δ = 3.23 (s, 1 H, NH), 4.28 (s, 5 H, 5 CH Cp2), 4.70 (m, 2 H, CH Cp1), 4.91 (m, 2 H, CH Cp1), 6.37 (s, 1 H, $CHCl_2$) ppm. ^{13}C NMR (75.5 MHz): δ = 68.0 (CH), 70.3 (CH), 70.6 (CH), 73.8 (CH), 86.9 (C Fc), 164.6 (C=N) ppm. MS (CI, NH_3): *m*/*z* = 313/315/317 (8/7/3) $[M + 18]^+$, 296/298/300/302 (100/99/30/2) $[M + 1]^+$. HRMS (CI, NH_3): calcd. for $C_{12}H_{11}{}^{35}Cl_2FeN$ $[M]^+$ 294.9618; found 294.9626.

(*S*)-2-Azido-2-ferrocenylpropanol[8e] [(*S*)-17]: A cold (–78 °C) solution of (*S*)-2-ferrocenyl-1,2-propanediol [(*S*)-**16**][8e] (79 mg, 0.30 mmol, 89% *ee*) and azidotrimethylsilane (0.17 mL, 1.2 mmol) in dry dichloromethane (5 mL) was added dropwise to a cold (–78 °C), stirred solution of indium tribromide (10 mg, 0.03 mmol) in dry dichloromethane (2 mL) under nitrogen and stirring was maintained at the same temperature for 2 h. At this point, the reaction vessel was stored in the refrigerator overnight (4 °C). After addition of water (7 mL), the reaction mixture was extracted with diethyl ether (3 × 10 mL). The organic phase was dried with magnesium sulfate and the solvent was removed under reduced pressure. The resulting brown-colored oil was taken up in methanol (3 mL) and stirred at 0 °C for 1 h after the addition of potassium carbonate (63 mg, 0.46 mmol). The mixture was diluted with water (5 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic phases were dried with magnesium sulfate and evaporated under reduced pressure. Chromatographic purification (silica gel, 95:5 hexanes/ethyl acetate) gave the title compound (43 mg, 51% yield) as a yellow-colored oil, whose spectroscopic data coincided with those previously described by us.[8e] The enantiomeric excess of (*S*)-**17**, checked by HPLC (Chiralcel® OD column, 90:10 hexane/isopropyl alcohol, 0.5 mL min^{-1}, λ = 220 nm) was 89% [$t_R(R)$ = 18.2 min, $t_R(S)$ = 21.3 min]. $[\alpha]_D$ = +41.9 (*c* = 0.86, CH_2Cl_2).

(*S*)-2-(*tert*-Butoxycarbonylamino)-2-ferrocenylpropanol [(*S*)-18]: A solution of bis(*tert*-butyl) dicarbonate (200 mg, 0.91 mmol) in ethyl acetate (1 mL) was added dropwise to a stirred solution of amino alcohol (*S*)-**5**[8e] (182 mg, 0.70 mmol, 90% *ee*) in ethyl acetate (7 mL) under nitrogen and the resulting mixture was stirred at room temp. for 20 h (TLC monitoring). Elimination of the solvents in vacuo and purification by column chromatography (silica gel, hexanes/ethyl acetate) afforded 240 mg (quantitative yield) of the *N*-protected amino alcohol (*S*)-**18** as an orange-colored semi-solid. $[\alpha]_D$ = +55.0 (*c* = 1.48, $CHCl_3$; 90% *ee*). IR (film): $\tilde{\nu}$ = 3409, 3094, 2980, 1720, 1691, 1494, 1356, 1245, 1168, 1064 cm^{-1}. ^1H NMR (400 MHz): δ = 1.48 [s, 9 H, $C(CH_3)_3$], 1.63 (s, 3 H, CH_3), 3.54 (m, 1 H, C*H*HOH), 3.78 (m, 1 H, CH*H*OH), 4.14–4.23 (s, m, 9 H, 5 CH Cp2, 4 CH Cp1), 4.78 (br. s, 1 H, OH), 5.51 (br. s, 1 H, NH) ppm. ^{13}C NMR (50.3 MHz): δ = 22.1 (CH_3), 28.3 [CH_3 $C(CH_3)_3$], 34.7 [C $C(CH_3)_3$], 65.1 (CH), 66.2 (CH), 68.0 (CH), 68.6 (CH), 71.6 (CH_2), 80.0 [C $C(CH_3)$N], 95.4 (C Fc), 156.1 (C CO) ppm. MS (CI, NH_3): *m*/*z* (%) = 370 (95) $[M + 1]^+$, 241 (100) $[M - 128]^+$. HRMS (CI, NH_3): calcd. for $C_{18}H_{35}FeNO_3$ $[M]^+$ 369.1957; found 369.1964.

(*S*)-2-(*tert*-Butoxycarbonylamino)-2-ferrocenylpropanal [(*S*)-19]: Dimethyl sulfoxide (0.20 mL, 2.78 mmol) was added dropwise through a syringe to a cold (–60 °C), stirred solution of oxalyl chloride (0.20 mL, 1.39 mmol) in anhydrous dichloromethane (6 mL) under nitrogen. After stirring for 15 min at the same temperature, a yellow-colored solution of the *N*-protected amino alcohol (*S*)-**18** (240 mg, 0.70 mmol) in dry dichloromethane (3 mL) was added very slowly with the aid of a cannula and the resulting green-colored solution was stirred at –60 °C for 2 h (TLC monitoring). At this point, triethylamine (0.48 mL, 3.50 mmol) was added dropwise and 10 min later the system was warmed to room temp. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with brine (2 × 10 mL). The organic phase was dried with magnesium sulfate. Elimination of the solvents in vacuo and purification by column chromatography (silica gel, hexanes/ethyl acetate) gave 237 mg (71% yield) of the *N*-protected amino aldehyde (*S*)-**19** as a rather unstable orange-colored oil which was directly used in the next reaction without further characterization. $[\alpha]_D$ = +138 (*c* = 2.05, CH_2Cl_2; 90% *ee*). IR (film): $\tilde{\nu}$ = 3096, 2979, 1738, 1708, 1482, 1368, 1242, 1167, 1058, 824 cm^{-1}. ^1H NMR (400 MHz): δ = 1.46 [s, 9 H, $C(CH_3)_3$], 1.68 (s, 3 H, CH_3), 4.24–4.28 (s, m, 9 H, 5 CH Cp2, 4 H CH Cp1), 5.29 (br. s, 1 H, NH), 9.40 (s, 1 H, CHO) ppm. ^{13}C NMR (100.6 MHz): δ = 19.9 (CH_3), 28.2 [CH_3 $C(CH_3)_3$], 29.6 [C $C(CH_3)_3$], 60.8 (CH), 65.4 (CH), 66.4 (CH), 68.9 (CH), 80.4 [C $C(CH_3)$N], 95.4 (C Fc), 154.3 (C CO), 195.8 (CH *C*HO) ppm.

(*S*)-2-Azido-2-ferrocenylpropanal [(*S*)-20]: Dimethyl sulfoxide (80 μL, 1.11 mmol) was added dropwise through a syringe to a cold (–60 °C), stirred solution of oxalyl chloride (50 μL, 0.56 mmol) in anhydrous dichloromethane (2.4 mL) under nitrogen. After stirring for 15 min at the same temperature, a yellow-colored solution of the azido alcohol (*S*)-**17** (79 mg, 0.28 mmol, 91% *ee*) in dry dichloromethane (0.8 mL) was added slowly with the aid of a cannula and the resulting green-colored solution was stirred at –60 °C for 2 h (TLC monitoring). At this point, triethylamine (0.19 mL, 1.40 mmol) was added dropwise and 10 min later the system was

warmed to room temp. The reaction mixture was diluted with ethyl acetate (5 mL) and washed with brine (2 × 10 mL). The organic phase was dried with magnesium sulfate. Elimination of the solvents in vacuo and purification by column chromatography (silica gel, hexanes/ethyl acetate) gave 57 mg (72% yield) of the azido aldehyde (*S*)-**20** as an orange-colored oil. $[\alpha]_D$ = –96.1 (*c* = 0.98, CH_2Cl_2; 91% *ee*). IR (film): $\tilde{\nu}$ = 3097, 2986, 2827, 2111, 1734, 1451, 1377, 1033, 823 cm^{-1}. ^1H NMR (200 MHz): δ = 1.65 (s, 3 H, CH_3), 4.17–4.31 (s, m, 9 H, 5 CH Cp2, 4 CH Cp1), 9.54 (s, 1 H, CHO) ppm. ^{13}C NMR (100.6 MHz): δ = 20.1 (CH_3), 65.6 (CH), 66.4 (CH), 68.2 [C *C*(CH_3)N], 69.1 (CH), 84.2 (C Fc), 193.8 (CH *C*HO) ppm. MS (MALDI-TOF): *m*/*z* (%) = 283 (18) $[M]^+$, 241 (100) $[M – 42]^+$. HRMS (ESI): calcd. for $C_{13}H_{13}FeN_3O$ $[M]^+$ 283.0403; found 283.0401.

1-(2-Hydroxy-3-methylbutyl)allyl (2*S*)-2-Azido-2-ferrocenylpropanoate (22): A 0.1 M tetrahydrofuran solution of samarium diiodide (5.4 mL, 0.54 mmol) was added slowly with the aid of a syringe to a cold (–10 °C), stirred solution of aldehyde (*S*)-**20** (155 mg, 0.55 mmol) and racemic 5-hydroxy-2-methylhept-6-en-3-one (**21**)[26] (76 mg, 0.54 mmol) in anhydrous tetrahydrofuran (9.3 mL) under nitrogen. After 3 h of stirring at the same temperature (TLC monitoring), the reaction mixture was poured over aqueous saturated sodium hydrogen carbonate (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried with sodium sulfate and evaporated under reduced pressure. After chromatographic purification (silica gel, hexanes/ethyl acetate), the ester **22** (192 mg, 85% yield; ca. 2:1 diastereomeric mixture) was isolated as an orange-colored oil. IR (film): $\tilde{\nu}$ = 3461, 3095, 2960, 2112, 1738, 1375, 1257, 1000, 822 cm^{-1}. ^1H NMR (400 MHz): δ = 0.87–0.92 [m, 6 H, CH(CH_3)$_2$], 1.60–1.69 [m, 2 H + 1 H, CH_2, CH(CH_3)$_2$], 1.75 (s, 3 H, CH_3), 2.08 (br. s, 1 H, OH), 3.23 (m, 1 H, CHOH, major diast.), 3.30 (m, 1 H, CHOH, minor diast.), 4.21–4.31 (s, m, 9 H, 5 CH Cp2, 4 CH Cp1), 5.20–5.29 (m, 2 H, CH=CH_2), 5.60 (m, 1 H, CHOOC), 5.92 (m, 1 H, CH=CH_2) ppm. ^{13}C NMR (100.6 MHz): δ = 17.5 [CH_3, CH(*C*H_3)$_2$], 18.4 [CH_3, CH(*C*H_3)$_2$], 23.6 (CH_3, major diast.), 23.7 (CH_3, minor diast.), 33.6 [CH, *C*H(CH_3)$_2$], 39.1 (CH_2), 66.1 (CH), 67.0 (CH), 68.4 (CH), 68.8 (CH), 71.8 (CH, *C*HOH), 74.4 (CH, *C*HOOC), 88.2 (C), 88.8 (C), 117.3 (CH_2, CH=*C*H_2, minor diast.), 117.5 (CH_2, CH=*C*H_2, major diast.), 135.9 (CH, *C*H=CH_2), 171.0 (C *C*OO) ppm. MS (CI, NH_3): *m*/*z* (%) = 426 (8) $[M + 1]^+$, 383 (100) $[M – 42]^+$.

Methyl (*S*)-2-Azido-2-ferrocenylpropanoate [(*S*)-23]: A cold (0 °C) solution of sodium methoxide in methanol (0.60 mmol), obtained by portionwise addition of metallic sodium (43 mg) over anhydrous methanol (13.6 mL), was added through a syringe to a flask containing ester **22** (161 mg, 0.40 mmol). After stirring for 10 min at 0 °C and for 15 h (TLC monitoring) at room temp. under nitrogen, the reaction mixture was poured into a 10% aqueous solution of citric acid (15 mL). The resulting solution was extracted with ethyl acetate (2 × 20 mL) and the combined organic extracts were successively washed with aqueous saturated sodium hydrogen carbonate (2 × 20 mL) and brine (2 × 20 mL). Drying with magnesium sulfate, elimination of the solvents under vacuum, and chromatographic purification (silica gel, hexanes/ethyl acetate) gave the azido ester (*S*)-**23** (97 mg, 82%) as an orange-colored oil. $[\alpha]_D$ = –97.2 (*c* = 0.78, CH_2Cl_2; 91% *ee*). IR (film): $\tilde{\nu}$ = 3097, 2951, 2107, 1740, 1452, 1256, 1108, 977, 821 cm^{-1}. ^1H NMR (200 MHz): δ = 1.72 (s, 3 H, CH_3), 3.86 (s, 3 H, $COOCH_3$), 4.17–4.31 (s, m, 9 H, 5 CH Cp2, 4 CH Cp1) ppm. ^{13}C NMR (100.6 MHz): δ = 24.3 (CH_3), 52.7 (CH_3 COO*C*H_3), 65.9 (CH), 66.3 [C *C*(CH_3)N], 66.8 (CH), 68.3 (CH), 69.2 (CH), 87.5 (C Fc), 171.5 (C *C*OOCH$_3$) ppm. MS (MALDI-TOF): *m*/*z* (%) = 313 (8) $[M]^+$, 271 (100) $[M – 42]^+$. HRMS (ESI): calcd. for $C_{14}H_{15}FeN_3O_2$ $[M]^+$ 313.0508; found 313.0516.

Methyl (*S*)-2-Amino-2-ferrocenylpropanoate [(*S*)-24]: A solution of azido ester (*S*)-**23** (72 mg, 0.23 mmol) in methanol (1.5 mL) was added with the aid of a cannula to a stirred suspension of 10% Pd/C (7 mg) in methanol (2 mL) under nitrogen. The flask was evacuated and filled with hydrogen (balloon, three cycles), and stirred at room temp. After 1 h (TLC monitoring), the system was purged with nitrogen, the suspension was filtered through a short Celite® pad, washed with ethyl acetate, and the solvent was eliminated under vacuum to give 65 mg (quantitative yield) of the title compound as an orange-colored oil. $[\alpha]_D$ = +8.0 (*c* = 0.34, CH_2Cl_2; 91% *ee*). IR (film): $\tilde{\nu}$ = 3400, 3377, 3094, 2949, 1734, 1452, 1307, 1205, 1106, 1000, 820 cm^{-1}. ^1H NMR (400 MHz): δ = 1.65 (s, 3 H, CH_3), 2.16 (br. s, 2 H, NH_2), 3.78 (s, 3 H, $COOCH_3$), 4.19–4.29 (s, m, 9 H, 5 CH Cp2, 4 CH Cp1) ppm. ^{13}C NMR (100.6 MHz): δ = 28.3 (CH_3), 52.3 (CH_3 COO*C*H_3), 57.2 [C *C*(CH_3)N], 65.7 (CH), 66.0 (CH), 67.7 (CH), 68.0 (CH), 68.6 (CH), 93.8 (C Fc), 175.8 (C *C*O-OCH$_3$) ppm. MS (MALDI-TOF): *m*/*z* (%) = 287 (39) $[M]^+$, 271 (100) $[M – 16]^+$. HRMS (ESI): calcd. for $C_{14}H_{17}FeNO_2$ $[M]^+$ 287.0603; found 287.0609.

Methyl (*S*)-2-(*tert*-Butoxycarbonylamino)-2-ferrocenylpropanoate [(*S*)-25]: A solution of bis(*tert*-butyl) dicarbonate (40 mg, 0.18 mmol) in ethyl acetate (0.5 mL) was added with the aid of a cannula to a stirred solution of amino ester (*S*)-**24** (40 mg, 0.14 mmol) in ethyl acetate (1.5 mL) under nitrogen, and the resulting mixture was stirred at room temp. for 20 h (TLC monitoring). Elimination of the solvent under reduced pressure, followed by chromatographic purification (silica gel, hexanes/ethyl acetate) afforded the *N*-protected amino ester (*S*)-**25** (28 mg, 54%) as an orange-colored semi-solid. $[\alpha]_D$ = +51.8 (*c* = 0.55, CH_2Cl_2; 91% *ee*). IR (film): $\tilde{\nu}$ = 3433, 3096, 2949, 1744, 1717, 1482, 1367, 1166, 1057 cm^{-1}. ^1H NMR (200 MHz): δ = 1.46 [s, 9 H, C(CH_3)$_3$], 1.83 (s, 3 H, CH_3), 3.73 (s, 3 H, $COOCH_3$), 4.22–4.28 (s, m, 9 H, 5 CH Cp2, 4 CH Cp1), 5.33 (br. s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz): δ = 23.5 (CH_3), 28.3 [CH_3 OC(*C*H_3)$_3$], 52.2 (CH_3 COO*C*H_3), 58.3 [C *C*(CH_3)N], 65.9 (CH), 66.7 (CH), 68.5 (CH), 69.1 (CH), 69.7 [C O*C*(CH_3)$_3$], 91.5 (C Fc), 154.3 (CON), 172.8 (C *C*OOCH$_3$) ppm. MS (MALDI-TOF): *m*/*z* (%) = 387 (100) $[M]^+$, 271 (100) $[M – 116]^+$. HRMS (ESI): calcd. for $C_{19}H_{25}FeNO_4$ $[M]^+$ 387.1128; found 387.1123.

Electrochemical Studies: Electrochemical data for the compounds under study were obtained by cyclic voltammetry under nitrogen at 298 K using acetonitrile (HPLC grade) as the solvent, 0.1 M tetrabutylammonium hexafluorophosphate as the supporting electrolyte, and a M263A potentiostat from EG&G. The measured potentials were referenced to an $Ag/AgNO_3$ (0.1 M in CH_3CN) electrode separated from the solution by a medium-porosity fritted disk. A platinum wire auxiliary electrode was used in conjunction with a platinum disk working TACUSSEL-EDI rotatory electrode (3.14 mm^2). Cyclic voltammograms of ferrocene were recorded before and after each sample to ensure the repeatability of the results, in particular to test and monitor the stability of the $Ag/AgNO_3$ electrode. Cyclic voltammograms of freshly prepared solutions (10^{-3} M) of the samples in acetonitrile were run and average *E* values were referenced to ferrocene. Under these experimental conditions, the standard error of the measured experimental potentials was 5 mV. In all cases, the cyclic voltammograms were registered using scan speeds varying from *v* = 10 to 100 $mV\,s^{-1}$.

Supporting Information (see also the footnote on the first page of this article): ^{13}C NMR spectra of (*S*)-**18**–(*S*)-**20**, **22**, and (*S*)-**23**–(*S*)-**25**.

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[1] For two leading reviews, see: a) D. R. van Staveren, N. Metzler-Nolte, *Chem. Rev.* **2004**, *104*, 5931–5985; b) M. F. R. Fouda, M. M. Abd-Elhazer, R. A. Abdelsamaia, A. A. Labib, *Appl. Organomet. Chem.* **2007**, *21*, 613–625.

[2] For recent examples, see: a) B. Ferber, S. Top, A. Vessières, R. Welter, G. Jaouen, *Organometallics* **2006**, *25*, 5730–5739; b) L. Barisic, M. Cakic, K. A. Mahmoud, Y.-n. Liu, H.-B. Kraatz, H. Prtizkow, S. I. Kirin, N. Metzler-Nolte, V. Rapic, *Chem. Eur. J.* **2006**, *12*, 4965–4980; c) P. James, J. Neudörff, M. Eissmann, P. Jesse, A. Prokop, H.-G. Schmalz, *Org. Lett.* **2006**, *8*, 2763–2766; d) C. Baldoli, C. Rigamonti, S. Maiorana, E. Licandro, L. Falciola, P. R. Mussini, *Chem. Eur. J.* **2006**, *12*, 4091–4100; e) U. Schatzschneider, N. Metzler-Nolte, *Angew. Chem. Int. Ed.* **2006**, *45*, 1504–1507; f) A. Anne, C. Demaille, *J. Am. Chem. Soc.* **2006**, *128*, 542–557; g) T. Moriuchi, T. Nagai, T. Hirao, *Org. Lett.* **2006**, *8*, 31–34; h) A. Goel, D. Savage, S. R. Alley, T. Hogan, P. N. Kelly, S. M. Draper, C. M. Fitchett, P. T. M. Kenny, *J. Organomet. Chem.* **2006**, *691*, 4686–4693; i) D. Freisleben, T. Hauck, K. Sünkel, W. Beck, *Z. Anorg. Allg. Chem.* **2007**, *633*, 1100–1106; j) J. Lykkesfeldt, E. Morgan, C. Stephan, L. T. Skovgaard, T. Moos, *J. Biochem. Mol. Tox.* **2007**, *21*, 145–155; k) A. Dallas, H. Kuhtz, A. Farrell, B. Quilty, K. Nolan, *Tetrahedron Lett.* **2007**, *48*, 1017–1021.

[3] a) K. Schlögl, *Monatsh. Chem.* **1957**, *88*, 601–621; b) C. R. Hauser, J. K. Lindsay, *J. Org. Chem.* **1957**, *22*, 1246–1247; c) J. M. Osgerby, P. L. Pauson, *J. Chem. Soc.* **1958**, 656–660.

[4] a) T. J. Kealy, P. L. Pauson, *Nature* **1951**, *168*, 1039–1040; b) G. Wilkinson, M. Rosenblum, M. C. Whiting, R. B. Woodward, *J. Am. Chem. Soc.* **1952**, *74*, 2125–2126.

[5] See, for example: a) H. Eckert, C. Seidel, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 159–160; b) A.-S. Carlström, T. Frejd, *J. Org. Chem.* **1990**, *55*, 4175–4180; c) R. F. W. Jackson, D. Turner, M. H. Block, *Synlett* **1996**, 862–864; d) M. Kira, T. Matsubara, H. Shinohara, M. Sisido, *Chem. Lett.* **1997**, 89–90; e) B. Basu, S. K. Chattopadhyay, A. Rizén, T. Frejd, *Tetrahedron: Asymmetry* **1997**, *8*, 1841–1846; f) A. Nomoto, T. Moriuchi, S. Yamazaki, A. Ogawa, T. Hirao, *Chem. Commun.* **1998**, 1963–1964; g) W. Bauer, K. Polborn, W. Beck, *J. Organomet. Chem.* **1999**, *579*, 269–279; h) M. Adamczyk, R. E. Reddy, S. D. Rege, *Synth. Commun.* **2000**, *30*, 1389–1400; i) S. Maricic, A. Ritzén, U. Berg, T. Frejd, *Tetrahedron* **2001**, *57*, 6523–6529; j) H. Dialer, K. Polborn, W. Ponikbar, K. Sünkel, W. Beck, *Chem. Eur. J.* **2002**, *8*, 691–699; k) S. Maricic, T. Frejd, *J. Org. Chem.* **2002**, *67*, 7600–7606.

[6] P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson, G. M. Whitman, *J. Am. Chem. Soc.* **1957**, *79*, 3416–3419.

[7] H. Dialer, W. Steglich, W. Beck, *Tetrahedron* **2001**, *57*, 4855–4861.

[8] a) M. Catasús, A. Bueno, A. Moyano, M. A. Maestro, J. Mahía, *J. Organomet. Chem.* **2002**, *642*, 212–226; b) R. M. Moreno, A. Bueno, A. Moyano, *J. Organomet. Chem.* **2002**, *660*, 62–70; c) A. Moyano, M. Rosol, R. M. Moreno, C. López, M. A. Maestro, *Angew. Chem. Int. Ed.* **2005**, *44*, 1865–1869; d) A. Bueno, R. M. Moreno, A. Moyano, *Tetrahedron: Asymmetry* **2005**, *16*, 1763–1778; e) R. M. Moreno, A. Bueno, A. Moyano, *J. Org. Chem.* **2006**, *71*, 2528–2531; f) R. M. Moreno, M. Rosol, A. Moyano, *Tetrahedron: Asymmetry* **2006**, *17*, 1089–1103; g) R. M. Moreno, A. Moyano, *Tetrahedron: Asymmetry* **2006**, *17*, 1104–1110; h) A. Bueno, M. Rosol, J. García, A. Moyano, *Adv. Synth. Catal.* **2006**, *348*, 2590–2596.

[9] a) P. H. J. Carlsen, T. Katsuki, V. S. Martín, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938; b) M. Caron, P. R. Carlier, K. B. Sharpless, *J. Org. Chem.* **1988**, *53*, 5185–5187; c) T. Martín, C. M. Rodríguez, V. S. Martín, *J. Org. Chem.* **1996**, *61*, 6450–6453; d) T. Q. Dinh, X. Du, C. D. Smith, R. W. Armstrong, *J. Org. Chem.* **1997**, *62*, 6773–6783.

[10] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165–185.

[11] A. Bueno, Ph. D. Thesis, University of Barcelona, **2005**.

[12] E. J. Corey, J.-O. Link, *J. Am. Chem. Soc.* **1992**, *114*, 1906–1908.

[13] W. Reeve, E. F. Group, *J. Org. Chem.* **1967**, *32*, 122–125.

[14] R. Choukroun, D. Gervais, *J. Chem. Soc., Dalton Trans.* **1980**, 1800–1802.

[15] Note that under these conditions, the use of sodium azide instead of diazido(diisopropoxido)titanium led to the competitive formation of an unexpected reductive elimination product, 1,1-dichloro-2-ferrocenylethene.

[16] X. Liu, M. L. Maddox, J. M. Muchowski, E. Galeazzi, A. Guzmán, J. C. Nava, *J. Org. Chem.* **1995**, *60*, 1090–1092.

[17] V. Fechtel, K. Westphal, V. Rüger, H. Matschiner, *Synthesis* **1991**, 399–401.

[18] See: a) X. Creary, *Org. Lett.* **2002**, *4*, 2069–2072; b) L. E. Harrington, I. Vargas-Baca, N. Reginato, M. J. McGlinchey, *Organometallics* **2003**, *22*, 663–669; c) R. Gleiter, C. Bleiholder, F. Rominger, *Organometallics* **2007**, *26*, 4850–4854, and references cited therein.

[19] a) H. C. Kolb, M. S. Van Nieuwehnze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547; b) I. E. Markó, J. S. Svendsen in *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, vol. 2, pp. 713–787; c) A. B. Zaitsev, H. Adolfsson, *Synthesis* **2006**, 1725–1756.

[20] For a related transformation, see: P. Vicennati, P. G. Cozzi, *Eur. J. Org. Chem.* **2007**, 2248–2253.

[21] S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi, H. Irie, *J. Org. Chem.* **1997**, *62*, 2275–2279.

[22] A. Abiko, J. C. Roberts, T. Takemasa, S. Masamune, *Tetrahedron Lett.* **1986**, *27*, 4537–4540.

[23] Adapted from S. G. Davies, S. W. Epstein, A. C. Garner, O. Ichihara, A. D. Smith, *Tetrahedron: Asymmetry* **2000**, *11*, 1555–1565.

[24] A. Ogundabenigi, J. Shen, A. Adejare, *J. Fluorine Chem.* **2000**, *103*, 107–109.

[25] K. Biswas, S. Pal, J. D. Carbeck, D. Kahne, *J. Am. Chem. Soc.* **2000**, *122*, 8413–8420.

[26] K. Yamamoto, D. Monozono, S. Yamada, *Tetrahedron Lett.* **1992**, *33*, 4329–4332.

[27] A. B. Smith III, D. Lee, C. M. Adams, M. C. Kozlowski, *Org. Lett.* **2002**, *4*, 4539–4541.

[28] D. A. Evans, A. H. Hoveyda, *J. Am. Chem. Soc.* **1990**, *112*, 6447–6449.

[29] See: J. T. Kuethe, D. R. Gauthier Jr, G. L. Beutner, N. Yasuda, *J. Org. Chem.* **2007**, *72*, 7469–7472, and references cited therein.

[30] a) E. R. Brown, J. R. Sandifer in *Physical Methods in Chemistry. Electrochemical Methods* (Eds.: B. W. Rossiter, J. H. Hamilton); Wiley, New York, **1986**, vol. 14, chapter 4; b) P. Zanello, *Inorganic Electrochemistry. Theory, Practice and Applications*, RSC, Cambridge, U.K., **2003**.

[31] R. Bosque, J. Sales, C. López, *Inorg. Chim. Acta* **1996**, *244*, 141–145.

[32] W. L. Davis, R. F. Shago, E. H. G. Langner, J. C. Swarts, *Polyhedron* **2005**, *24*, 1611–1616.

[33] S. Pérez, C. López, A. Caubet, A. Roig, E. Molins, *J. Org. Chem.* **2005**, *70*, 4857–4860.

[34] a) G. W. Gokel, D. Marquarding, I. Ugi, *J. Org. Chem.* **1972**, *37*, 3052–3058; b) W. S. Lam, S. H. Kok, T. T.-L. Au-Yeung, J. Wu, H. Y. Cheung, F. L. Lam, C.-H. Yeung, A. S. C. Chan, *Adv. Synth. Catal.* **2006**, *348*, 370–374.

[35] a) G. L. Hoh, W. E. McEwen, J. S. Kleinberg, *J. Am. Chem. Soc.* **1961**, *83*, 3949–3953; b) W. F. Little, C. N. Reilley, J. D. Johnson, A. P. Saunder, *J. Am. Chem. Soc.* **1964**, *86*, 1376–1381; c) N. F. Blom, W. W. Neuse, H. G. Thomas, *Trans. Met. Chem.* **1987**, *12*, 301–306; d) P. Zanello, A. Cinquantini, S. Mangani, G. Opromolla, L. Pardi, C. Janiak, M. D. Rausch, *J. Organomet. Chem.* **1994**, *471*, 171–177; e) A. Benito, J. Cano, R. Martínez-Mañez, J. Soto, J. Payá, F. Lloret, M. Julve, J. Faus, M. D. Cano, *Inorg. Chem.* **1993**, *32*, 1197–1203; f) A. Louati, M. Gross, L. Douce, D. Matt, *J. Organomet. Chem.* **1993**, *463*, 167–182; g) M. Bracci, E. Ercolani, B. Floris, M. Bassetti, A. Chiesi-Vila, C. Guastini, *J. Chem. Soc., Dalton Trans.* **1990**, 1357–1364.

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