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Chiral C_2-symmetric 2,3-disubstituted aziridine and 2,6-disubstituted piperidine as chiral ligands in the addition reaction of diethylzinc with arylaldehydes

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Abstract

Chiral C_2-symmetric 2,3-disubstituted aziridines and 2,6-disubstituted piperidines having a β-amino alcohol moiety have been successfully synthesized and their catalytic chiral induction properties have been examined in the asymmetric addition reactions of diethylzinc with arylaldehydes in hexane. When *N*-(2,2-diphenyl-2-hydroxyethyl)-(*S*,*S*)-2,3-bis(methoxymethyl)aziridine **11** was used as a catalytic chiral ligand, *sec*-alcohols having (*S*)-configuration formed in high yields of 86–92% but low enantiomeric excesses (ee's) of 11–13%. However, when *N*-(2,2-diphenyl-2-hydroxyethyl)-(*R*,*R*)-2,6-disubstituted piperidine derivatives **16** and **20** were used as the chiral ligands under the same reaction conditions, the ee's of the corresponding *sec*-alcohols were 20–30 and 5–6%, respectively, along with the inversion of absolute configuration. A plausible mechanism for this inversion is proposed.

1. Introduction

The high efficiencies of C_2-symmetric chiral reagents, including auxiliaries and catalyst ligands, in asymmetric induction has attracted much attention in asymmetric synthesis.[1] Previously, we reported chiral C_2-symmetric 2,4-disubstituted azetidine and 2,5-disubstituted pyrrolidine derivatives as chiral catalyst ligands in the reaction of diethylzinc with aldehydes.[2] Very high yields and very high enantioselectivities have been achieved in this asymmetric addition reaction.[2,3] The relatively rigid C_2-symmetric four- and five-membered ring structures are considered to be the determining factor for the effectiveness of these ligands in such asymmetric catalytic reactions. Although the backbone structures of chiral scaffolds are important to chiral induction, little is known about the real influence of chiral C_2-symmetric cyclic amines of

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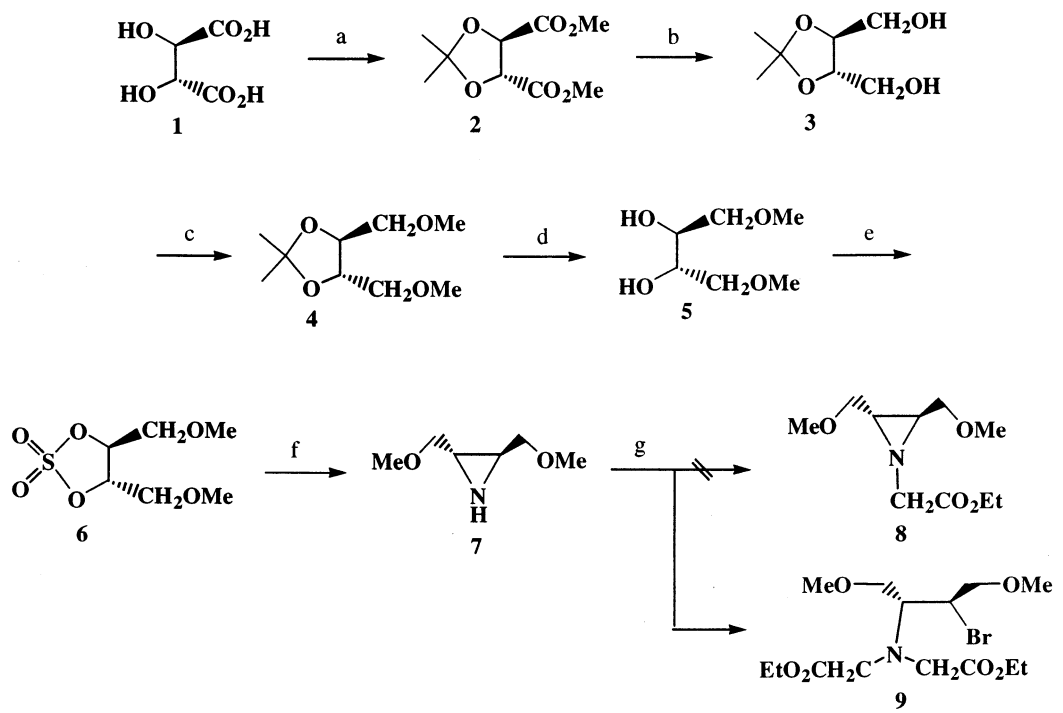
different ring sizes on chiral induction. As such, our aim is to design and synthesize novel chiral ligands with C_2-symmetric three- and six-membered ring structures to enable us to observe the effect of ring structure variations of the catalyst on chiral induction. This systematic investigation will give us useful information for the future design and synthesis of these ligands. Herein, we present the synthesis of some novel chiral C_2-symmetric aziridine and piperidine derivatives bearing a β-amino alcohol moiety and their use as asymmetric catalysts in the reaction between diethylzinc and arylaldehydes.

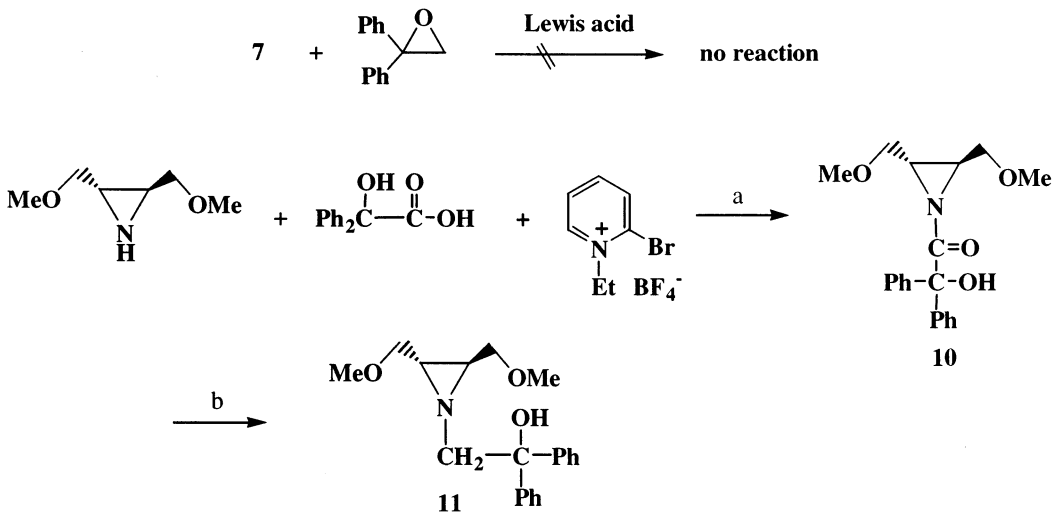
2. Results and discussion

The key intermediate of C_2-symmetric aziridine **7** was prepared from the chiral pool L-tartaric acid according to the literature[4] (Scheme 1). But when compound **7** was treated with ethyl α-bromoacetate, we found that a ring opened compound **9** was obtained as the major product rather than *N*-(ethoxycarbonylmethyl)-(*S*,*S*)-2,3-bis(methoxymethyl) **8**. We examined this reaction under various conditions and eventually we confirmed that **8** could not be obtained from the reaction of **7** with ethyl α-bromoacetate. Somfai also reported in 1994 that attempts to benzylate aziridine using triethylamine and benzyl bromide in THF gave, somewhat surprisingly, only a low yield of *N*-benzylated aziridine along with considerable amounts of *N*,*N*-dibenzylated amines.[5] They gave the plausible mechanism to explain why the ring opened amine could be



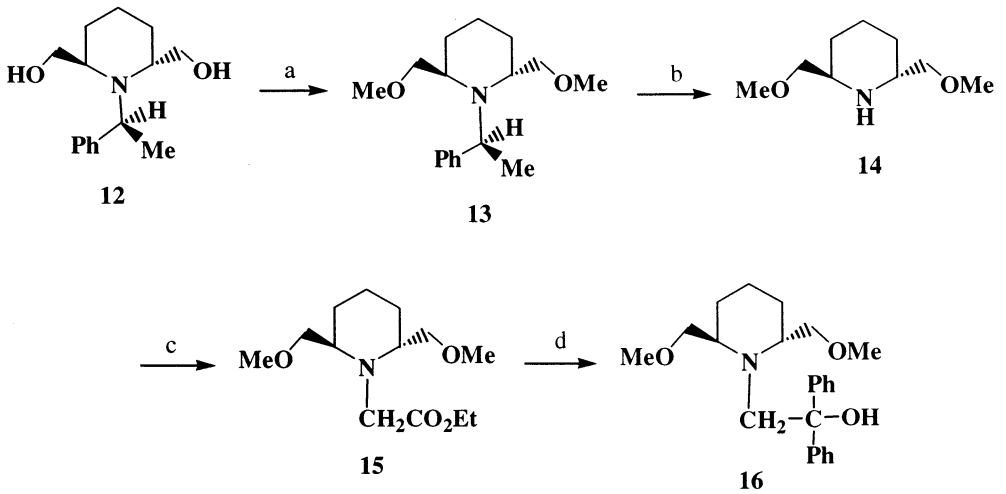
Scheme 1. Conditions: (a) $Me_2C(OMe)_2$, TsOH, MeOH, reflux; 83%. (b) $LiAlH_4$, THF, reflux, 3 h; 85%. (c) MeI, NaH, THF, rt–reflux; 89%. (d) 9% H_2SO_4 in MeOH, 0°C–rt, 2 h; 90%. (e) $SOCl_2$, $NaIO_4$, $RuCl_3{\cdot}3H_2O$, THF, reflux; 90%. (f) LiN_3, THF, reflux, 8 h then $LiAlH_4$, THF, reflux, 30 h; 40%. (g) $BrCH_2CO_2Et$, K_2CO_3, MeCN, 0°C–rt, 24 h; 50%

formed. Meanwhile, they found an improved procedure for achieving the *N*-alkylation of aziridine using K_2CO_3/18-crown-6 in THF.[5] But in the reaction of **7** with ethyl α-bromoacetate or ethyl α-chloroacetate, only the ring opened amine formed even when Somfai's improved reaction procedure was employed. We believe that this is due to the highly strained aziridine ring which can be easily opened by nucleophilic attack of bromide or chloride ion. In an alternative approach we also tried to utilize **7** to directly react with 1,1-diphenylethylene oxide in the presence of Lewis acids such as $Cu(OTf)_2$, $Yb(OTf)_3$ or $Ti(OPr^i)_4$ to synthesize the desired ligand. But we found that no reactions occurred (Scheme 2). Thus, we finally utilized the Mukaiyama condensation reagent (2-bromo-1-ethylpyridinium tetrafluoroborate: BEP)[6] to successfully prepare the desired chiral β-amino alcohol **11**, in a low 26% yield (Scheme 2).



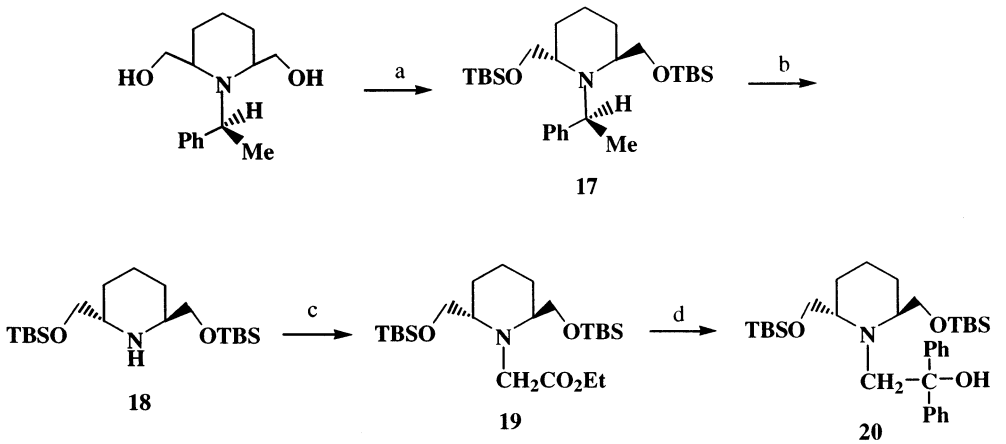
Scheme 2. Conditions: (a) CH_2Cl_2, DIPEA, 2 days, –20°C–rt; 41%. (b) $LiAlH_4$, THF, 0°C, 24 h; 26%

The optically active C_2-symmetric 2,6-disubstituted piperidine derivatives could be synthesized by the method reported for the preparation of chiral C_2-symmetric azetidine 2,4-dicarboxylic acid esters and pyrrolidine 2,5-dicarboxylic acid esters.[4,7] Optical resolution was achieved by silica gel column chromatographic separation (eluent: methanol/dichloromethane = 1/100) to afford the (2*R*,6*R*)-diol **12**[8] (Scheme 3). We could readily introduce protecting methoxy groups on the 2,6-position of the ring to obtain compound **13** (Scheme 3). The 2-phenethyl chiral auxiliary was then removed by catalytic hydrogenation over $Pd(OH)_2/C$ (20%) to give the corresponding chiral C_2-symmetric 2,6-disubstituted piperidine **14** which was subsequently treated with ethyl α-bromoacetate and then phenylmagnesium bromide in a Grignard reaction to afford the desired β-amino alcohol **16**. All of the synthetic steps are very similar to those used in the synthesis of the corresponding 2,4-disubstituted azetidine and 2,5-disubstituted pyrrolidine derivatives[2,3] (Scheme 3). It should be emphasized here that the separation of the diol **12** was very difficult because of its high polarity and additionally the three diastereomers have very similar R_f in TLC. Only the (2*R*,6*R*)-diastereomer could be isolated in pure form, and we obtained only 120 mg of pure compound **12** from 6 g of diastereomeric mixture. The optical purity of **12** was checked by comparison of the specific rotation of **14** $\{[\alpha]_D^{20}$ −7.8 (*c* 0.6, $CHCl_3)\}$ with that of an authentic sample $\{[\alpha]_D^{20}$ −7.9 (*c* 0.6, $CHCl_3)\}$.[8]



Scheme 3. Conditions: (a) MeI, NaH, THF, rt–reflux, 89%. (b) H_2, $Pd(OH)_2$, MeOH; 80%. (c) $BrCH_2CO_2Et$, K_2CO_3, MeCN, 0°C–rt, 24 h; 50%. (d) PhMgBr, THF, 0°C, 12 h; 75%

Moreover, we found that the (2*S*,6*S*)-diastereomer **17** could be isolated in pure form if TBS (*tert*-butyldimethylsilyl) groups were introduced on the 2,6-positions of the six-membered ring (Scheme 4). Compound **17** (100 mg) was obtained from 2.24 g of diastereomeric mixture using silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 100/1). After removal of the 2-phenethyl chiral auxiliary by catalytic hydrogenation over $Pd(OH)_2/C$ (20%), the optical purity was checked by comparison of the specific rotation of **18** {$[\alpha]_D^{20}$ +18.2 (*c* 0.44, $CHCl_3$)} with that of an authentic sample {$[\alpha]_D^{20}$ +18.9 (*c* 0.9, $CHCl_3$)}.[8] The novel chiral C_2-symmetric β-amino alcohol **20** was then prepared by treating **18** with ethyl α-bromoacetate and then phenylmagnesium bromide (Scheme 4). Thus, the (2*S*,6*S*)-diastereomer with a six-membered ring could be isolated in pure form by changing the alcohol protecting group.



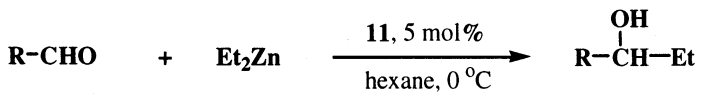
Scheme 4. Conditions: (a) TBDMSCl, imidazole, CH_2Cl_2, rt, 30 h; 76%, then silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 100/1). (b) H_2, $Pd(OH)_2$, MeOH; 90%. (c) $BrCH_2CO_2Et$, K_2CO_3, MeCN, 0°C–rt, 24 h; 90%. (d) PhMgBr, THF, 0°C, 12 h; 70%

It is well known that the reaction of aldehydes with diethylzinc to give the corresponding *sec*-alcohols takes place in the presence of a catalytic amount of β-amino alcohol.[9] Excellent chiral inductions including asymmetric amplifications by use of chiral β-amino alcohols in this reaction have been reported.[10]

In order to clarify the chiral induction properties of these C_2-symmetric aziridine, pyrrolidine and piperidine functionalised β-amino alcohols and the difference on chiral induction between the three-, five- and six-membered ring, we examined the asymmetric addition reaction of diethylzinc with arylaldehydes in the presence of a catalytic amount (5 mol%) of chiral β-amino alcohols **11**, **16** and **20**. The results are summarized in Tables 1 and 2.

The enantiomeric excesses (ee's) of the products were determined by HPLC analysis using chiral stationary-phase column (Chiralcel OD and OJ), and the absolute configuration of the major enantiomer was assigned according to the sign of their specific rotations.[11,12] As shown in Table 1, very high yields (86–92%) but low enantiomeric excesses (11–13%) were achieved by

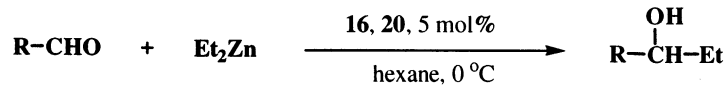
Table 1
Asymmetric addition reaction of diethylzinc with aldehydes in the presence of 5 mol% chiral C_2-symmetric 2,3-disubstituted aziridine **11**



R	Cat.	Yield (%)[a]	Ee (%)[b]	Absolute configuration
Ph	**11**	91	11	*S*
p-ClPh	**11**	92	13	*S*
Ph-CH=CH	**11**	86	12	*S*

[a] Isolated yields.
[b] Determined by chiral HPLC.

Table 2
Asymmetric addition reaction of diethylzinc with aldehydes in the presence of 5 mol% chiral C_2-symmetric 2,6-disubstituted piperidines **16** and **20**



R	Cat.	Yield (%)[a]	Ee (%)[b]	Absolute configuration
Ph	**16**	88	24	*S*
p-MePh	**16**	83	20	*S*
p-ClPh	**16**	84	22	*S*
Ph-CH=CH	**16**	90	21	*S*
Ph	**20**	76	5	*R*
p-MePh	**20**	80	4	*R*
p-ClPh	**20**	86	5	*R*
p-MeOPh	**20**	82	5	*R*

[a] Isolated yields.
[b] Determined by chiral HPLC.

using 5 mol% of the chiral C_2-symmetric β-amino alcohol **11**. However, we previously reported that, using the azetidine or pyrrolidine β-amino alcohol, the ee can reach 90% for the same reaction under the same conditions.[2] We were very surprised to find that the most rigid three-membered aziridine ring gave the lowest ee's. Comparing the space-filling models of C_2-symmetric aziridine, azetidine and pyrrolidine, we found that for C_2-symmetric aziridine **11** the two substituents are further away from the nitrogen atom than in an azetidine or pyrrolidine complex. The methoxy group on the side chain of aziridine **11** cannot therefore provide additional coordination to the β-amino alcohol-chelated zinc atom.[13] This is not the case in the azetidine or pyrrolidine complexes (Fig. 1).[2,3] Thus, **11** cannot affect the stereoselectivity of the addition reaction.

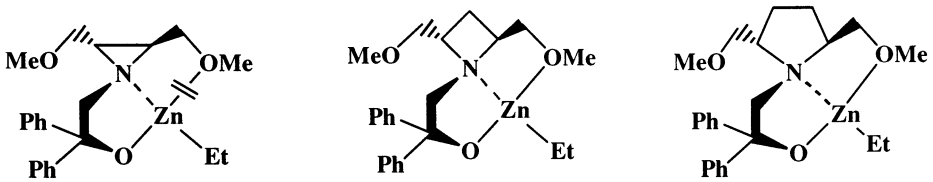


Figure 1.

On the other hand, when the chiral C_2-symmetric (2*R*,6*R*)-disubstituted piperidine **16** was used as the catalytic ligand in the same addition reaction, the ee's of the corresponding *sec*-alcohols increased to 20% with (*S*)-configuration (Table 2). Meanwhile, chiral C_2-symmetric (2*S*,6*S*)-disubstituted piperidine derivative **20** having bulky substituents on the 2,6-position was also used as the chiral ligand under the same reaction conditions; the ee's of the corresponding *sec*-alcohols decreased to 5% with the (*R*)-configuration preferred. A similar effect has been observed in the same addition reaction using chiral C_2-symmetric 2,4-disubstituted azetidine and 2,5-disubstituted pyrrolidine derivatives as the chiral ligands.[2]

As can be seen from Fig. 2, (2*R*,6*R*)-disubstituted piperidine should give *sec*-alcohols with (*R*)-configuration. But we surprisingly found that β-amino alcohol **16** gave the opposite absolute configuration as β-amino alcohol ligands having three-, four- or five-membered rings (Fig. 2).[2,3] This may be due to the fact that the six-membered rings do not have the same degree of rigidity as four- or five-membered rings, therefore, the *sec*-alcohol products were formed via sterically different transition states to those of complexes with ligands containing four- or five-membered rings.

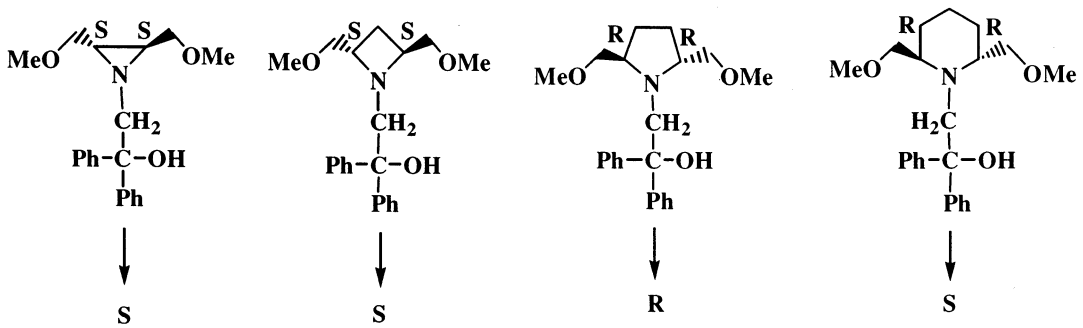


Figure 2.

Thus, C_2-symmetric chiral ligands **16** or **20** having flexible ring structure can give the product with opposite absolute configuration to that formed when a catalyst with relatively rigid ring substituents is used, although a detailed mechanism for this interesting inversion phenomenon is presently unclear.

In conclusion, we found that, in the preparation of C_2-symmetric chiral ligands from the chiral scaffold of cyclic amines, the four- and five-membered rings, azetidine and pyrrolidine, are excellent candidates. The three-membered aziridine ring would be problematic during synthetic processes because its backbone structure is too unstable to nucleophilic attack and can be easily opened by even a very poor nucleophile such as a chloride ion. The six-membered piperidine ring has given an unusual result and very low enantioselectivity owing to its flexible backbone structure, for example, C_2-symmetric β-amino alcohol **16** having a six-membered ring backbone structure gave the opposite absolute configuration of the *sec*-alcohol compared to those of C_2-symmetric β-amino alcohols having a three-, four- or five-membered ring for catalytic asymmetric addition reactions of diethylzinc to aldehydes.

We are now planning to synthesize more ligands based upon C_2-symmetric cyclic amines of different ring size to assess them as novel chiral catalysts for other asymmetric reactions in order to gain more information on this mode of chiral induction. Undoubtedly these results give us helpful information on the design and synthesis of new catalysts. Further work in this direction is currently in progress.

3. Experimental

Mps were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined in a solution of $CHCl_3$ and methanol at 20°C by using a Perkin–Elmer 241 MC digital polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard on a Bruker AMX-300 spectrometer; J values are in Hz. IR spectra were determined by a Perkin–Elmer 983 spectrometer. Mass spectra were recorded with a HP-5989 instrument. High mass spectra were recorded on a Finnigan MA+ instrument. Compounds **1**–**7**, **12** and **13** were prepared according to the literature.[4,5] Their spectral data have been checked with those reported in previous papers.[4,5] Benzilic acid was purchased from Aldrich Co.

3.1. Preparation of ring opened compound *9*

To a solution of (*S*,*S*)-2,3-bis(methoxymethyl)aziridine **7** (175 mg, 1.34 mmol) and potassium carbonate (257 mg, 1.88 mmol) in acetonitrile (10 mL) was added ethyl α-bromoacetate (266 mg, 1.60 mmol) and the reaction mixture was stirred at 0°C for 18 h. The solvent was removed under reduced pressure and the residue was washed with brine and extracted with ethyl acetate (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give compound **9** (266 mg, 52%) as a colorless oil (eluent: ethyl acetate/petroleum ether = 1/4). $[\alpha]_D$ −15.7 (*c* 0.98, $CHCl_3$); IR (neat) ν 1730 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (6H, t, J = 7.2 Hz), 3.19 (1H, ddd, J = 9.4, 4.4, 2.1 Hz), 3.29 (3H, s, OMe), 3.40 (3H, s, OMe), 3.56 (2H, d, J = 7.8 Hz), 3.77 (2H, d, J = 7.8 Hz), 3.82 (2H, dd, J = 6.0, 3.2 Hz), 3.85 (2H, dd, J = 5.4, 2.7 Hz), 4.18 (4H, q, J = 7.2 Hz), 4.30–4.43 (1H, m); HRMS (EI) m/z 383.0930 (M^+), $C_{14}H_{26}BrNO_6$ requires 383.0944.

3.2. Preparation of N-(2,2-diphenyl-2-hydroxyacetyl)-(S,S)-2,3-bis(methoxymethyl)aziridine **10**

To a solution of (*S*,*S*)-2,3-bis(methoxymethyl)aziridine **7** (60 mg, 0.46 mmol) and benzilic acid (105 mg, 0.46 mmol) in dichloromethane (4 mL) was added 2-bromo-1-methylpyridinium tetrafluoroborate (BEP) (138 mg, 0.51 mmol) at room temperature. The reaction mixture was cooled to −20°C and diisopropylethylamine (DIPEA) (198 mg, 0.25 mL, 1.37 mmol) was added dropwise in 30 min at −20°C. The reaction solution was stirred for 24 h at room temperature. The reaction mixture was directly subject to flash chromatography to give **10** as a colorless oil (eluent: ethyl acetate/petroleum ether = 1/4). Yield: 64 mg, 41%; $[\alpha]_D$ +18.7 (*c* 1.6, $CHCl_3$); IR (neat) *v* 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.31 (1H, t, J = 4.3 Hz, CH), 2.71 (1H, t, J = 4.4 Hz, CH), 2.94 (1H, br. s, OH), 3.20 (1H, dd, J = 10.7, 3.2 Hz, CH), 3.12–3.20 (2H, m, CH_2), 3.25 (6H, s, OMe), 3.78 (1H, dd, J = 10.7, 3.2 Hz, CH_2), 7.20–7.60 (10H, m, Ar); [HRMS (EI) *m*/*z* 325.1670 (M^+), $C_{20}H_{23}NO_3$ requires 325.1678].

3.3. Preparation of N-(2,2-diphenyl-2-hydroxyethyl)-(S,S)-2,3-bis(methoxymethyl)aziridine **11**

To a solution of **10** (68 mg, 0.20 mmol) in THF (5 mL) was added $LiAlH_4$ (22.8 mg, 0.60 mmol) at 0°C and the reaction mixture was stirred overnight at 0°C. The reaction was quenched with 10% NaOH aqueous solution (0.5 mL) and the mixture was filtered. The filtrate was extracted with dichloromethane (3×5 mL). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give **11** as a colorless oil (eluent: ethyl acetate/petroleum ether = 1/4). Yield: 17 mg, 26%; $[\alpha]_D$ +10.4 (*c* 0.65, $CHCl_3$); IR (neat) *v* 3380 cm^{-1} (O–H); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.35 (2H, t, J = 5.3 Hz, CH), 3.01 (2H, dd, J = 10.0, 6.8 Hz, CH_2), 3.17 (2H, dd, J = 10.0, 5.7 Hz, CH_2), 3.23 (6H, s, OMe), 3.47 (1H, br. s, OH), 4.2 (1H, d, J = 10.6 Hz, CH), 4.33 (1H, d, J = 10.6 Hz, CH), 7.10–7.60 (10H, m, Ar); [HRMS (EI) found: (MH^+) 328.1930. $C_{20}H_{26}NO_3$ requires 328.1913].

3.4. Preparation of (R,R)-2,6-bis(methoxymethyl)piperidine **14**

To a solution of **13** (110 mg, 0.40 mmol) in methanol (15 mL) was added $Pd(OH)_2/C$ (20%, 75 mg) and the reaction mixture was stirred at room temperature for 24 h under a hydrogen atmosphere. The solvent was removed under reduced pressure and the residue was used for the next reaction without purification. Yield: 52 mg, 76%; $[\alpha]_D^{20}$ −7.8 (*c* 0.6, $CHCl_3$);[7] IR (neat) *v* 3320 cm^{-1} (N–H); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29–1.71 (6H, m, CH_2), 2.49 (1H, br. s, NH), 3.0–3.15 (2H, m, CH), 3.36 (6H, s, OMe), 3.30–3.48 (4H, m, CH_2); [HRMS (EI) found: 173.1412 (M^+). $C_9H_{19}NO_2$ requires 173.1416].

3.5. Preparation of N-(ethoxycarbonylmethyl)-(R,R)-2,6-bis(methoxymethyl)piperidine **15**

To a solution of **14** (48 mg, 0.28 mmol) and potassium carbonate (57 mg, 0.41 mmol) in acetonitrile (20 mL) was added ethyl α-bromoacetate (56 mg, 37 μL, 0.33 mmol) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was extracted with ether (3×10 mL). The organic layer was washed with water, brine and dried over $NaSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give **15** as a colorless oil

(eluent: ethyl acetate/petroleum ether = 1/4). Yield: 42 mg, 58%; $[\alpha]_D$ +12.8 (*c* 0.31, $CHCl_3$); IR (neat) *v* 1740 cm^{-1} (C=O); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (3H, t, J = 7.1 Hz, Me), 1.50–1.80 (6H, m, CH_2), 3.10–3.30 (2H, m, CH_2), 3.28 (6H, s, OMe), 3.40 (2H, dd, J = 9.8, 4.4 Hz), 3.51 (2H, dd, J = 4.4, 4.3 Hz), 3.54 (1H, d, J = 18.0 Hz), 3.67 (1H, d, J = 18.0 Hz), 4.16 (2H, q, J = 7.1 Hz); [HRMS (EI) found: 260.1863 (MH^+). $C_{13}H_{26}NO_4$ requires 260.1862].

3.6. Preparation of N-(2,2-diphenyl-2-hydroxyethyl)-(R,R)-2,6-bis(methoxymethyl)piperidine **16**

To a solution of phenylmagnesium bromide prepared from the reaction of bromobenzene (242 mg, 1.5 mmol) and magnesium (44 mg, 1.85 mmol) in THF (10 mL) was added **15** (40 mg, 0.15 mmol) at 0°C and the reaction mixture was stirred for 24 h. The reaction was quenched with saturated NH_4Cl aqueous solution and extracted with ether (3×15 mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give **16** as a colorless oil (eluent: ethyl acetate/petroleum ether = 1/3). Yield: 41 mg, 72%; $[\alpha]_D$ +31.5 (*c* 0.13, $CHCl_3$); IR (neat) *v* 3406 cm^{-1} (O–H); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22–1.42 (2H, m, CH_2), 1.50–1.72 (4H, m, CH_2), 2.60–2.73 (2H, m, CH_2), 3.16 (6H, s, OMe), 3.23 (4H, dd, J = 10.2, 1.0 Hz), 3.37 (1H, d, J = 13.9 Hz), 3.52 (1H, d, J = 13.9 Hz), 5.60 (1H, br. s, OH), 7.10–7.40 (6H, m, Ar), 7.40–7.60 (4H, m, Ar); [HRMS (EI) found: 370.2386 (MH^+). $C_{23}H_{32}NO_3$ requires 370.2382].

3.7. Preparation of (S,S)-2,6-bis[(tert-butyldimethylsiloxy)methyl]-N-[(S)-1-phenylethyl]-piperidine **17**

To a solution of **12** (1.50 g, 6.02 mmol) and imidazole (1.07 g, 15.66 mmol) in dichloromethane (50 mL) was added *tert*-butyldimethylsilyl chloride (2.23 g, 14.48 mmol) and the reaction mixture was stirred for 36 h at room temperature. The mixture was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue (2.24 g) was purified by flash chromatography to give **17** as a colorless oil (eluent: ethyl acetate/petroleum ether = 1/100). Yield: 100 mg, 4.5%; $[\alpha]_D$ −26.7 (*c* 0.4, $CHCl_3$); IR (neat) *v* 1598 cm^{-1} (C=C); ^1H NMR ($CDCl_3$, 300 MHz) δ −0.13 (6H, s, SiMe), −0.088 (6H, s, SiMe), 0.82 (18H, s, Me_3C), 1.47 (3H, d, *J* 6.8, Me), 1.40–1.63 (6H, m, CH_2), 2.90–3.12 (2H, m), 3.40 (2H, dd, J = 10.2, 5.3 Hz), 3.56 (2H, dd, J = 10.2, 10.1 Hz), 4.28 (1H, q, J = 6.2 Hz), 7.10–7.50 (5H, m, Ar); [HRMS (EI) found: 477.3451 (M^+). $C_{27}H_{51}NO_2Si_2$ requires 477.3458].

3.8. Preparation of (S,S)-2,6-bis[(tert-butyldimethylsiloxy)methyl]piperidine **18**

To a solution of **17** (100 mg, 0.14 mmol) in methanol (5 mL) was added $Pd(OH)_2/C$ (20%, 50 mg) and the reaction mixture was stirred at room temperature for 24 h under a hydrogen atmosphere. The solvent was removed under reduced pressure and the residue was used for the next reaction without purification. Yield: 69 mg, 89%; $[\alpha]_D$ +18.2 (*c* 0.44, $CHCl_3$); IR (neat) *v* 3332 cm^{-1} (N–H); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (12H, s, SiMe), 0.92 (18H, s, Me_3C), 1.30–1.60 (4H, m, CH_2), 1.62–1.84 (2H, m, CH_2), 2.34 (1H, br. s, NH), 3.0–3.13 (2H, m, CH_2), 3.48 (2H, dd, J = 9.8, 4.3 Hz), 3.67 (2H, dd, J = 9.8, 9.8 Hz); [HRMS (EI) found: 373.2836 (M^+). $C_{19}H_{39}NO_2Si_2$ requires 373.2832].

3.9. Preparation of N-(ethoxycarbonylmethyl)-(S,S)-2,6-bis[(tert-butyldimethylsiloxy)methyl]-piperidine **19**

To a solution of **18** (45 mg, 0.12 mmol) and potassium carbonate (25 mg, 0.18 mmol) in acetonitrile (4 mL) was added ethyl α-bromoacetate (24 mg, 0.14 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography to give **19** as a colorless oil (eluent: ethyl acetate/petroleum ether = 1/10). Yield: 48 mg, 87%; $[\alpha]_D$ −11.1 (*c* 0.94, $CHCl_3$); IR (neat) *v* 1740 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (6H, s, SiMe), 0.10 (6H, s, SiMe), 0.89 (18H, s, Me_3C), 1.26 (3H, t, $J = 7.2$ Hz, Me), 1.40–1.90 (6H, m, CH_2), 2.85–3.0 (2H, m, CH_2), 3.50–3.90 (6H, m, CH_2), 4.15 (2H, q, $J = 7.1$ Hz); [HRMS (EI) found: 460.3291 (MH^+). $C_{23}H_{50}NO_4Si_2$ requires 460.3278].

3.10. Preparation of N-(2,2-diphenyl-2-hydroxyethyl)-(S,S)-2,6-bis[(tert-butyldimethylsiloxy)-methyl]piperidine **20**

This compound was prepared in the same manner as that described above. Yield: 49 mg, 86%; $[\alpha]_D$ −3.8 (*c* 0.24, $CHCl_3$); IR (neat) *v* 3384 cm^{-1} (O–H); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.08 (12H, s, $SiMe_3$), 0.96 (18H, s, Me_3C), 1.10 (2H, m, CH_2), 1.40–1.53 (4H, m, CH_2), 2.50–2.62 (2H, m), 3.30–3.56 (6H, m, CH_2), 5.40 (1H, br. s, OH), 7.0–7.25 (6H, m, Ar), 7.40–7.52 (4H, m, Ar); [HRMS (EI) found: 570.3796 (MH^+). $C_{33}H_{56}NO_3Si_2$ requires 570.3799].

Typical reaction procedure: To a suspension of β-amino alcohol **16** (8.5 mg, 0.025 mmol) in hexane (1.0 mL), diethylzinc (1.1 mmol, 1.1 mL of 1.0 M hexane solution) was added at 0°C. After stirring for 0.5 h, benzaldehyde (53 mg, 0.5 mmol) was added and the reaction mixture was stirred for 24 h at 0°C. The reaction was quenched by the addition of a 3% HCl aqueous solution and the organic product was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel TLC to give the optically active 1-phenylpropanol (60 mg, 88%).

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