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Enantiopure *N*-ferrocenylmethylaziridin-2-ylmethanols from L-serine: synthesis, crystal structure and applications

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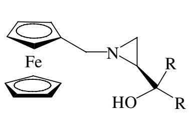
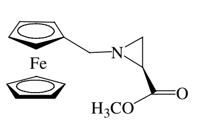
Abstract—A convenient and practical 'one-pot procedure' for the synthesis of methyl *N*-ferrocenylmethylaziridine-2-carboxylates **2** from the *N*-ferrocenylmethyl-L-serine methyl ester in the presence of *p*-toluenesulfonyl chloride and triethylamine is described. *N*-Ferrocenylmethylaziridin-2-ylmethanol **1** is a new type of β-amino alcohol ligand and is prepared from the corresponding methyl *N*-ferrocenylmethylaziridine-2-carboxylates **2** through a Grignard reaction. The crystal structures of compounds **1** and **2** reveal that the *N*-ferrocenylmethyl group is positioned *anti* to the hydroxymethyl group or ester group, respectively. X-ray analysis indicates that in aziridine alcohols **1**, an intramolecular hydrogen bond is present in the crystalline state. The chiral ligands **1** were used as catalyst to promote the asymmetric addition of diethylzinc to benzaldehyde affording 1-phenylpropanol in up to 92.7% enantiomeric excess with excellent yields.

1. Introduction

N-Ferrocenylmethylaziridin-2-ylmethanol **1**, as a new type of β-amino alcohol ligand, should be a very effective chiral inducer for asymmetric synthesis, because it not only possesses a rigid three-member ring backbone[1] but also effective N and O chelating atoms for transition metals.[2] Meanwhile, diverse chiral ferrocenyl derivatives have also proven to be highly enantioselective catalysts.[3,2c] Retrosynthetically, the enantiomerically pure aziridine-2-carboxylic ester **2** is a direct precursor for the preparation of chiral compound **1**. In fact, N-alkylated aziridine-2-carboxylic esters are important intermediates for preparing a wide range of chiral compounds, such as anomalous α-amino acid,[4] antibiotic,[5] selective enzyme inhibitors,[6] peptides,[7,4c] chiral catalysts,[1] etc.; hence, it is desirable to develop a convenient method for the synthesis of enantiomerically pure compound **2**.



1 R = Ph , **1a**
R = Pr-*i*, **1b**



2

Several approaches for the preparation of optically active aziridine-2-carboxylic esters have been reported.[7b] In 1960, Smrt et al.[8] described the synthesis of N-substituted aziridine-2-carboxylic esters from serine ester **3** by a modified procedure of Wenker's aziridine synthesis[9] (Scheme 1). In the first step, the hydroxyl group in N-tritylated α-amino acid ester **4** was converted into the corresponding methanesulfonate **5** using piperdine as the solvent. The second step was performed using *N*-ethylpiperidine as the base, which resulted in an intramolecular cyclization reaction[10] to give the *N*-tritylaziridine-2-carboxylic ester **6**. In another report,[11] Nadagawa et al. utilizing *p*-toluenesulfonyl chloride instead of methanesulfonyl chloride also obtained **6** (Scheme 1).

Several 'one-step procedures' for the synthesis of analogues of **6** have also been reported. Seebach converted *N*-benzyl-L-serine ester into the corresponding *N*-benzylaziridine-2-carboxylic ester in low yield[12] in the presence of PPh_3, CBr_4, and Et_3N. Van Boom and co-workers reported a 'one-pot, one-step' method for the preparation of the *N*-tritylaziridine-2-carboxylic ester from *N*-trityl-L-serine ester[13] by using sulfuryl chloride and an excess amount of Et_3N at −50 °C (Scheme 1). In another study,[7a] Kornm et al. compared the efficiency of the one-step preparation of enantiopure *N*-tritylaziridine-2-carboxylic ester as described by van Boom with that proposed by Nakajima. Both procedures led to the desired aziridine compound in nearly identical yields

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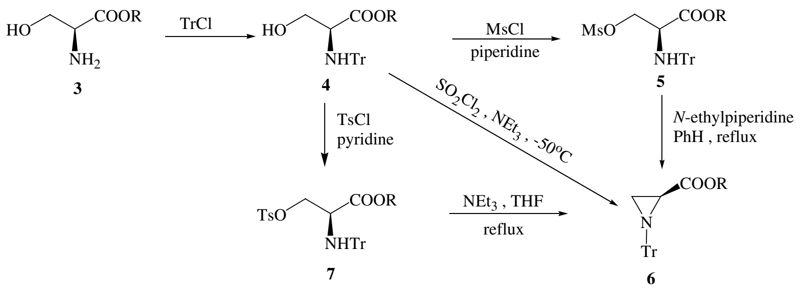


Tr = Ph_3C , Ms = $MeSO_2$, Ts = p-$MeC_6H_4SO_2$

Scheme 1.

(50–60%). In 1997, Zwanenburg and co-workers developed an improved Smrt et al. procedure for the synthesis of enantiopure *N*-tritylaziridine-2-carboxylic ester from *N*-trityl-L-serine ester with high yield in one step,[14] by using $MeSO_2Cl$ and an excess of Et_3N. We herein report the development of a modified and convenient procedure for the preparation of N-alkylated aziridine-2-carboxylic ester from *N*-alkyl-L-serine ester, the synthesis of the new potential chiral catalysts **1** from the simple aziridine-carboxylic ester **2** with high yields,and the stereochemical characterization of products **1** and **2** by X-ray diffraction (Scheme 2).

2. Results and discussion

2.1. Synthesis of chiral ligands

The aziridine-2-carboxylic ester **2** was used for the preparation of the ferrocenyl aziridino alcohols **1**. It was important to have access to a convenient synthesis of *N*-alkylaziridine ester **2**, the precursor of **1**. The literature on the synthesis of compound **2** indicated that improvements were needed. We tried several procedures for the transformation of **8** to **2**.[11–13] It was finally found that a convenient 'one-step procedure' for the preparation of **2** from the corresponding *N*-alkyl-L-serine ester **8** could be achieved (Scheme 2). The desired conversion was performed in THF using triethylamine (2.1 equiv) and *p*-toluenesulfonyl chloride (1.1 equiv) at reflux for 48 h. Product **2** was isolated by the preparative TLC in 71% yield with more than 99% ee according to HPLC analysis (Chiralcel OD). The single crystal growth was carried out in ether at 10 °C and the X-ray structure is shown in Figure 1.

The essential difference between the procedure described here and those reported previously is that the *p*-toluenesulfonylation of the hydroxyl group and the aziridine ring closure can be carried out in one step.

The *N*-ferrocenylmethyl-2-carboxylic ester **2** was converted into the corresponding *N*-ferrocenylmethylaziridin-2-ylmethanols **1** by using excess RMgBr in THF for 24 h. Purification of the crude products by preparative TLC afforded the *N*-ferrocenylmethylaziridin-2-ylmethanols **1** in good yield (**1a**, 95%; **1b** 72 %). The ee of **1** was determined by HPLC analysis using a chiral column (Chiralcel OD) and was more than 99%. The single crystal growth was performed in a mixture of hexane/ethyl acetate (2:1 volume) at room temperature for **1a** and in hexane for **1b**.

2.2. Crystal structure analysis

The *N*-ferrocenylmethylaziridin-2-ylmethanols **1** was further characterized by X-ray diffraction. X-ray struc-

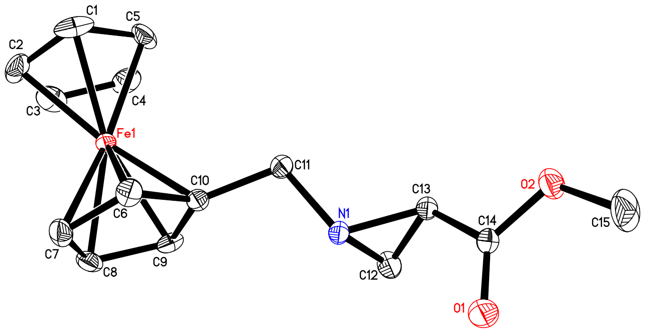
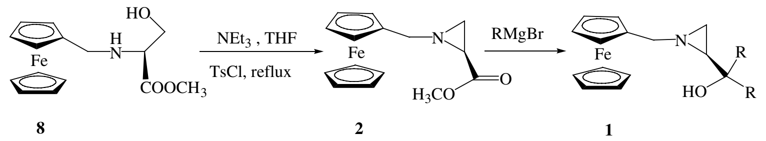


Figure 1. Perspective view of compound **2**. Selected bond distances (Å) and angles (°) are: N(1)–C(12), 1.451(4); N(1)–C(13), 1.469(4); N(1)–C(11), 1.488(4); O(1)–C(14), 1.205(3); O(2)–C(14), 1.326(4); O(2)–C(15), 1.443(4); C(12)–C(13), 1.468(5); C(13)–C(14), 1.474(4); C(12)–N(1)–C(13) 60.4(2); N(1)–C(12)–C(13), 60.4(2); C(12)–C(13)–N(1), 59.2(2); C(12)–N(1)–C(11), 115.2(3); C(13)–N(1)–C(11), 113.4(2); C(12)–C(13)–C(14), 119.6(3); N(1)–C(13)–C(14), 115.9(3); C(14)–O(2)–C(15), 116.4(3).



Scheme 2.

ture analysis revealed that the *N*-ferrocenylmethyl group was positioned *anti* to the methanol group in both **1a** (Fig. 2) and **1b** (Fig. 3). This kind of conformation might be due to the OH group in the aziridine alcohols forming an intramolecular hydrogen bond with the nitrogen of the three-member ring. It was therefore of interest to determine the orientation of the OH group in these alcohols more precisely. From the X-ray studies it was deduced that a hydrogen bond was present in compounds **1a** and **1b**. The N–H distances in **1a** and **1b** were determined from the X-ray diffraction data and were shown to be 2.13 and 1.98 Å, respectively. These distances between the aziridine nitrogen and the hydroxy hydrogen atom are indicative of the presence of an intramolecular hydrogen bond in both aziridine alcohols **1a** and **1b**. The N–H–O bond angles in **1a** and **1b** were 128° and 134°, respectively, which are close to the expected average value for a hydrogen bond present in a five-member ring structure. The absolute configurations of **2**, **1a**, and **1b**, which follow from L-serine, are (2*S*)-methyl 1-ferrocenylmethylaziridine-2-carboxylate, (2*S*)-1-ferrocenylmethylaziridin-2-yl(diphenyl)methanol, and (2*S*)-1-ferrocenylmethylaziridin-2-yl(di-*i*-propyl)-methanol, respectively.

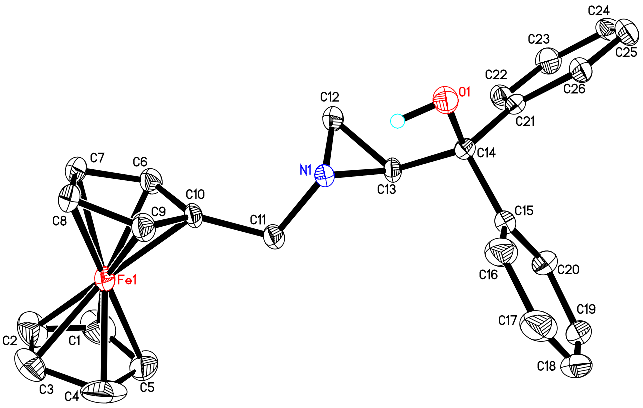


Figure 2. Perspective view of compound **1a**. Selected bond distances (Å) and angles (°) are: N(1)–C(13), 1.458(4); N(1)–C(12), 1.460(4); N(1)–C(11), 1.478(4); C(12)–C(13), 1.454(4); C(13)–C(14), 1.537(5); O(1)–C(14), 1.423(4); O(1)–H(1), 0.89(5). O(1)–N(1), 2.678(5); N(1)–H(1), 1.977(5). C(14)–O(1)–H(1), 97(3); C(13)–N(1)–C(12), 59.8(2); C(13)–N(1)–C(11), 115.8(3); C(12)–N(1)–C(11), 114.6(3); C(13)–C(12)–N(1), 60.1(2); C(12)–C(13)–N(1), 60.1(2); C(12)–C(13)–C(14), 122.1(3); N(1)–C(13)–C(14), 114.5(3); C(21)–C(14)–C(13), 111.8(3); N(1)–H(1)–O(1), 134.

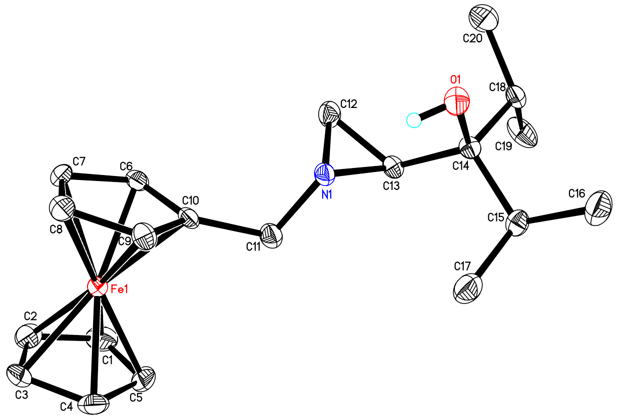
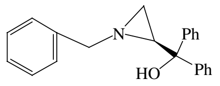


Figure 3. Perspective view of compound **1b**. Selected bond distances (Å) and angles (°) are: N(1)–C(12), 1.469(5); N(1)–C(11), 1.479(5); N(1)–C(13), 1.482(4); C(12)–C(13), 1.481(6); C(13)–C(14), 1.521(5); O(1)–C(14), 1.437(5); O(1)–H(1), 0.80(5); O(1)–N(1), 2.698(5); N(1)–H(1), 2.13(5). C(12)–C(13)–N(1), 59.5(3); C(12)–C(13)–C(14), 123.5(4); N(1)–C(13)–C(14), 115.3(3); O(1)–C(14)–C(13), 108.8(3); C(14)–O(1)–H(1),102(4); C(12)–N(1)–C(11), 113.8(3); C(12)–N(1)–C(13), 60.2(3); C(11)–N(1)–C(13), 116.1(3); N(1)–H(1)–O(1), 128.

2.3. Asymmetric addition of Et_2Zn to benzaldehyde

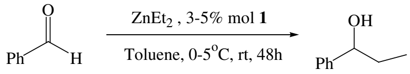
With chiral ligands **1** in hand, we examined the enantioselective addition of diethylzinc to benzaldehyde, as the model reaction, in the presence of 3–5% of the chiral ligands **1** in toluene from 0 °C to room temperature. The results are summarized in Table 1. The reactions using **1a** as catalyst afforded 1-phenylpropanol in excellent yields (97–99%) with high enantiomeric excesses (83.5–92.7% ee) (Table 1, entries 1–4). It was reported that the reaction conditions, such as temperature, and quantity of catalyst, could influence the enantioselectivity.[15] We first investigated the effect of reaction temperature on enantioselectivity. Lowering the reaction temperature from room temperature (20–25 °C) to 0 °C led to an enhancement in the addition of selectivity from 83.5% to 90.4% (Table 1, entries 1 and 2). We attempted to decrease the reaction temperature further for higher enantioselectivity, but at −20 °C there was almost no reaction. When 5 mol% **1a** was used, the ee value of 1-phenylpropanol was lower than that using 3 mol% **1a** (Table 1, entries 2 and 3). Chiral ligand **1b** gave 1-phenylpropanol with a low ee of 25.2% and was not studied further (Table 1, entry 5).



9 ee = 49%

This result was remarkable compared to the findings in a recent report where a modest ee of only 49% was obtained for the same reaction, employing *N*-benzylaziridin-2-yldiphenylmethanol **9**. Comparison of our results (92.7% ee) with that of Page et al. (49% ee),[1k] demonstrates that the replacement of the phenyl group on the nitrogen atom of aziridine-based skeleton with a ferrocenyl unit leads to a dramatic improvement in the enantioselectivity when used as the catalyst in the addition of diethylzinc to benzaldehyde. These results also suggested that the hindrance of the ferrocenyl group, compared to a phenyl group, played an important role in the enantioselection. In a similar manner, Watanabe et al. reported that the presence of a ferrocenyl moiety on the nitrogen atom of the ephedrine and norephedrine skeleton led to an enhancement in the enantioselectivity.[16] The chiral ligand **1a** was recovered

Table 1. Asymmetric addition of diethylzinc to benzaldehyde using ligand **1**[a]



Entry	PhCHO	Ligands	Mol% **1**	Yield (%)[b]	Ee (%)[c]	Configuration[d]
1[e]	C_6H_5CHO	**1a**	5	99	83.5	*S*
2	C_6H_5CHO	**1a**	5	98	90.4	*S*
3	C_6H_5CHO	**1a**	3	97	92.7	*S*
4	C_6H_5CHO	**1a**	3[f]	97	92.7	*S*
5	C_6H_5CHO	**1b**	3	86	25.2	*S*

[a] The mol ratio Et_2Zn/aldehyde was 2/1.

[b] Isolated yields.

[c] Determined by HPLC using a chiral OD column.

[d] Absolute configuration assigned by comparison with known elution order from a Chiralcel OD column according to the literature.[17]

[e] The reaction proceeded at rt.

[f] The recovered ligand was used.

in excellent yield (96%) from the reaction mixture by preparative TLC and re-used without any loss of enantiomeric purity of the product (Table 1, entry 4).

3. Conclusion

In conclusion, we have developed a modified 'one-pot procedure' for the synthesis of enantiopure *N*-ferrocenylmethyl-2-carboxylic esters **2** from the *N*-ferrocenylmethyl-L-serine ester using *p*-toluenesulfonyl chloride and triethylamine. The derivatives **1** of compound **2**, a new type of β-amino alcohol ligands, have been prepared readily through a Grignard reaction. The crystal structure of compounds **1** and **2** reveals that the *N*-ferrocenylmethyl group is positioned *anti* to the methanol group or ester group, respectively. X-ray analysis indicates that in aziridine alcohols **1** there exists an intramolecular hydrogen bond in the crystalline state. We have demonstrated that chiral ligand **1a** is an efficient catalyst for the enantioselective addition of diethylzinc to benzaldehyde. Further application of chiral compounds **1** and **2** for asymmetric synthesis is currently under investigation in our laboratory.

4. Experimental

4.1. General

Melting points were determined using YRT-3 melting point apparatus and are uncorrected. Elemental analyses were determined with a Carlo Erba 1160 elemental analyzer. Optical rotations were measured with Perkin Elmer, model 341 Polarimeter at 20 °C in $CHCl_3$. The enantiomeric purity of **1a**, **1b**, and **2** was determined by HPLC using a chiral column with hexane/propan-2-ol (ratio as indicated) as the eluent. The chromatographic system consisted of a JASCO model PU-1580 intelligent HPLC pump and a JASCO model UV-1575 intelligent UV–vis detector (254 nm). The injection loop had a 20 μL capacity. The column used was a Chiralcel OD (250 × 4.6 mm) from Daicel Chemical Ind., Ltd (Japan). The column was operated at ambient temperature. NMR spectra (^1H and ^{13}C) were performed on a Bruker DPX 400 (400 MHz) spectrometer using solutions in $CDCl_3$ (referenced internally to Me_4Si); *J* values are given in Hz. IR spectra were determined on a Thermo Nicolet IR 200 spectrophotometer. TLC was performed on dry silica gel plates developed with hexane/ethyl acetate. Mass spectra were obtained using a Bruker esquire-3000 instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent.

4.2. Reagents and solvents

Tetrahydrofuran (THF) was pre-dried over calcium chloride, then distilled from $LiAiH_4$ before use. Et_3N was dried with KOH pellets, then refluxed for 2 h with *p*-toluenesulfonyl chloride and distilled. *p*-Toluenesulfonyl chloride was purified by dissolving (10 g) in the minimum volume of $CHCl_3$ (ca. 25 mL) filtered, and diluted with five volumes (i.e., 125 mL) of petroleum ether (bp 30–60 °C) to precipitate impurities. The solution was filtered, clarified with charcoal, concentrated to 15 mL by evaporation, and gave 7 g of white crystals. All other reagents were commercially available and used as received.

4.3. Preparation of methyl aziridine-2-carboxylates 2

4.3.1. (−)-(2*S*)-Methyl 1-ferrocenylmethylaziridine-2-carboxylate 2. *Method A*: Compound **8** (0.94 g, 3.14 mmol) was dissolved in THF (10 mL) at room temperature. Triethylamine (0.9 mL, 6.9 mmol, 2.2 equiv) was added, followed by the addition of *p*-toluenesulfonyl chloride (0.6 g, 3.45 mmol, 1.1 equiv), and the mixture stirred for 30 min at 20 °C. The temperature was then raised to 66 °C and the reaction mixture heated to refluxing. The reaction was monitored by TLC. After 48 h the reaction was finished and quenched by cooling to room temperature. The solution was filtered and the solid washed with THF. After removal of the solvent, the resulting residue was purified by the preparative TLC with hexane/EtOAc (4:1) as developing solvent to give **2** in 71% yield (629 mg). Mp 85.5–86.5 °C (orange red crystals from diethyl ether). $[\alpha]_D = -99.4$ (*c* 1.028, in $CHCl_3$); ee >99% (determined by HPLC on a Chiralcel OD column with 100:2 hexane/isopropanol as eluent, 1 mL min^{-1}, $t_r =$ 31.91 min). ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (dd, 1H, $J_1 = 6.4$ Hz, $J_2 = 0.8$ Hz, H-3); 2.13 (dd, 1H, $J_1 = 3.2$ Hz, $J_2 = 0.8$ Hz, H-3); 2.16 (dd, $J_1 = 3.2$ Hz, $J_2 = 2.8$ Hz, 1H, H-2); 3.35 (d, $J = 3.2$ Hz, 2H, N*CH*$_2$); 3.70 (s, 3H, O*CH*$_3$); 4.10–4.21 (m, 9H, Fc*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.64, 36.74, 52.13, 59.11, 68.18, 68.44, 68.46, 68.48, 68.53, 68.56, 68.58, 68.59, 68.92, 69.17, 89.92, 171.26. IR (KBr pellet): 3083, 3033, 2986, 2935, 1739, 1440, 1400, 1334, 1226, 1177, 1103, 1085, 1023, 961, 811. *m*/*z* (ESI) 322 (M^++Na). Anal. Calcd for $C_{15}H_{17}FeNO_2$ requires: C, 60.22; H, 5.73; N, 4.68. Found:C, 60.34; H, 5.69; N, 4.70.

Method B: To a solution of PPh_3 (1.75 g, 6.67 mmol) and CBr_4 (2.2 g, 6.67 mmol) in CH_2Cl_2 (20 mL), compound **8** (1.49 g, 4.73 mmol), and Et_3N (1.5 mL, 10.8 mmol) were added at 0 °C. After addition of $CHCl_3$ (15 mL), the mixture was stirred overnight at rt. After cooling again to 0 °C, PPh_3 (1.75 g, 6.67 mmol), and CBr_4 (2.2 g, 6.67 mmol), Et_3N (1.5 mL, 10.8 mmol) were added, and after refluxing for 2 h, the reaction was quenched (monitored by TLC). The solution was cooled to 0 °C, filtered, and workup as method A obtained **2** (0.45 g) and yield was only 31%.

4.4. Preparation of aziridine alcohols 1 using Grignard reactions

4.4.1. (−)-(2*S*)-1-Ferrocenylmethylaziridin-2-yl(diphenyl)-methanol 1a. To the Grignard reagent solution prepared from 817 mg (5.2 mmol) bromobenzene in 3 mL THF and 124 mg (5.2 mmol) magnesium in 5 mL THF was gradually added 380 mg (1.27 mmol) compound **2** dissolved in 1 mL THF at −20 °C over a period of 30 min. The mixture was then allowed to reach room temperature. After stirring for 24 h the reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C. The product was separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purified by the preparative TLC with hexane/EtOAc (4:1) as the developing solvent to give **1a** in 95% yield (510 mg). Mp 134–134.5 °C (orange red crystals from 3:1 hexane/EtOAc), ee >99% (determined by HPLC on a Chiralcel OD column with 100:3 hexane/isopropanol as eluent, 0.6 mL min^{-1}, $t_r =$ 23.81 min). $[\alpha]_D = -26.1$ (*c* 0.964, in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (d, $J = 6.4$ Hz, 1H, H-3), 1.89 (d, $J = 3.6$ Hz, 1H, H-3), 2.40 (dd, $J_1 = 6.4$ Hz, $J_2 = 3.6$ Hz, 1H, H-2), 3.21, 3.48 (d, $J = 13.2$ Hz, 2H, Fc*CHH*′N), 3.98–4.07 (m, 9H, Fc*H*), 7.12–7.37 (m, 10H, Ph*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.83, 45.43, 57.92, 68.02, 68.06, 68.37, 68.74, 68.91, 74.01, 83.49, 126.23, 126.29, 126.69, 126.85, 127.86, 127.94, 144.89, 147.47. IR (KBr pellet): 3368, 3071, 3035, 2989, 1642, 1598, 1448, 1323, 1235, 1181, 1031, 997, 817, 760, 702. *m*/*z* (ESI) 424 (M^++1), 446 (M^++Na). Anal. Calcd for $C_{26}H_{25}FeNO$ requires:C, 73.77; H, 5.95; N, 3.31. Found: C, 73.80; H, 5.90; N, 3.22.

4.4.2. (−)-(2*S*)-1-Ferrocenylmethylaziridin-2-yl(di-i-propyl)methanol 1b. A Grignard reagent was prepared in the usual way from 13 mg (5.6 mmol) magnesium and *i*-propyl bromide 689 mg (5.6 mmol) in THF (5 mL). The solution was cooled to −20 °C before addition of a solution of **2** 210 mg (0.7 mmol) in THF (1 mL). The mixture was then allowed to reach room temperature. After stirring for 24 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL) at 0 °C. The organic phase was separated and the aqueous phase extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The resulting residue was purified by the preparative TLC with hexane/EtOAc (3.5:1) as the developing solvent to give **1b** in 72% yield (180 mg). Mp 122–122.5 °C (orange red crystals from hexane), ee >99% (determined by HPLC on a Chiralcel OD column with 100:2 hexane/isopropanol as eluent, 0.6 mL min^{-1}, $t_r = 13.05$ min). $[\alpha]_D = -74.9$ (*c* 1.128, in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.91–0.98 (m, 12H, 4 × *CH*$_3$), 1.30 (d, $J = 6.4$ Hz, 1H, H-3), 1.49 (dd, $J_1 = 6.4$ Hz, $J_2 = 3.6$ Hz, 1H, H-2), 1.82 (d, $J = 3.2$ Hz, 1H, H-3), 1.95–2.00 (m, 2H, 2 × *CH*), 2.49 (br, 1H, *OH*), 2.78, 3.88 (d, $J = 12.8$ Hz, 2H, Fc*CHH*′N), 4.11–4.21 (m, 9H, Fc*H*). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.27, 17.51, 17.71, 17.78, 29.08, 33.34, 34.86, 39.79, 57.62, 68.09, 68.14, 68.54, 68.79, 68.92, 72.77, 84.12. IR (KBr pellet): 3419, 3096, 2967, 2929, 1643, 1464, 1393, 1315, 1035, 994, 818. *m*/*z* (ESI) 356 (M^++1), 378 (M^++Na). Anal. Calcd for $C_{20}H_{29}FeNO$ requires: C, 67.61; H, 8.23; N, 3.94. Found: C, 67.89; H, 8.13; N, 3.75.

4.5. General procedure for the enantioselective addition of Et_2Zn to benzaldehyde

A solution of diethylzinc (1 M in *n*-hexane, 1.1 mL) was added to a solution of a chiral catalyst (0.015 mmol, 6.3 mg, 3 mol %) in dry toluene under a nitrogen atmosphere. The mixture was cooled to 0 °C, and stirred for 30 min. Freshly distilled benzaldehyde (0.05 mL, 0.5 mmol) was added to the mixture. The resulting mixture was stirred for 10 h at 0–5 °C and then allowed to warm to room temperature, and kept stirring for another 38 h at the same temperature.[18] The reaction was quenched by the addition of saturated aqueous NH_4Cl (4 mL). The mixture was extracted with Et_2O (3 × 8 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by the preparative silica gel TLC plate (hexane/EtOAc = 4/1) afforded the (*S*)-1-phenyl-1-propanol in 97% yield. The ee was determined by HPLC analyses using a chiral column.

Table 2. Crystal data for **1a**, **1b**, and **2**

	1a	**1b**	**2**
Formula	$C_{26}H_{25}FeNO$	$C_{20}H_{29}FeNO$	$C_{15}H_{17}FeNO_2$
F_w	423.32	355.29	299.15
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$
Crystal size (mm)	0.20×0.18×0.18	0.20×0.18×0.18	0.20×0.18×0.18
a (Å)	8.5957(17)	11.302(2)	7.6029(15)
b (Å)	10.372(2)	11.331(2)	11.742(2)
c (Å)	12.380(3)	14.473(3)	15.540(3)
β (°)	103.54(3)	90	90
V (Å^3)	1073.1(4)	1853.4(6)	1387.3(5)
Z	2	4	4
F (000)	444	760	624
D_{calcd} g cm^{-3}	1.310	1.273	1.432
μ (Mo K$_\alpha$) (mm^{-1})	0.719	0.818	1.083
R	0.0398	0.0533	0.0425
R_w	0.0753	0.0697	0.0645

4.6. Crystallographic studies

Crystallographic data for **1a**, **1b**, and **2** were measured on a Rigaku RAXIS-IV imaging plate area detector, and summarized in Table 2. The data were collected at 291(2) K using graphite monochromated Mo K$_\alpha$ ($\lambda = 0.71073$ Å), $3.38° < 2\theta < 55.14$ for **1a**, $4.56° < 2\theta < 50°$ for **1b**, and $4.34° < 2\theta < 55°$ for **2**. The structures were solved by a direct method and expanded using Fourier techniques. The nonhydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. All calculations were performed using the teXsan crystallographic software package.

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