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The effect of direct steric interaction between substrate substituents and ligand substituents on enantioselectivities in asymmetric addition of diethylzinc to aldehydes catalyzed by sterically congested ferrocenyl aziridino alcohols

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Abstract—The direct strong steric interaction between substrate substituents and ligand substituents was first discovered in asymmetric addition of diethylzinc to aldehydes catalyzed by sterically congested ferrocenyl aziridino alcohol derivatives. In addition, this nonbonded steric repulsion influenced significantly enantioselectivities of this reaction, and even led to inversion of the absolute configuration. This fact was further confirmed by the theoretical calculations and the design of a new chiral ferrocenyl aziridino alcohol ligand. A plausible mechanism for this asymmetric reaction was also proposed.

1. Introduction

Since the initial report of Oguni and Omi on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (*S*)-leucinol with moderate enantioselectivity (49% ee) in 1984,[1] many chiral ligands have been synthesized to induce asymmetry in this reaction, the majority of which have been β-amino alcohols.[2] Several types of transition states for this transformation have been proposed in the literature.[2a,3] Noyori and co-workers have studied the reaction mechanism extensively, both experimentally[4] and theoretically.[5] In 1995, based on the molecular orbital calculations at the restricted Hartree–Fock (RHF) level,[5a] Yamakawa and Noyori established the 5/4/4-fused tricyclic transition states (TS)—*syn*- and *anti*-orientation of the terminal rings and one bicyclic TS (Fig. 1). Among the three possible stereoisomeric TS, the tricyclic *anti*-configuration is the most favored, being 12–13 kJ/mol more stable than tricyclic *syn*-configuration, and 29 kJ/mol more stable than the bicyclic TS. In the tricyclic *anti*-TS, alkyl migration takes place with retention of configuration, whereas the high-energy bicyclic pathway would give inversion of the migrating alkyl group. These results have been reproduced by Houk and Goldfuss in the PM3 and ONIOM (EHF/LanL2DZ:UFF) TS models.[6]

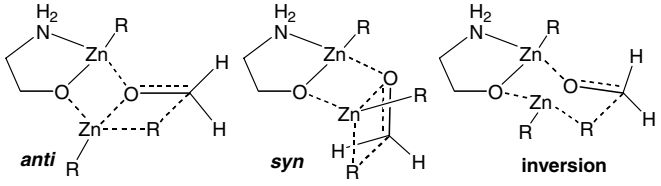

Figure 1. Transition states characterized by Yamakawa and Noyori.

According to these theoretical studies, the tricyclic transition state model of the *anti*-type correctly predicts the absolute configuration of products.[2a,5] As illustrated in Figure 2, diethylzinc reacts firstly with the ligand β-amino alcohols to afford the corresponding zinc aminoalkoxide **1** and then is converted to the zinc monoalkoxide–diethylzinc complex **2**. Benzaldehyde coordinates at the less hindered face of the five-membered ring chelate **1**. The ethyl group transfers from the diethylzinc to the aldehyde both from the *Si*-face and *Re*-face results in the *anti*-5/4/4-fused tricyclic transition states **3** and **4**, respectively. In the transition state **3**, a nonbonded repulsion between Et and Ph is absent. As

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a result, this transition state is the favored structure and leads to (*S*)-1-phenyl-1-propanol. On the other hand, the significant steric interaction between the Et and Ph groups disfavors transition state **4**, which leads to (*R*)-1-phenyl-1-propanol.

The tricyclic transition state model of the *anti*-type qualitatively predicts the degree of enantioselectivity as well.[2a] As is seen in Figure 2, two bulky *cis*-disubstituted groups (R_L and R'_L) in the five-membered chelate complexes **1** are the most desirable, because the directing effects of the vicinal substituents cooperate in keeping a single chiral integrity **3**, which leads to excellent enantioselectivities. If two bulky groups (R_L and R'_L) in the Zn chelate **1** are positioned *anti* to each other, the directing effects partly offset each other, but the α stereogenic center is more influential than the β center. As a result, a decrease in enantioselectivity is generated compared to two *cis*-disubstituted groups (R_L and R'_L).

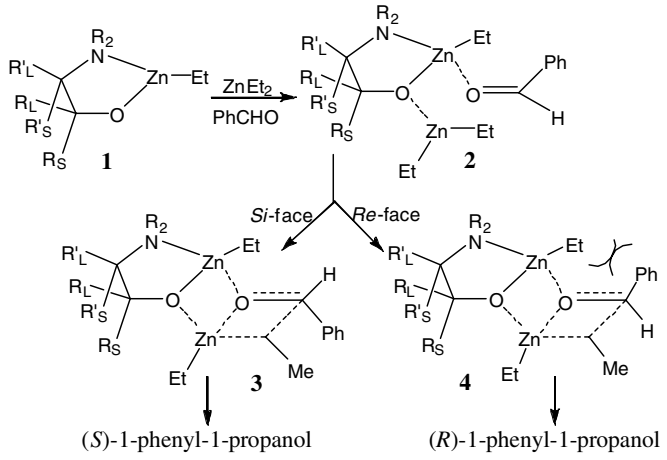


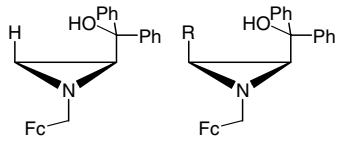
Figure 2. Transition structures derived from β-amino alcohol.

Noyori and Yamakawa,[5b] based on transition state model and theoretical calculations, believed that steric repulsions between substituents are absent in the tricyclic transition state model of the *anti*-type **3**, which is the most favored transition structure possessing an electronically favored *anti*-5/4/4 tricyclic alignment, which contains little steric constraint, suitably accommodating the substituents in space. So, direct steric interaction between carbonyl substituents and α- or β-substituents of the chiral auxiliaries is also unimportant.[2a] To the best of our knowledge, studies on the effect of nonbonded repulsion between carbonyl substituents and chiral ligand substituents on enantioselectivities have never been reported. Interestingly, in the presence of rigid and sterically congested ferrocenyl aziridino alcohol ligands, the remarkable effect of strong direct steric interaction between substrate substituents and ligand substituents on enantioselectivities was firstly observed in asymmetric addition of diethylzinc to aldehydes. In this paper, we report our findings on the effect of strong direct steric interaction between substrate substituents and ligand substituents on enantioselectivities and theoretical calculations.

2. Results and discussion

More recently, a variety of chiral ferrocenyl aziridino alcohol ligands such as **5** and **6** were designed and synthesized[7,8] because they were β-amino alcohols possessing unique structural characteristics as follows: (1) the aziridine ring has the smallest ring area, but most rigid three-membered ring backbone, as compared with the corresponding azetidine and pyrrolidine rings. Therefore, we call chiral ferrocenyl aziridino alcohols 'rigid and sterically congested ligands'. (2) The introduction of bulky and rigid ferrocenyl groups on the nitrogen atom makes this structure become more rigid. In addition, the crystal structures of some chiral ferrocenyl aziridino alcohols reveal that the nitrogen atom on the aziridine ring becomes also a stereocenter.[7a,8b] One possible reason is that the strong repulsive interaction between the bulky and rigid ferrocenyl group on the nitrogen atom of the aziridine ring and the bulky diphenylhydroxymethyl group on the three-membered ring leads to this tetrahedral structure that is a stable conformation. Another reason is due to formation of an intramolecular hydrogen bond, which further prevents nitrogen pyramidal inversion.

In our previous papers,[7] we reported the synthesis of chiral ferrocenyl aziridino alcohol ligands **5** possessing only one single stereogenic center and application in the enantioselective addition of diethylzinc to aldehydes with excellent enantioselectivities of up to 98.8% ee (substrate: *m*-ClC_6H_4CHO). When we investigated the effect of newly introduced methyl group ($R = Me$) on the aziridine ring and newly formed stereogenic carbon on the reactivity and enantioselectivity of reaction in the presence of chiral ferrocenyl aziridino alcohol ligands **6** bearing two stereogenic centers,[8a] we found that introduction of a methyl group, which was positioned *syn* to the dialkylhydroxymethyl group on the aziridine ring, sharply decreased the enantioselectivity from 92.6% ee to 8% ee in the addition of diethylzinc to benzaldehyde. The results suggested that the steric hindrance of the methyl group, compared to hydrogen atom, led to the remarkable drop in ee values.



5: 92.6% ee **6** (R = Me): 8% ee

According to Noyori and Yamakawa's reaction mechanism (Fig. 3),[5] the steric hindrance of the methyl group of **6** can strengthen the directing effects in the five-membered chelate complexes **7**, followed by forming the favored *anti*-5/4/4-fused tricyclic transition state **8**, which gives (*R*)-1-phenyl-1-propanol, by the reaction of **7** with diethylzinc and benzaldehyde. Based on transition state model **8**, it is very difficult to explain our experimental results. How does the steric hindrance of the methyl group work?

For many catalytic processes, the use of different ligands belonging to the same family does not provoke any mechanistic change. Based on a great number of previous theo-

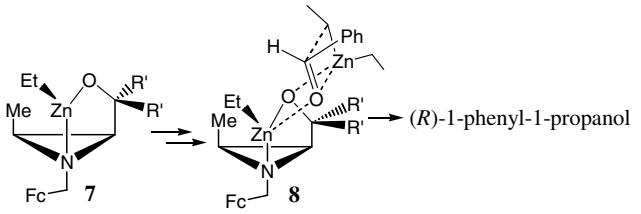


Figure 3. Transition structures derived from ferrocenyl aziridino alcohols.

retical studies on the mechanism of this reaction[2a,3–6] and our results,[7,8] a plausible mechanism for the enantioselective addition of diethylzinc to benzaldehydes catalyzed by ligands **5** and **6** is proposed (Fig. 4).

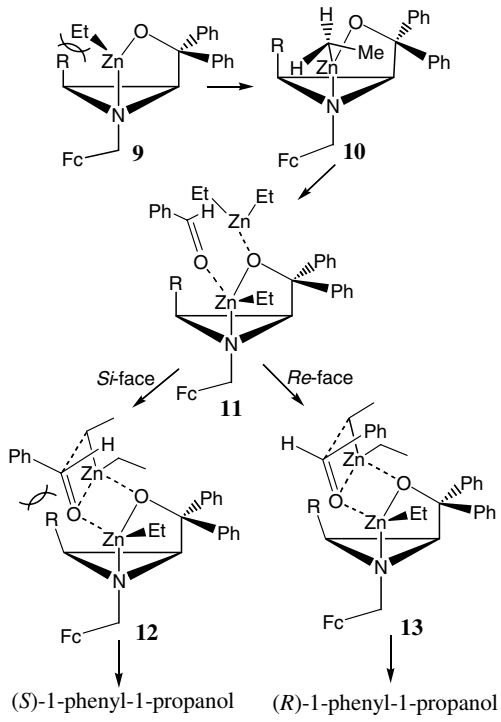


Figure 4. Transition structures derived from ferrocenyl aziridino alcohols.

The reaction of diethylzinc with the ligand **5** and **6** first generates the corresponding zinc aminoalkoxide **9**, which acts as a bifunctional catalyst.[5a] In this sterically congested structure **9**, the presence of nonbonded repulsions between R and Et groups makes Me group of the tricoordinate Zn atom far away from R group, as envisaged from **10** shown in Figure 4. The lone pair electrons of the oxygen atom of benzaldehyde coordinate the Lewis acidic Zn atom at the less hindered face of the five-membered ring chelate **10**, and then the adjacent basic oxygen accepts diethylzinc at Zn to form the product-forming, mixed-ligand complex **11**. The ethyl group transfer from the diethylzinc to the aldehyde both from the *Si*-face and *Re*-face results in the *anti*-5/4/4-fused tricyclic transition states **12** and **13**, respectively. In the transition state **12**, a nonbonded repulsion between Et and Ph is absent, but steric repulsive interaction between the R and Ph groups disfavors the transition state **12**. The more bulky the R group is, the stronger the direct steric interaction between the R and Ph groups is. When R = H (the ligand **5**), this steric nonbonded repulsion between H and Ph is not obvious. Consequently, the transition state **12** is the favored structure and leads to (*S*)-1-phenyl-1-propanol with outstanding enantioselectivity of up to 92.6% ee. When R = Me (the ligand **6**), this direct steric interaction between Me and Ph increases and leads to (*S*)-1-phenyl-1-propanol with poor enantioselectivity of 8% ee. The results suggested that the direct nonbonded repulsion between carbonyl substituents and substituents of chiral ligands exists in the asymmetric addition of diethylzinc to aldehydes catalyzed by aziridino alcohol derivatives. In addition, this interaction is very strong and has a significant impact on enantioselectivities.

In order to verify this fact, the activation energies of structures **12** and **13** were calculated for formation of the *R* and *S* enantiomers at HF/6-31G level. Due to calculation difficulty, a ferrocenyl group of ligands **5** and **6** is replaced by a phenyl group. The results are summarized in Table 1. As can be seen from Table 1, the favored (*S*)-generating structure, *anti-Si*-**12**, is 16.60 kJ/mol more stable than the forming structure *anti-Re*-**13** when R group is hydrogen atom, while the favored (*S*)-generating structure, *anti-Si*-**12**, is only 9.78 kJ/mol more stable than the forming structure *anti-Re*-**13** when R is methyl group. The smaller difference ($\Delta E_a = 9.78$ kJ/mol) between these activation energies (R = Me), as compared to 16.60 kJ/mol (R = H), appears to arise mainly from nonbonded repulsion between the phenyl group of benzaldehyde and methyl group of chiral ligands.

In order to further verify this fact, we designed and synthesized a new chiral ferrocenyl aziridino alcohol ligand **18** from starting material *allo*-L-threonine according to our previous reported procedure.[8] The preparation of aziridino alcohol **18** is shown in Scheme 1. First, ferrocene-carboxaldehyde **14** was reacted in CH_3OH in the presence of Et_3N with methyl *allo*-L-threonine ester hydrochloride giving the corresponding imine **15**. Then, reduction of **15**, carried out on the crude reaction mixtures, with sodium borohydride in methanol provided the compound **16** in 60% overall yield after work-up. Next, **16** was cyclized to the aziridino ester **17** in 95% yield by reaction with Ph_3P in the presence of CCl_4 in CH_3CN. Treatment of **17** with excess of PhMgBr, afforded the ligand **18** (99%).

With the new chiral ligand **18** in hand, under conditions identical to those for **6**, the reaction of diethylzinc with benzaldehyde afforded (*S*)-1-phenyl-1-propanol in excellent yield (99%) with outstanding enantioselectivity of up to 96% ee (Scheme 2). As expected, the absolute configuration change at 3-position on the aziridine ring led to a substantial increase in enantioselectivity from 8% to 96% ee.

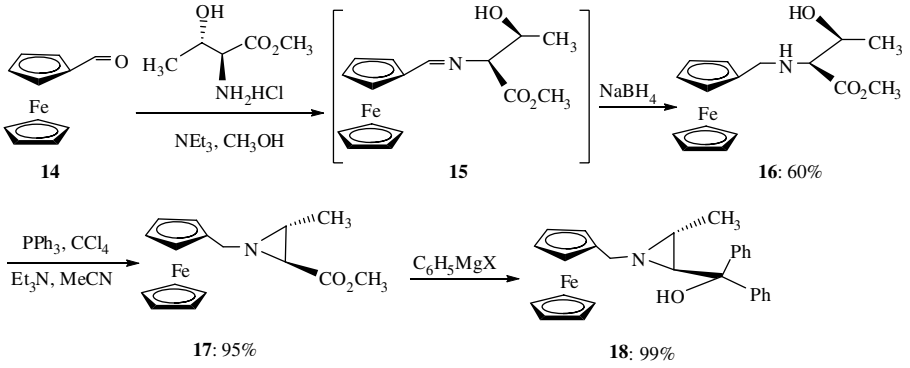
Comparing the structure of **18** with that of **6**, the differences of the compounds **18** and **6** are that methyl group on the aziridine ring was positioned *anti* to the diphenylhydroxymethyl group in **18**; whereas the methyl group was *syn* to the diphenylhydroxymethyl group in **6**. Based on our proposed mechanism, the reaction of the chiral ligand **18** with diethylzinc and benzaldehyde generated

Table 1. Calculated activation energies of structures **12** and **13**[a]

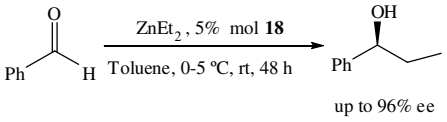
TS	R	E (Hartree)[b]	TS (Hartree)	E_a (kJ/mol)	ΔE_a (kJ/mol)
anti-Si-**12**	H	−1679.869555	−1679.838344	81.94	16.60
anti-Re-**13**			−1679.832022	98.54	
anti-Si-**12**	CH_3	−1718.884552	−1718.849591	91.79	9.78
anti-Re-**13**			−1718.845868	101.57	

[a] All calculations were performed using GAUSSIAN 03 program. All geometries of transition states as well as the reactants were optimized at the HF level using the 6-31G basis set for C, H, N, and O, LanL2DZ basis set for Zn. The frequency analysis was carried out on the basis of the RHF calculations. The single-point energy was determined at the same level.

[b] Energies of reactants.

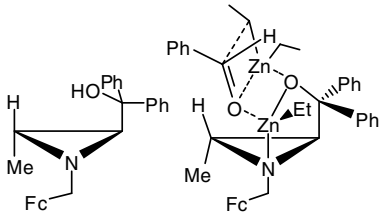


Scheme 1. Synthesis of chiral ligand **18**.



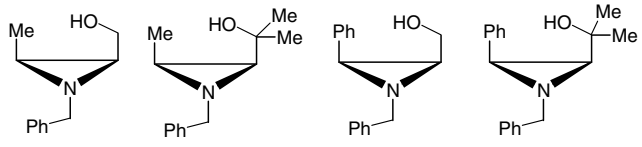
Scheme 2. Addition of diethylzinc to benzaldehyde.

the transition state **19**, which was the favored structure because a direct strong steric interaction between methyl and Ph was absent. Therefore, (*S*)-1-phenyl-1-propanol with high enantioselectivity of up to 96% ee was obtained.



Based on our proposed mechanism and transition state model, the direct nonbonded repulsion between R and phenyl groups will further be strengthened when the steric hindrance of R group on the aziridine ring of chiral ligands **6** increases further. Therefore, the significant steric interaction between the R and Ph groups makes the transition state **12** become the disfavored structure, which gives (*S*)-1-phenyl-1-propanol. On the other hand, the absent steric interaction between the R and Ph groups favors the transition state **13**, which affords (*R*)-1-phenyl-1-propanol. According to the above analyses, we predict that an inversion of absolute configuration in product will take place when the steric hindrance of R group on the aziridine ring of chiral ligands **6** is big enough.

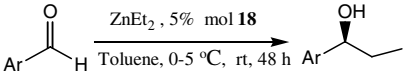
Our prediction was supported by Tanner and Andersson's experimental results.[9] For instance, the replacement of a methyl group with a bulky phenyl group led to the inversion from (*S*)-configuration to the (*R*)-configuration, comparing compounds **20** and **21** with **22** and **23**, respectively. However, these phenomena could not be rationalized by Tanner and Andersson.



20: *S*, 38% ee **21:** *S*, 30% ee **22:** *R*, 87% ee **23:** *R*, 42% ee

To the best of our knowledge, this is the first discovery that the direct strong nonbonded interaction between substrate substituents and ligand substituents leads to remarkable differences of enantioselectivities in asymmetric addition of diethylzinc to aldehydes, and even inversion of the configuration. We believe that this direct strong nonbonded repulsion between substrate substituents and ligand substituents exists when rigid and sterically congested aziridino alcohol ligands are used as catalysts for asymmetric addition of diethylzinc to aldehydes. As a supplement to Noyori and Yamakawa's transition state model, we expect the present work to be of interest to all scientists dealing with the design of chiral ligands and reaction mechanism and asymmetric catalysis.

Table 2. Asymmetric addition of diethylzinc to aldehydes using ligands **7**[a]



Entry	ArCHO	Yield (%)[b]	Ee (%)[c]	Confign.[d]
1	C_6H_5CHO	99	96	*S*
2	*p*-$MeOC_6H_4CHO$	81	85	*S*
3	*m*-$MeOC_6H_4CHO$	88	90	*S*
4	*o*-$MeOC_6H_4CHO$	96	83	*S*
5	Heliotripine	92	92	*S*
6	*m*-ClC_6H_4CHO	82	99.8	*S*
7	*m*-BrC_6H_4CHO	91	91	*S*
8	Ferronenyl aldehyde	89	92	*S*
9	PhCH=CHCHO	92	81	*S*

[a] The mole 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 the sign of specific rotation of a known compound and the known elution order from a Chiralcel OD column.

The above exciting results prompted us to probe whether this improvement existed in other aldehydes. Thus, a variety of aldehydes were used subsequently with chiral ligand **18**. The results are summarized in Table 2. The results reveal that the new chiral ligand **18** is a highly efficient catalyst for the reaction of diethylzinc with arylaldehydes to afford optically active secondary alcohols in high yield (81–99%) and with excellent enantioselectivities in the range 83–99.8% ee. The ligand **18** was also tested with an α,β-unsaturated aliphatic aldehyde. It was found that this catalyst is also very effective in the enantioselective addition of diethylzinc to α,β-unsaturated aliphatic aldehyde (Table 2, entry 9).

3. Conclusion

In conclusion, we have reported a new discovery of the presence of the strong direct steric interaction between substrate substituents and ligand substituents in the asymmetric addition of diethylzinc to aldehydes catalyzed by ferrocenyl aziridino alcohol derivatives and the significant effect of this nonbonded repulsion on enantioselectivities. In addition, this fact was verified by theoretical calculations and the design of a new chiral ferrocenyl aziridino alcohol ligand **18**. A plausible mechanism for this asymmetric reaction is proposed. Based on our transition state model, a prediction of the inversion of configuration was made, and then was supported by Tanner and Andersson's experimental results. Our efforts to develop novel ferrocenyl aziridino alcohols as chiral ligands for asymmetric synthesis are underway in our laboratory and will be reported in due time.

4. Experimental

4.1. General

Melting points were determined using YRT-3 melting point apparatus, and were uncorrected. Optical rotations were measured with Perkin ELmer, model 341 Polarimeter at 20 °C in $CHCl_3$. The ee value 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 hertz. IR Spectra were determined on a Therme Nicolet IR 200 spectrophotometer. TLC was performed on dry silica gel plates developed with hexane/ethyl acetate. Mass spectra were obtained using a Waters a-Tof micro™ instrument with an electrospray ionization source (ESIMS). All the ESIMS spectra were performed using MeOH as the solvent.

4.2. Reagents and solvents

Methyl *allo*-L-threonine ester hydrochloride was prepared according to a published procedure.[10] Ether was distilled from sodium benzophenone ketyl. Tetrahydrofuran (THF) was pre-dried over calcium chloride, and then distilled from $LiAiH_4$. 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 pet ether (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 are commercially available and were used as received.

4.3. Synthesis of methyl (2*S*,3*S*)-*N*-ferrocenylmethyl-*allo*-L-threomine ester 16

Methyl *allo*-L-threonine ester hydrochloride (1.55 g) was dissolved in 8 mL of anhydrous methanol and cooled to 0 °C. Triethylamine (1.4 mL) was added, and the reaction was stirred for 10 min. Ferrocene carboxaldehyde **14** (1.95 g) was added, and the reaction was monitored by TLC. After the reaction mixture was stirred for 4 h, sodium borohydride (0.4 g) was added portionwise to the reaction mixture over a period of 0.5 h. After stirring for 5 h, methanol was evaporated under reduced pressure at 40 °C. The resulting residue was carefully neutralized with 3% HCl to pH = 7–8, and extracted three times with 3 × 20 mL portion of EtOAc. The combined ether extract was washed with brine, dried over Na_2SO_4, and evaporated under the reduced pressure. The resulting residue was purified by the preparative TLC with petroleum (60–90 °C)/Et_2O (1:1) as developing solvent to give **16** in 60% yield (1.8 g); mp 87.8–88.8 °C; $[\alpha]_D^{20} = -40.8$ (*c* 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.09 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 2.1–2.8 (br s, 2 H, *OH*, *NH*), 3.46 (d, *J* = 7.6 Hz, 1H, $COCH$), 3.42, 3.58 (dd, *J* = 12.4 Hz, each 1H, $NHCH_2$), 3.76 (s, 3H, OCH_3), 4.01–4.09 (m, 1H, CH_3CH), 4.12–4.24 (m, 9H, Fc*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ

18.62, 47.83, 51.88, 65.34, 66.85, 67.72, 67.78, 68.34, 68.45, 85.75, 173.25. IR (KBr): 3322, 3171, 2982, 2943, 2907, 2851, 1726, 1479, 1377, 1318, 1264, 1206, 1171, 1128, 1093, 1030, 1008, 987, 917, 818 cm^{-1}. HRMS (ESI): *m/z* $(M+H)^+$ calcd for $C_{16}H_{21}FeNO_3$ 331.0871; found: 331.0875.

4.4. Synthesis of methyl (2*S*,3*R*)-1-ferrocenylmethyl-3-methylaziridine-2-carboxylate 17

To a stirred solution of triphenylphosphine (3.5 g, 13.3 mmol) in acetonitrile (40 mL) was added carbon tetrachloride (20 mL). The solution turned yellow over a period of 0.5 h, at which time **16** (1.5 g, 4.5 mmol) was added dropwise in a solution of Et_3N (2 mL, 14.4 mmol) and acetonitrile (15 mL). The reaction mixture was stirred for 2 h at 0 °C, 14 h at room temperature. Removal of the solvent, followed by the preparative TLC of the residue with petroleum (60–90 °C)/Et_2O (1:1) as developing solvent afforded **17**: 1.34 g (95%). **17** was obtained as a 1.7:1 mixture of invertomers at nitrogen: $[\alpha]_D^{20} = -86.6$ (*c* 0.77, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ major invertomer: 1.20 (d, $J = 5.6$ Hz, 3H, CH*CH*$_3$); 2.24–2.28 (m, 1H, CH_3*CH*); 2.34 (d, $J = 2.8$ Hz, 1H, CO*CH*); 3.63, 4.07 (dd, $J = 12.8$ Hz, each 1H, N*CHH′*); 3.75 (s, 3H, O*CH*$_3$); 4.10–4.26 (m, 9H, Fc*H*). Minor invertomer: 1.39 (d, $J = 6.0$ Hz, 3H, CH*CH*$_3$); 1.99 (d, $J = 2.8$ Hz, 1H, CO*CH*); 2.48–2.51 (m, 1H, CH_3*CH*); 3.34, 3.57 (dd, $J = 12.8$ Hz, each 1H, N*CHH′*); 3.70 (s, 3H, O*CH*$_3$); 4.10–4.26 (m, 9H, Fc*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ major invertomer: 17.91, 40.99, 42.75, 50.63, 67.83, 67.89, 68.04, 68.48, 68.61, 68.74, 85.12, 170.28. Minor invertomer: 10.92, 40.03, 44.15, 51.99, 67.83, 67.89, 68.04, 68.48, 68.61, 68.74, 84.89, 171.64. IR (KBr): 3100, 2994, 2952, 2925, 1729, 1438, 1400, 1341, 1202, 1179, 1126, 1105, 1054, 1023, 1001, 925, 818 cm^{-1}. HRMS (ESI): *m/z* $(M+Na)^+$ calcd for $C_{16}H_{19}FeNO_2$: 336.0663; found: 336.0668.

4.5. Synthesis of (2*S*,3*R*)-1-ferrocenylmethyl-3-methylaziridin-2-yl(diphenyl)methanol 18

A Grignard reagent was prepared in the usual way from 76.8 mg (3.2 mmol) of magnesium and bromobenzene 3.2 mmol in THF (5 mL). The solution was cooled to −20 °C before addition of a solution of **17** (125 mg, 0.4 mmol) in THF (2 mL). The mixture was 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 phases were separated and the aqueous phase was extracted with Et_2O (3×5 mL). The combined organic phases were washed with brine (15 mL), dried over Na_2SO_4, and after filtration, the solvent was removed under reduced pressure. The resulting residue was purified by preparative TLC with hexane/EtOAc (4:1) as developing solvent to give **18** (173 mg, 99%); mp 144–145 °C; $[\alpha]_D^{20} = -10.0$ (*c* 0.46, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (d, $J = 5.8$ Hz, 3H, *CH*$_3$); 2.12–2.16 (m, 1H, CH_3*CH*); 2.20 (d, $J = 3.2$ Hz, 1H, CH_3CH*CH*); 3.20, 3.64 (dd, $J = 13.2$ Hz, each 1H, *CHH′*N); 3.89–4.09 (m, 9H, Fc*H*); 7.23–7.38 (m, 10H, Ph*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.15, 35.06, 49.51, 53.05, 65.90, 67.93, 68.48, 68.92, 73.97, 126.12, 126.50, 127.01, 128.06, 128.11. IR (KBr): 3314, 3085, 3055, 3024, 2994, 2854, 1667, 1597, 1489, 1447, 1387, 1319, 1265, 1180, 1114, 1084, 1029, 997, 901, 818, 750, 698, 488. HRMS (ESI): *m/z* $(M+H)^+$ calcd for $C_{27}H_{27}FeNO$: 438.1520; found: 438.1508.

4.6. General procedure for the enantioselective addition of Et_2Zn to arylaldehydes

A solution of diethylzinc (1 M in *n*-hexane, 1.1 mL) was added to a solution of a chiral catalyst (0.025 mmol, 5 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 in 0–5 °C and was allowed to warm to room temperature, and kept stirring for another 38 h at the same temperature. 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. The ee was determined by HPLC analyses using a chiral column.

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