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Aziridino Alcohols as Catalysts for the Enantioselective Addition of Diethylzinc to Aldehydes

David Tanner*[a], Hanne T. Kornø[a], David Guijarro[b], Pher G. Andersson*[b]

[a] *Department of Organic Chemistry, The Technical University of Denmark, Building 201, DK-2800 Lyngby, Denmark*
[b] *Uppsala University, Department of Organic Chemistry, Box 531, S-751 21 Uppsala, Sweden*

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Abstract

The chiral aziridino alcohols **1** - **3** have been prepared either from amino acids (**1a** from serine; **1b** - **1i** and **3** from threonine; **2a** - **2e** from *allo*-threonine) or via asymmetric synthesis (**1j**, **1k**, **1l** and **2f** from methyl cinnamate). These easily available ligands act as catalysts for the enantioselective addition of diethylzinc to benzaldehyde, with up to 90% stereoselectivity. The absolute configuration of the alcohol product is dependent on the substitution pattern of the aziridine ring, and different transition state models are proposed to explain the observed switch in enantioselectivity. The C_2-symmetric aziridino diols **4a** - **4h** have been prepared from tartaric acid, and also catalyze the organozinc addition reaction with high chemicals yields and up to 94% *e.e.* C_2-symmetric ligands **5a** - **5c**, with ether side-chains, were less efficient (46% *e.e.* at best). The most efficient ligand (**4c**) was also tested in the addition to aldehydes **9** - **11**, with 97% *ee* at best.

Keywords: Aziridines; Catalysis; Enantioselection; Zinc and compounds.

Introduction. The nucleophilic addition of organometallic reagents to carbonyl compounds is of fundamental importance to organic synthesis. Recently, much interest has been focused on the ligand-assisted reaction of dialkylzinc reagents with aldehydes, leading to chiral alcohols [1,2]. A wide variety of chiral ligands, particularly amino alcohols capable of forming five-membered chelates with the organozinc species, has been developed, and detailed mechanistic studies have been performed in some cases [1].

For the last few years we have been exploring the use of chiral aziridines as ligands for a variety of metal-mediated asymmetric transformations [3]. The simple aziridino alcohols shown below, readily available either from the chiral pool or via asymmetric synthesis, have proved to be very efficient catalysts for the addition of organozinc reagents to imines [4], and we now report on the use of this type of ligand in the enantioselective addition of diethylzinc to aldehydes.

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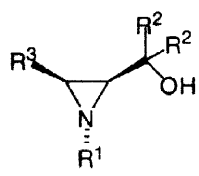
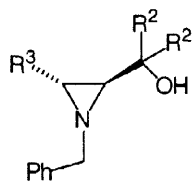
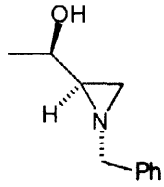


1a: R^1 = $PhCH_2$; R^2 = R^3 =H
1b: R^1 = $PhCH_2$; R^2 = H; R^3 = Me
1c: R^1 = $PhCH_2$; R^2 = R^3 = Me
1d: R^1 = $PhCH_2$; R^2 = Ph; R^3 = Me
1e: R^1 = Ph_3C; R^2 = H; R^3 = Me
1f: R^1 = R^2 = H; R^3 = Me
1g: R^1 = R^3 = Me; R^2 = H
1h: R^1 = *n*-Bu; R^2 = H; R^3 = Me
1i: R^1 = *i*-Pr; R^2 = H; R^3 = Me
1j: R^1 = $PhCH_2$; R^2 = H; R^3 = Ph
1k: R^1 = $PhCH_2$; R^2 = Me; R^3 = Ph
1l: R^1 = Et; R^2 = H; R^3 = Ph



2a: R^2 = H; R^3 = Me
2b: R^2 = Et; R^3 = Me
2c: R^2 = *i*-Pr; R^3 = Me
2d: R^2 = *c*-Hex; R^3 = Me
2e: R^2 = Ph; R^3 = Me
2f: R^2 = H; R^3 = Ph



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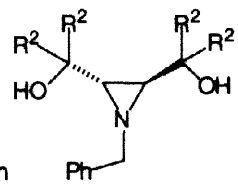
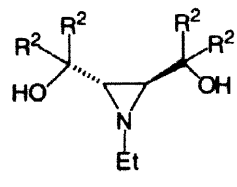
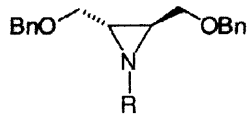


4a: R^2 = H
4b: R^2 =Me
4c: R^2 = Et
4d: R^2 = *n*-Pr
4e: R^2 =*n*-Bu
4f: R^2 = $(CH_2)_4$

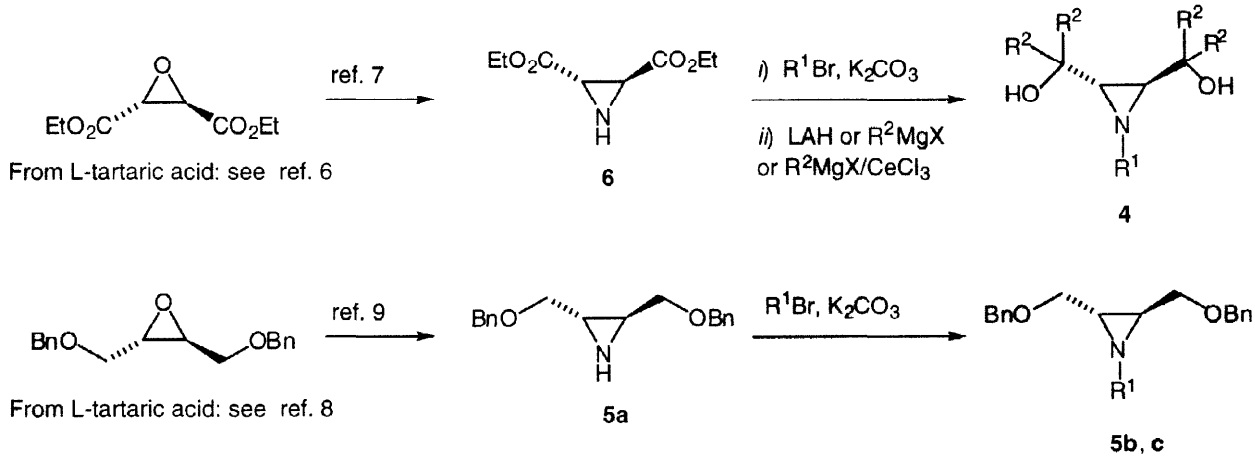


4g: R^2 = Et
4h: R^2 = Ph



5a: R = H
5b: R = Bn
5c: R = $CH_2C(OH)Ph_2$

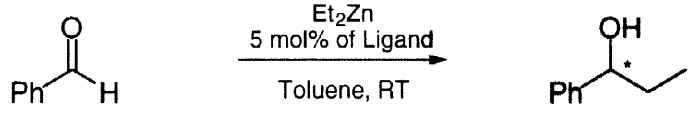
Results and Discussion. Aziridino alcohols **1a - k**, **2a, b, e, f** and **3** were prepared from either serine, threonine, *allo*-threonine or methylcinnamate as previously described [4]. The preparation of ligands **1l** (from ethyl cinnamate) and **2c - e** (from the chiral pool) is described in the Experimental, while the new C_2-symmetric compounds **4** and **5** were derived from tartaric acid as shown in Scheme 1. For efficient introduction of all four alkyl groups in **4d, e** and **4g, h** it was necessary to use cerium trichloride [5] together with the Grignard reagent. Attempts to prepare the *N*-benzyl ligand **4** with R^2 = Ph failed. The ligands **1 - 3** were tested first and the results are presented in Table 1.



Scheme 1. Preparation of C_2-symmetric aziridine ligands.

Table 1.

Addition of Diethylzinc to benzaldehyde catalyzed by ligands **1-3**.



Entry	Ligand	Yield (%)[a]	*ee* (%)[b]	Configuration[c]
1	**1a**	59	49	*S*
2	**1b**	75	38	*S*
3	**1c**	83	30	*S*
4	**1d**	81	17	*S*
5	**1e**[d]	23	2	*S*
6	**1f**[e]	70	43	*S*
7	**1g**	66	53	*R*
8	**1h**	--[f]	--	--
9	**1i**	62	29	*R*
10	**1j**[g]	61	87	*R*
11	**1k**	44	42	*R*
12	**1l**	50	90	*R*
13	**2a**	58	61	*S*
14	**2b**	79	90	*S*
15	**2c**	65	87	*S*
16	**2d**	>95	87	*S*
17	**2e**	90	75	*S*
18	**2f**	69	52	*S*
19	**3**	73	67	*R*

[a] Isolated after flash chromatography (silica gel, pentane/ether). [b] Determined by HPLC analysis, using a chiral column (ChiralCel OD-H) and 5% *i*-PrOH in hexane as eluent. [c] Determined by comparisor of the optical rotation with the data given in the literature (see experimental part). [d] The reaction was stirred for five days at RT. [e] The reaction was stirred for one day at 0°C and three more days at RT. [f] After three days at RT less than 5% of addition product could be detected by ^{1}H-NMR spectroscopy. [g] The reaction was stirred for one day at 0°C and one more day at RT.

Of the results in Table 1, those with aziridine **1a** and the *cis*-ligands **1b - 1l** are worthy of comment, since a switch in enantioselectivity is observed (compare entries 1-6 with entries 7, 9-12). For entries 1-4 we suggest that the *S* alcohol is formed via the transition state **A** shown in Figure 1, with the aldehyde *trans* to the *N*-benzyl group on the five-membered ring.

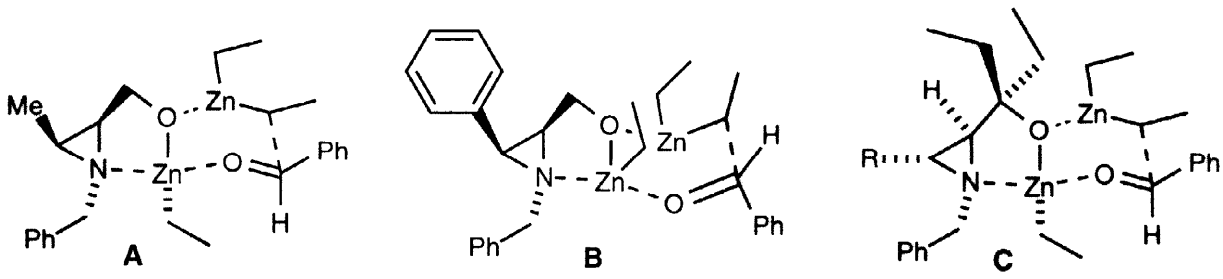


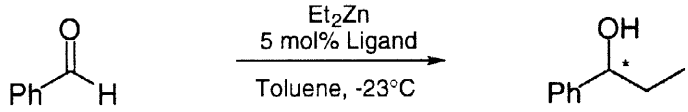
Figure 1. Proposed transition states for the addition of diethylzinc to benzaldehyde.

A *N*-trityl group (entry 5) is presumably too large to allow efficient chelate formation, with low chemical yield and very poor enantioselectivity as a result. The result with the *N*-H aziridine **1f** (entry 6) is more difficult to rationalize, but a different type of transtition state may be operative if the ligand is deprotonated at both nitrogen and oxygen. Surprisingly, replacing the *N*-benzyl group with methyl or isopropyl (entries 7 and 9) leads to a switch in enantioselectivity, for reasons we do not yet understand. The complete lack of reactivity with the N-butyl ligand **1h** (entry 8) is also difficult to explain.

Ligands **1j**, **1k** and **1l** with a C3 phenyl group give the *R* alcohol and we propose the transition state structure **B** shown in Figure 1, with the C3 phenyl rather than the *N*-substituent determining the orientation of the aldehyde.

All six ligands having the trans configuration at C2-C3 (**2a** - **f**) gave the *S* configuration of the alcohol and this can be explained by the transition state structure **C** shown in Figure 1. The best ligand in terms of enantioselectivity, was **2b** (79% yield, 90% *ee*). We propose that a transition state assembly similar to **C** (Figure 1) is also involved in the reaction of the C2-symmetric ligands **4** (Table 2).

Table 2. Addition of Diethylzinc to benzaldehyde catalyzed by ligands **4**.



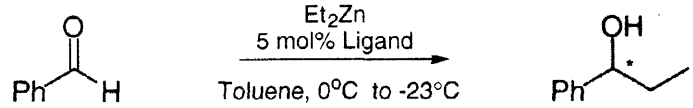
Entry	Ligand	equiv.	Yield (%)[a]	*ee* (%)[b]	Configuration[c]
1	**4a**	0.05	>95	32	*S*
2	**4b**	0.05	76	62	*S*
3	**4c**	0.03	83	94	*S*
4	**4c**	0.003	>95	85	*S*
5	**4c**	0.06	92	94	*S*
6	**4d**	0.05	>95	86	*S*
7	**4e**	0.05	84	84	*S*
8	**4f**	0.03	>95	78	*S*
9	**4g**	0.05	>95	89	*S*
10	**4h**	0.05	69	47	*S*

[a] Isolated after flash chromatography (silica gel, pentane/ether). [b] Determined by GC analysis, using a chiral column (ChromPack 7502, WCOT fused silica coated with CP-Chirasil-DEX CB). [c] Determined by comparison of the optical rotation with the data given in the literature (see experimental part).

Once again, the best *e.e.* value (94%) was provided by the ligand (**4c**) having geminal ethyl groups next to the hydroxyl (Table 2, entry 3). Switching the *N*-substituent from benzyl to ethyl (Table 2, compare entries 3 and 10) caused a pronounced drop in both chemical yield and *e.e.*, while the *N*-ethyl ligand **4g**, with geminal ethyls on the carbinol carbon, restored high levels of efficiency and enantioselectivity (Table 2, entry 9). It is noteworthy that the C_2-symmetric ligands generally gave higher chemical yields and better *e.e.* than their *trans* aziridine counterparts **2a** - **f**. Furthermore, the reactions with the tartrate-derived ligands could be run at lower temperature.

We also made a brief investigation of the C_2-symmetric ligands **5a** - **c** which have ether groups in the side-chains. These were all prepared from tartaric acid *via* the known [9] **5a** as described in the Experimental, and the results are collected in Table 3.

Table 3. Addition of Diethylzinc to benzaldehyde catalyzed by ligands **5**.

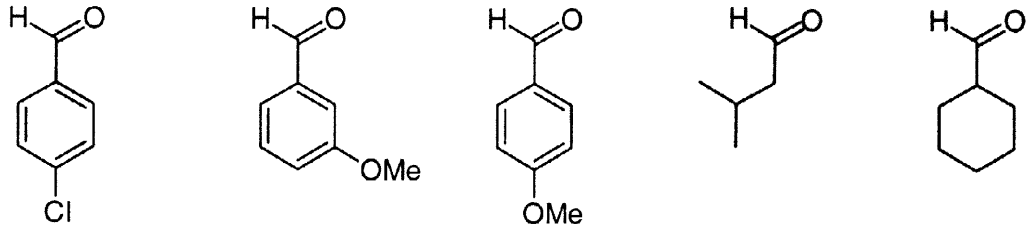


Entry	Ligand	Yield (%)[a]	*ee* (%)[b]	Configuration[c]
1	**5a**[d]	>95	46	*R*
2	**5b**[e]	76	6	*R*
3	**5c**[f]	83	20 - 27	*S*

[a] Isolated after flash chromatography (silica gel, pentane/ether). [b] Determined by GC analysis, using a chiral column (ChromPack 7502, WCOT fused silica coated with CP-Chirasil-DEX CB). [c] Determined by comparison of the optical rotation with the data given in the literature (see experimental part). [d] The reaction was carried out at -23 °C. [e]The reaction was carried out at 0 °C. [f]The reaction was carried out at -23 °C to 0 °C.

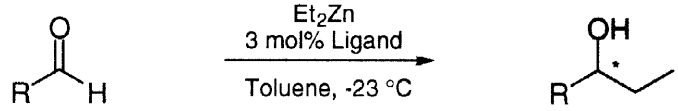
Although none of these ligands was efficient in terms of *e.e.*, it is nevertheless instructive to compare the performance of **5a** and **5b** (Table 3, entries 1 and 2) with that of the closely related **4a** (Table 2, entry 1). A switch of enantioselectivity was observed on going from **4a** to **5a**, **b**, indicating a different type of transition state, while the poor *e.e.* induced by **5b** highlights the need for an acidic proton in the ligand (either on oxygen or nitrogen). Surprisingly enough, use of ligand **5c** caused another reversal of enantioselectivity, but since the *e.e.* values were quite poor, this class of ligand was not further investigated.

Finally, the best ligand (**4c**) was evaluated for a variety of different aldehydes, **7** - **11**.



7 8 9 10 11

Table 4. Addition of Diethylzinc to various aldehydes catalyzed by ligand **4c**.



Entry	Aldehyde	Yield (%)[a]	*ee* (%)[b]	Configuration[c]
1	**7**	85	91	*S* [15]
2	**8**	>95	97	*S* [16]
3	**9**	>95	94	*S* [17]
4	**10**	>70[d]	65	*S* [18]
5	**11**	>95	10	*R* [17]

[a] Isolated after flash chromatography (silica gel, pentane/ether). [b] Determined by GC analysis, using a chiral column (ChromPack 7502, WCOT fused silica coated with CP-Chirasil-DEX CB).
[c] Determined by comparison of the optical rotation with the data given in the literature.
[d] The product was volatile.

Gratifyingly high levels of enantioselectivity were obtained for the aromatic aldehydes **7** - **9** and there was little evidence for any electronic effects of the ring substituents. On the other hand, the two aliphatic aldehydes proved to be poor substrates in terms of enantioselectivity.

In conclusion, we have developed a family of simple aziridino alcohol ligands which are readily available from the chiral pool or *via* asymmetric synthesis; these new chiral compounds efficiently catalyze the addition of diethylzinc to benzaldehyde and related aldehydes, with up to 97% *e.e.* Our efforts to develop novel aziridine derivatives as chiral ligands are continuing, and results will be reported elsewhere.

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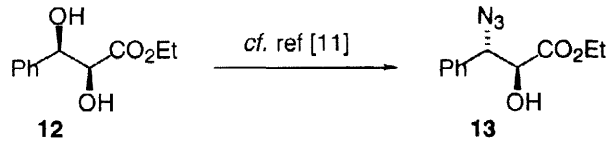
EXPERIMENTAL

All reactions were carried out under a nitrogen atmosphere. ^{1}H and ^{13}C NMR spectra were recorded for $CDCl_3$ solutions at 500/400/300/250 and 125/100.4/75.5/62.9 MHz respectively. Chemical shifts for protons are reported using the residual ^{1}H in $CDCl_3$ as the internal reference (δ 7.26). Carbon shifts are referenced to the ^{13}C signal of $CDCl_3$ at 77.0 ppm. Optical rotations were recorded on a thermostatted Perkin-Elmer 241 polarimeter using a 1.0 dm cell. Infrared spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. Mass spectra were recorded on INCOS 50 GC/MS system. Melting points were determined on a Leitz apparatus and are uncorrected. GC analysis was performed on a Varian 3400 capillary gas chromatograph using a 25 m SE 54 column. HPLC analysis was performed on a Varian 9012 pump coupled with a Varian 9065 diode array detector. HPLC analysis was carried out using a chiral column (Chiral Cel OD-H), a 254 nm UV detector and a 0.5 mL/min flow rate of hexane/2-propanol: 95/5. Toluene, methylene chloride and chloroform were dried over calcium hydride and freshly distilled under nitrogen. Styrene and α-methyl styrene were distilled prior to use. THF and diethyl ether were distilled over sodium/benzophenone under nitrogen. Preparative TLC plates, SIL G-100 UV_{254} were purchased from Macherey-Nagel. Absolute configurations were assigned by comparison of the sign of optical rotation with those available for commercial products or reported in the literature. Elemental analysis was performed by the Microanalysis Laboratory, Institute of Physical Chemistry, University of Vienna, Austria.

Ligand 11.

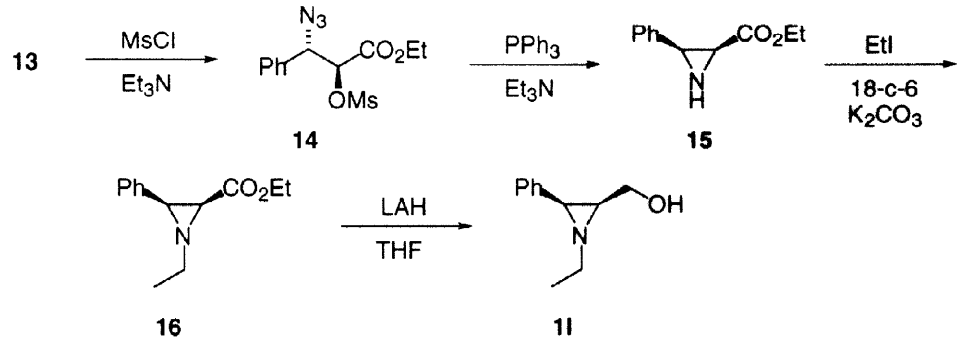


12 **13**

(see ref. [10])

Ethyl cinnamate was first subjected to Sharpless asymmetric dihydroxylation [10] (AD mix ß) and the resultant diol **12** was converted in *ca.* 55% overall yield to azido alcohol **13** by the method described by Greene for the methyl ester analogue [11]. Compound **13** was found to be of 92% *ee* by comparison of optical rotation data [12]. The synthesis was

completed *via* mesylation to give **14**, ring closure to **15**, *N*-alkylation [13] to **16** and $LiAlH_4$ reduction.



Mesylate 14. Et_3N (0.39 mL, 2.80 mmol) was added to a solution of the azido alcohol **13** (0.44 g, 1.87 mmol) in CH_2Cl_2 (25 mL) at 0_C. Then MsCl (0.16 mL, 2.06 mmol) was added. The reaction mixture was stirred over night (18 h) and then heated to room temperature. Water (25 mL) and CH_2Cl_2 (25 mL) were added and the phases were separated. The organic phase was washed with sat. $NaHCO_3$ (25 mL) and brine (2x30 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure to give a pale yellow oil. The oil was further purified by flash chromatography giving a clear oil (0.54 g, 92%).

$[\alpha]_D^{22}$ +116.4 (*c* 1.0 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.20 (3H, CH_3, t, J = 7.2); 2.96 (3H, CH_3SO_2OR, s); 4.20 (2H, CH_2, q, J = 7.2); 5.07 (1H, CH, d, J = 5); 5.14 (1H, CH, d, J = 5); 7.37-7.49 ppm (5H, C_6H_5, m).

^{13}C-NMR (63 MHz, $CDCl_3$): δ13.7 (CH_3); 38.7 (CH_3SO_3); 62.5 (CH_2); 65.4 (CHN_3); 79.7 (CHOR); 127.5, 128.9, 129.4, 133.5 (C_6H_5); 166.2 ppm (CO).

IR($CDCl_3$) υ: 2986 (CH); 2112 (N_3, s); 1753 (CO, s); 1372 (N_3, SO_2, s); 1179 cm^{-1}(SO_2, C-OR, s).

Anal.: Calcd. for $C_{12}H_{15}N_3O_5S$ C, 46.00; H, 4.83; N, 13.41; S, 10.23. Found: C, 46.32; H, 4.82; N, 13.54; S, 10.06.

Aziridine 15. Et_3N (0.84 mL, 6.03 mmol) and PPh_3 (0.83 g, 3.16 mmol) were added to the mesylate (0.90 g, 2.87 mmol) in dry THF (52.2 mL) and water (5.2 mL). The reaction mixture was stirred at room temperature overnight (14 h). The organic phase was washed with brine (3x40 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash chromatography gave a white solid (0.504 g, 91.6%).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.97 (3H, CH_3, t, J = 7); 2.98 (1H, CH, d, J = 6.5); 3.45 (1H, CH, d, J = 6.5); 3.84-4.03 (2H, CH_2, m); 7.18-7.36 ppm (5H, C_6H_5, m).
^{13}C-NMR (63 MHz, $CDCl_3$): δ 13.5 (CH_3); 36.7, 39.3 (2xCH); 60.6 (2xCH_2); 127.1, 127.6, 134.6 (C_6H_5); 168.6 ppm (CO).

Aziridine 16. K_2CO_3 (0.17 g, 1.23 mmol), 18-crown-6 (38 mg, 0.14 mmol) and EtI (0.40 mL, 0.50 mmol, filtered through neutral Al_2O_3 act.1 before use) were added to the aziridine **15**, (0.22, 1.16 mmol) in CH_3CN (20 mL) at room temperature. The reaction mixture was heated to 60 °C and stirred at that temperature for 5 days. After 1.5 days more EtI (0.40 mL, 0.50 mmol) was added. The reaction mixture was transferred to a separatory funnel and washed with brine (3x50 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash chromatography gave a colourless oil which turned yellow quite rapidly (0.13 g, 50%).

^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.92 (3H, C<u>H</u>$_3$CH$_2$O, t, J = 7.3); 1.26 (3H, C<u>H</u>$_3$CH$_2$N, t, J = 7.2); 2.28-2.41 (1H, C<u>H</u>H'N, m); 2.49 (1H, CH, d, J = 7); 2.78-2.86 (1H, CH<u>H</u>'N, m); 2.89 (1H, CHPh, d, J = 7); 3.81-4.08 (2H, OCH_2, m), 7.18-7.44 ppm (5H, C_6H_5, m).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ13.7, 13.8 (CH_3); 45.6, 47.6 (2xCH); 54.8, 60.5 (2xCH_2); 127.2, 127.66, 127.70, 135.3 (C_6H_5); 168.3 ppm

(CO).IR($CDCl_3$) υ: 2979, 2842 (C H, s); 1740 (CO, s); 1450, 1382 (CH); 1203, 1183, 1038 cm^{-1}(C-OR, s).

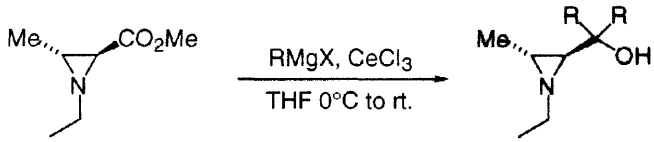
Ligand **11.** A solution of the aziridine (0.10 g, 0.46 mmol) in THF (1.0 mL) was added dropwise to a suspension of $LiAlH_4$ (42.6 mg, 1.12 mmol) in THF (0.5 mL) at -5 to 0 °C. After 3.5 days at 0 °C water (50 mL) then aqueous NaOH (15%, 50 mL) then water (130 mL) were added very carefully at 0 °C. The mixture was stirred for 1 h, then the precipitate was filtered off and washed carefully with EtOAc. The organic phase was washed with brine (2x5 mL) dried over $MgSO_4$ and the solvent removed under reduced pressure. Purification by flash chromatography gave an oil (81mg, 99%). $[\alpha]_D^{22}$ +133.3 (*c* 0.7 in $CHCl_3$)
^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.22 (3H, CH_3, t, J = 7.2); 1.20 (1H, C<u>H</u>CH_2, m); 2.28 (1H, OH, br s) 2.39-2.66 (2H, N-CHH', m); 2.69 (1H, CHPh, d, J = 6.5); 3.21 (1H, C<u>H</u>H'(OH), dd, J = 7.5 and 12); 3.44 (1H, CH<u>H</u>'(OH), dd, J = 5.5 and 12); 7.18-7.34 ppm (5H, C_6H_5, m).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 14.3 (CH_3); 45.9, 46.7 (2xCH); 55.0, 60.5 (2xCH_2); 126.8, 127.3, 128.0, 136.8 ppm (C_6H_5).

IR($CDCl_3$) υ: 3200-3600 (OH, br); 2970, 2934, 2849 (C H, s); 1449, 1380 (CH); 1028 cm^{-1}(C-OH).

Anal.: Calcd. for $C_{11}H_{15}NO$ C, 74.54; H, 8.53; N, 7.90. Found: C, 74.63; H, 8.32; N, 7.99.

Ligands **2c - e.**

These ligands were prepared from aziridine **17** [4b] as shown below. For **2c** and **2d**, the Grignard reagents were formed from the corresponding alkyl chlorides, while phenylmagnesium bromide was used for **2e**.



17 see ref [4b]

2c R = *i*-Pr
2d R = *c*-Hex
2e R = Ph

A typical procedure is as follows (ligand **2c**).

$CeCl_3 \cdot 7H_2O$ (4.45 g) was heated to 140 °C ± 5 °C under oil-pump vacuum and the temperature was maintained for 2 hours with careful stirring. The flask was then cooled to room temperature under argon atmosphere. The amount of dry $CeCl_3$ (2.93 g, 11.89 mmol) was determined. The flask was cooled to 0 °C, then dry (not warm!) THF (40 mL) was added. The white suspension was left at room temperature over night. The suspension was cooled to 0 °C and isopropylmagnesium chloride (5.7 mL, 2M in THF) was added. After 2 h at 0 °C the aziridino ester **16** (0.58 g, 2.83 mmol) in THF (4 mL) was added, and the reaction was left at room temperature over night. After 12 h, saturated NH_4Cl(aq) (30 mL) was added to the reaction mixture and water (50 mL) was added after 0.5 h. The phases were separated and the aqueous phase was extracted with Et_2O (2x50 mL). The combined organic phases were washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$ and after filtration the solvents were removed under reduced pressure giving a yellow oil. Purification by flash chromatography gave a clear oil (0.61 g, 82.4%). $[\alpha]_D^{23}$ -92.8 (*c* 0.9 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.90-0.99 (12H, CH_3, m); 1.12 (3H, $C\underline{H}_3(CH)_2N$, d, J = 6.0); 1.39 (CH-N, d, J = 3.2); 1.86-2.11 (2H, 2xCH, 2xseptet, J = 6.9 and 7.0); 2.18 (1H, N-C$\underline{H}$-CH_3, dq, J = 3.2 and 6.0); 2.84 (1H, OH, s); 3.44, 4.10 (2H, Ph$C\underline{H}_2$, 2xd, J = 14.5); 7.18-7.39 ppm (5H, C_6H_5, m).

^{13}C-NMR (63 MHz, $CDCl_3$): δ 0.4, 17.1, 17.5, 17.6, 17.7 (5xCH_3); 33.0, 33.2 (2x$\underline{C}H(CH_3)_2$); 34.6, 47.4 ($(CH)_2N$); 52.9 ($\underline{C}H_2Ph$); 72.8 (C-OH); 126.4, 127.3, 128.0, 140.1 ppm (C_5H_6).

IR($CDCl_3$) υ: 3600-3200 (O-H, br); 3087, 3027 (CH); 2964, 2877 (C H, s); 1464, 1381, 1351, (CH); 1157, 1090, 1030, 1005 cm^{-1}(C-N, C-O).

Anal.: Calcd. for $C_{17}H_{27}NO$ C, 78.11; H, 10.41; N, 5.36. Found: C, 77.90; H, 10.52; N, 5.35.

Data for ligand **2d**. Yield 81%. mp 135-6 °C. $[\alpha]_D^{22}$ -57.8 (*c* 1.0 in $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.02-1.35 (12H, CH_3, d, J = 6.0, CH_2, m); 1.39 (1H, C$\underline{H}$-C(chex)$_2$OH, d, J = 3.2); 1.50-1.91 (13H, 2xCH, CH_2, m) 2.15 (1H, C$\underline{H}$-CH_3, dq, J = 3.2 and 6); 2.78 (1H, OH, br s); 3.49, 4.08 (2H, PhC$\underline{H}_2$, 2xd, J = 14.5); 7.21-7.42 ppm (5H, C_6H_5, m).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 10.6 (CH_3); 26.5, 26.7, 26.8, 26.88, 26.9, 27.1, 27.59, 27.6, 27.8 (10xCH_2); 33.2, 48.4 ($(CH)_2N$); 43.5, 45.3 (2xCH); 53.2 (Ph$\underline{C}H_2N$); 73.0 (CH-OH); 126.5, 127.5, 128.1, 140.3 ppm (C_6H_5).

IR($CDCl_3$) υ: 3200-3600 (OH, br); 3065 (CH); 2931, 2853 (C H, s); 1451, 1381 (CH); 1097 cm^{-1}(C-OH).

Anal.: Calcd. for $C_{23}H_{35}NO$ C, 80.89; H, 10.33; N, 4.10. Found: C, 80.61; H, 10.51; N, 4.08.

Data for ligand **2e**. Yield 67%. mp 119-121 °C. $[\alpha]_D^{22}$ +23.4 (*c* 1.1 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.34 (3H, CH_3, d, J = 6.0); 2.24-2,32, 2.34 (2H, $(CH)_2N$, m, d, J = 3.5); 3.70, 3.79 (2H, PhC$\underline{H}_2$, 2xd, J = 14.0); 4.29 (1H, OH, br s); 7.12-7.44 ppm (15H, C_6H_5, m).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 10.8 (CH_3); 34.8, 53.2 ($(CH)_2N$); 54.0 (Ph$\underline{C}H_2N$); 73.9 (CH-OH); 126.0, 126.4, 126.5, 126.8, 126.9, 127.8, 127.9, 128.0, 128.2, 145.1 ppm (3xC_6H_5).

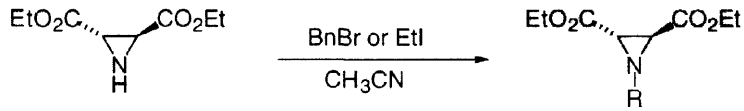
IR($CDCl_3$) υ: 3200-3600 (OH, br); 3030 (CH); 1449, 1382 (CH); 1097 cm^{-1}(C-OH).

FABMS calcd $C_{23}H_{23}NO$ 329.1780 Found: *m/z* 330.1865 $[M+H]^+$

Ligands **4a** - **h**.

Diethyl (2*R*, 3*R*)-2,3.epoxysuccinate (see Scheme 1) was prepared from diethyl (-)-L-tartrate essentially according to the literature [14] with the exception that potassium carbonate in acetonitrile was used in the second step instead of NaOEt in ethanol. The epoxide was converted to the aziridine **6** (Scheme 1) by the two.step method of Zwanenburg

[7b], with the following modifications: (*i*) ring-opening of the epoxide with $TMSN_3$ was carried out in the presence of 0.36 equiv. of methanol and 0.3 equiv. of DMAP; (*ii*) ring closure to **6** with triphenylphosphine required heating in DMF at 100 °C for 13 h for completion. *N*-alkylation of **6** with either benzyl bromide or ethyl iodide gave **18 a, b** (the precursors to ligands **4**).



6

18a R = Bn
18b R = Et

Aziridine **18a**. The aziridine **6** (2.06 g, 11.0 mmol) was dissolved in CH_3CN (15 mL). K_2CO_3 (3.05 g, 22.1 mmol) and 18-crown-6 (0.33 g, 0.12 mmol) were added followed by BnBr (1.3 mL, 10.9 mmol) which was added dropwise, and the reaction mixture was heated to 50 °C. After 20 hours more BnBr (1.05 mL, 8.8 mmol) was added. After 44 hours the reaction mixture was cooled to room temperature, the salts were removed by filtration, and the filtrate was washed carefully with Et_2O. The solvent was removed under reduced pressure and the resulting yellow oil was further purified by chromatography, giving a pale yellow oil, (3.02 g, 99%). $[\alpha]_D^{22}$ -48.5 (*c* 1.9 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ1.2 (6H, 2xCH_3, br); 3.05 (2H, 2xCH-NR, br d); 4.1 (6H, 2xOCH_2, N-CH_2-Ph, br s and 2xd, J = 13.5); 7.20-7.38 ppm (5H, C_6H_5, m).

^{13}C-NMR (63 MHz, $CDCl_3$): δ13.7 (CH_3); 40.7, 43.7 (CH); 54.3 (N-CH_2-Ph); 61.2 (CH_2-OCO); 126.8, 127.7, 128.0, 128.2, 137.7 (C_6H_5), 167 ppm (COOR).

IR(neat) υ: 3064, 3031 (CH_{AR}, m); 2983, 2938, 2873 (C H, s); 1731 (CO, s); 1454, 1370, 1330 (CH); 1186, 1095, 1000 cm^{-1}(C-O-C, s).

Anal.: Calcd. for $C_{15}H_{19}NO_4$ C, 64.97; H, 6.91; N, 5.05. Found: C, 65.13; H, 6.86; N, 4.99.

Aziridine **18b**. NaH (0.25 g, 5.73 mmol, 55% suspension in mineral oil) was washed with dry hexane (2x1 mL). To the NaH was added a solution of the aziridine **6** (0.51 g, 2.71 mmol) and ethyl iodide (0.44 mL, 5.45 mmol) (purified by filtration through neutral, activated alumina, grade I) in dry DMF (2.5 mL). The reaction mixture was left at room temperature for 7 h. Then surplus NaH was quenched by careful addition of sat. NH_4Cl(aq) (2 mL) and Et_2O (15 mL). The organic phase was washed with water (5 mL) and brine (10 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. The resultant oil

was further purified by flash chromatography giving the *N*-alkylated aziridine as a yellow oil (0.53 g, 91.4%). $[\alpha]_D^{23}$ -46.9 (*c* 1.1 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.12 (3 H, CH_3, t, J = 7); 1.30 (6 H, CH_3, t, J = 7); 2.72-2.86 (2H, N-CH, N-CHH, br, dq, J = 7, J = 11.9); 2.90-3.04 (2H, N-CH, N-CHH, br, dq, J = 7, J = 11.9); 4.22 ppm (4H, CH_2, q, J = 7).

^{13}C-NMR (63 MHz, $CDCl_3$): δ 13.9, 14.1 (CH_3); 40.7, 43.4 (2xCH); 45.5 (N-CH_2); 61.3 ppm (O-CH_2).

IR($CDCl_3$) υ: 2982 (C H, s),1733 (CO, s) 1191, 1033 cm^{-1}(C-O-C).

Anal.: Calcd. for $C_{10}H_{17}NO_4$ C, 55.80; H, 7.96; N, 6.51. Found: C, 56.04; H, 8.17; N, 6.49.

Ligand **4a**. A suspension of $LiAlH_4$ (0.44 g, 11.6 mmol) in THF (14 mL) was cooled to –10 °C. The diester **18a** (0.41 g, 1.48 mmol) in THF (3 mL) was added. After 4 h at –10 °C EtOAc (5 mL) followed by wet EtOAc (5 mL) and water (5 mL) were added carefully. The resultant gel was filtered through glass wool and washed carefully with EtOAc. The filtrate was dried over $MgSO_4$, and the solvents were removed under reduced pressure giving a pale yellow solid. This was further purified by flash chromatography giving a solid (0.24 g, 83%). mp 111-112 °C. $[\alpha]_D^{22}$ = +25.5 (*c* 1.1 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.89 (1H, CH, m); 2.32 (1H, CH, m); 2.6-2.9 (2H, 2xOH, br s); 3.45 (1H, CHH', dd, J = 5, 11.5); 3.64, 3.87 (2H, N-CH_2-Ph, 2xd, J = 14); 3.69 - 4.01 (3H, CHH', CH_2, m); 7.25 - 7.41 ppm (5H, C_6H_5, m).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ41.1, 43.8 ($(CH)_2$N-R); 54.9 (N-CH_2-Ph); 58.6, 61.8 (CH_2-OH); 127.2, 127.7, 128.5, 139.1 ppm (C_6H_5).

IR($CDCl_3$) υ: 3200-3600 (O-H, br), 2985, 2900 (CH), 1470, 1384 (CH), 1094 cm^{-1} (C-O-C).

Anal.: Calcd. for $C_{11}H_{15}NO_2$ C, 68.37; H, 7.82; N, 7.25. Found: C, 68.17; H, 7.80; H, 7.22.

Ligand **4b**. A Grignard reagent was prepared in the usual way from magnesium turnings (0.32g, 13.16 mmol) and methyl iodide (0.82 mL, 13.14 mmol) in Et_2O (10 mL). The solution was cooled to 0 °C before addition of a solution of **18a** (0.45g, 1.62 mmol) in Et_2O (10 mL). The reaction mixture was heated to reflux for 5 h, then left at room temperature over night (14 h). Then sat. NH_4Cl(aq) (10 mL) was added at 0 °C. The phases were separated and the aqueous phase was extracted with Et_2O (3x20 mL), the combined organic phases were washed with brine (2x50 mL), dried over $MgSO_4$, filtered and the

solvent was removed under reduced pressure. The resulting oil was purified by column chromatography, giving a solid (0.33 g, 82%). mp 95-97 °C. $[\alpha]_D^{20}$ +65.3 (*c* 1.1 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.6 - 1.5 (13H, 4xCH_3, OH, br); 1.92 (2H, $(CH)_2$N-R, s); 2.5 (1H, OH, br s); 4.05 (2H, N-CH_2-Ph, 2xd, J = 13); 7.2-7.4 ppm (5H, C_6H_5, m). The NMR spectrum was temperature dependent due to slow inversion at nitrogen.

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ25.9, 32.0 (CH); 28.7, 46.8 (4xCH_3); 53.6 (N-CH_2-Ph); 65.9, 69.4 (2xC-OH); 126.9, 128.1, 128.7, 140.5 ppm (C_5H_6).

IR($CDCl_3$) υ: 3200-3600 (O-H, br); 3031 (C_6H_5); 2973, 2930 (C H, s); 1369 (CH), 1169, 1103 cm^{-1} (C-OH, m).

Anal.: Calcd. for $C_{15}H_{23}NO_2$ C, 72.25; H, 9.30; N, 5.62. Found: C, 72.48; H, 9.39; N, 5.49.

Ligand **4c**. A Grignard reagent was prepared in the usual way from magnesium turnings (0.33g, 13.57 mmol) and ethyl iodide (1.05 mL, 13.00 mmol) in Et_2O (15 mL). The solution was cooled to 0 °C before addition of a solution of **18a** (0.40g, 1.44 mmol) in Et_2O (6 mL). After 19 h the reaction was quenched with sat. NH_4Cl(aq) (10 mL) at 0 °C and water (10 mL) was added. The aqueous phase was extracted with Et_2O (4x25 mL) and the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$, filtrated and the solvent removed under reduced pressure. The resulting yellow oil was purified by column chromatography, giving a solid (0.34 g, 77%). mp 73-73.5 °C. $[\alpha]_D^{22}$ +35.4 (*c* 0.9 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.66, 0.9, 1.45, 1.65, 2.1, 3.0 (3H, 9H + 2H, 7H, 2H, 1H, bb, bt + bb, 2xbb, bb, bb, CH_3, 3xCH_3 + CH_2, 3xCH_2 + OH, 2xCH, OH); 4.12 (2H, N-CH_2-Ph, 2xd, J = 13); 7.19-7.38 ppm (5H, C_6H_5). The NMR spectrum was temperature dependent due to slow inversion at nitrogen.

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ 7.3, 7.4, 7.6, 8.2 (CH_3); 28.3, 32.0 ($(CH)_2$N-R); 29.9 (CH_2); 43.7 (CH_2); 53.8 (N-CH_2-Ph); 69.9, 73.9 (C-OH); 126.7, 127.0, 128.0, 128.3, 140.7 ppm (C_6H_5).

IR($CDCl_3$) υ: 3200-3600 (OH, br), 2971, 2940, 2882 (C H, s), 1460, 1386 (CH); 967 cm^{-1} (C-OH).

Anal.: Calcd. for $C_{19}H_{31}NO_2$ C, 74.71; H, 10.23; N, 4.59. Found: C, 74.98; H, 10.44; N, 4.68.

Ligand **4d**. Anhydrous cerium trichloride (1.49 g, 6.05 mmol, prepared as described above for the synthesis of ligand **2c**) was suspended in THF (20 mL) and cooled to 0 °C before addition of a freshly prepared solution of *n*-propylmagnesium bromide (5.67 mmol)

in THF (8 mL). After 2 h at 0 °C, a solution of diester **18a** (0.20 g, 0.72 mmol) in THF (1.6 mL) was added and stirring was continued at 0 °C. After 23 h, saturated NH_4Cl(aq) (4 mL) was added to the reaction mixture and water (20 mL) was added after 0.5 h. The phases were separated and the aqueous phase was extracted with Et_2O (4x25 mL), the combined organic phases were washed with brine (50 mL), dried over $MgSO_4$ and after filtration the solvent was removed under reduced pressure giving a yellow oil. Purification by column chromatography gave a solid (0.26 g, 100%). mp 64-65 °C. $[\alpha]_D^{23}$ +22.9 (*c* 1.3 in $CHCl_3$)
^{1}H-NMR (250 MHz, $CDCl_3$): δ0.6-1.0 (12H, 4xCH_3, br m); 1.0-1.9 (17H, 8xCH_2, br); 2.1 (2H, CH, 2xbr s); 4.14 (2H, N-CH_2-Ph, 2xd, J = 13); 7.19-7.4 ppm (5H, C_6H_5, m).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ14.3, 14.4 (4xCH_3); 16.5, 17.2, 40.6, 44.2 (8xCH_2); 39.0, 42.9 ((CH)$_2$N-R); 53.8 (N-CH_2-Ph); 69.6, 73.5 (C-OH); 126.7, 128.0, 128.3, 140.7 ppm (C_6H_5).
IR($CDCl_3$) υ: 3200-3600 (OH, br), 2971, 2940, 2882 (C H, s), 1460, 1386 (CH); 967 cm^{-1} (C-OH).
Anal.: Calcd. for $C_{23}H_{39}NO_2$ C, 76.40; H, 10.87; N, 3.87. Found: C, 76.66; H, 10.67; N, 3.96.

Ligand **4e**. The ligand was prepared in essentially quantitative yield from **18a** in the same way as for **4d**, using the Grignard reagent from *n*-butyl bromide. (For both **4d** and **4e** it was essential to use the alkyl bromide or chloride to form the Grignard reagent. Use of the alkyl iodide gave much inferior results.) Data for **4e**: mp 61-62 °C. $[\alpha]_D^{22}$ = +24.5 (*c* 1.0 in $CHCl_3$)
^{1}H-NMR (250 MHz, $CDCl_3$): δ0.8 (3H, CH_3, br); 0.9 (12H, 3xCH_3, br t); 0.95-1.75 (26H, 12xCH_2, OH, CH, br); 2.09 (1H, CH, br); 4.12 (2H, N-CH_2-Ph, 2xd, J = 13.0); 7.19-7.40 ppm (5H, C_6H_5).
^{13}C-NMR (62.9 MHz, $CDCl_3$): δ13.8, 13.9 (CH_3); 23.0, 23.2, 25.4, 36.5, 38.2, 40.2 (CH_2); 44.4 ((CH)$_2$N-R); 54.0 (N-CH_2-Ph); 69, 74 (CHOH); 126.8, 128.1, 128.4 ppm (C_6H_5).
IR($CDCl_3$) υ: 3200-3600 (O-H, br); 2958, 2935, 2863 (C H,s); 1466, 1374 cm^{-1} (CH).
Anal.: Calcd. for $C_{27}H_{47}NO_2$ C, 77.64; H, 11.34; N, 3.35. Found: C, 77.93; H, 11.44; N, 3.43.

Ligand **4f**. Magnesium turnings (0.14 g, 5.76 mmol) were heated under vacuum with a heat gun, and then were allowed to cool to room temperature with magnetic stirring. this was repeated 3 times. THF (3 mL) was added, followed by 1,4-dibromobutane (0.34 mL, 2.88 mmol) in THF (5.6 mL) which was added slowly, to maintain reflux. After addition the reaction mixture was heatd to reflux for 1 hour, then it was cooled to 0 °C. The diester **18a**

(0.21 g, 0.75 mmol) in THF (0.8 mL) was added, and the reaction mixture was left at room temperature. After 19 h saturated $NH_4Cl_{(aq)}$ (2 mL) was added slowly at 0 °C. Water (10 mL) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 15 mL). The combined organic phases were washed with brine (2 x 50 mL), dried over $MgSO_4$ and the solvents removed under reduced pressure. The resultant yellow oil was further purified by column chromatography giving a solid (0.18 g, 82%). mp 55-56 °C

$[\alpha]_D^{22}$ = +61.6 (*c* 0.8 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ1.22 (2H, CH_2, br s); 1.45-1.95 (14H, 7xCH_2, 2xbr s); 2.1 (2H, 2xCH, s); 2.98 (2H, OH, br s); 4.6 (2H, N-CH_2-Ph, 2xd, J = 13.0); 7.19-7.39 ppm (5H, C_6H_5, m).

^{13}C-NMR (62.9 MHz, $CDCl_3$): δ23.6, 24.0, 36.9, 39.3, 39.7, 42.5 (8xCH_2); 46.4 ($(CH)_2$N-R); 54.0 (N-CH_2-Ph); 77.8, 80.1 (2xCOH); 126.8, 128.1, 128.3, 140.4 ppm (C_5H_6).

IR($CDCl_3$) υ: 3200-3600 (O-H, br); 3030 (C_6H_5, w); 2962, 2875 (C H, s); 1453, 1381 (CH), 1028, 1002 cm^{-1} (C-OH, m).

FABMS calcd $C_{19}H_{27}NO_2$: 301.2042 Found: *m/z* 302.2122 $[M+H]^+$

Ligand **4g**. This was prepared from **18b** by reaction with ethylmagnesium bromide (8.9 equiv.) and anhydrous cerium trichloride (9.0 equiv.) using the procedure described above for ligands **4d** and **e**. Conversion was quantitative, but the isolated yield was only 35% due to the volatility of the product. Data for **4g**:

^{1}H-NMR (250 MHz, $CDCl_3$): δ0.91 (12H, CH_3, t, J = 7.7); 1.12 (3H, CH_3, t, J = 7); 1.25-1.75 (8H, CH_2, br); 1.96 (2H, s); 2.8-3.1 ppm (2H, CH_2-N, m).

^{13}C-NMR (63 MHz, $CDCl_3$): δ7.8, 8.3 (4 x CH_3); 16.1 (CH_3); 28.1, 29.8, 30.4, 32.1 (4 x CH_2); 43.3, 44.5 (2 x CH); 44.4 (N-CH_2); 70, 74 ppm (2xC-OH).

FABMS calcd $C_{14}H_{29}NO_2$: 243.2198 Found: *m/z* 244.2286 $[M+H]^+$

Ligand **4h**. This was prepared in essentially quantitative yield from **18b** by reaction with phenylmagnesium bromide (8.0 equiv.) and anhydrous cerium trichloride (8.6 equiv.) using the procedure described above for ligands **4d** and **e**. Data for **4h**:

mp 185-187 °C. $[\alpha]_D^{21}$ -60.7 (*c* 0.9 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 0.53 (3 H, CH_3, t, J = 7.1); 1.25 (1 H, OH, br); 2.40-2.50 (1H, br, OH); 2.64 (2H, N-CH_2, m); 2.9-3.3 (2H, $(CH)_2$N-Et, br); 7.99-7.59 ppm (20 H, C_6H_5, br).

^{13}C-NMR (63 MHz, $CDCl_3$): δ 15.6 (CH_3); 44.6 (N-CH_2); 46.6 (CH); 126.0, 126.4, 126.7, 127.8 ppm (C_6H_5).

IR($CDCl_3$) υ: 3200-3600 (OH, br), 3061, 3027 (CH_{AR}, s), 2972, 2930 (C H, s), 1492, 1448, 1378, 1325 (C H,CC_{AR}) 1176, 1066 cm^{-1}(C-OH).

Anal.: Calcd. for $C_{30}H_{29}NO_2$ C, 82.73; H, 6.71; N, 3.22. Found: C, 82.60; H, 6.93; N, 3.16.

Ligand **5b**. Aziridine **5a** [9] (0.33 g, 1.16 mmol) was dissolved in CH_3CN (4 mL). Vacuum dried K_2CO_3 (0.66 g, 4.78 mmol) was added and the mixture was stirred for half an hour at room temperature. Then benzyl bromide (0.15 mL, 1.28 mmol) was added and the reaction mixture was heated to 50 °C. After 3.5 h the mixture was cooled to room temperature. Et_2O (15 mL) was added, and the solid as filtered off and carefully washed with more Et_2O. The organic phase was washed with brine (2 x 30 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resultant oil was further purified by flash chromatography furnishing an oil (0.18 g, 42%). $[\alpha]_D^{23}$= +17.8 (*c* 2.0 in $CHCl_3$)

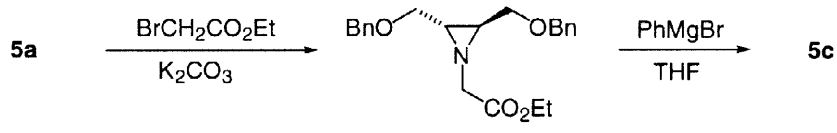
^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.90 (1H, CH, m); 2.30 (1H, CH, m); 3.40-3.56 (2H, CH_2-OBn, 2xdd, J = 5, J = 3, J = 10.5); 3.50 (1H, N-C<u>H</u>H'Ph, d, J = 14.0); 3.64-3.84 (2H, CH_2-OBn, 2xdd, J = 3.8, J = 8, J = 11); 3.93 (1H, N-CH<u>H'</u>Ph, d, J = 14); 4.43 (2H, PhCH_2-OR, 2xd, J = 11); 4.52 (2H, PhCH_2-OR, 2xd, J = 12); 7.18-7.42 ppm (15H, 3xC_6H_5, m).

^{13}C-NMR (63 MHz, $CDCl_3$): δ 39.5, 42.1 (2xCH); 55.3 (N-<u>C</u>H_2Ph); 66.0, 72.2 (2 x CH_2-OBn); 72.7 (2 x Ph-<u>C</u>H_2-OR); 126.6, 127.4, 127.5, 127.6, 127.8, 128.1, 128.3, 137.8, 138.1, 139.6 ppm (3 x C_6H_5).

IR($CDCl_3$) υ: 3066, 3031(CH), 2859 (C H, s), 1096 cm^{-1}(C-O-C, s).

Anal.: Calcd. for $C_{25}H_{27}NO_2$ C, 80.40; H, 7.29; N, 3.75. Found: C, 80.15; H, 7.17; N, 3.73.

Ligand **5c**. This was prepared from **5a**, *via* **19**, as shown below.



19

(*i*) Aziridine **5a** (0.30 g, 1.07 mmol) was dissolved in CH_3CN (50 mL), K_2CO_3 (0.59 g, 4.27 mmol) and ethyl bromoacetate (0.15 mL, 1.36 mmol) were added. The reaction mixture was heated to 50 °C and left at this temperature for 14.5 h. After cooling to room temperature the solid was filtered off and the filtrate was washed carefully with Et_2O. The organic phase was washed with brine (2 x 20 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure giving a yellow oil. The compound was further purified by flash chromatography furnishing **19** as an oil (0.23 g, 59%). $[\alpha]_D^{24}$ = - 10.7 (*c* 1.1 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.23 (3H, CH_3, t, J = 7.1); 1.92 (1H, CH, m); 2.30 (1H, CH, m); 3.3 (1H, N-C<u>H</u>H', d, J = 16); 3.50 (1H, N-CH<u>H</u>', d, J = 16); 3.42-3.84 (4H, 2x CH_2-OBn, m); 4.14 (2H, CH_2OCO, q, J = 7.1); 4.42-4.60 (4H, 2xPhC<u>H</u>$_2$-OR, m); 7.15-7.35 ppm (10H, 2xC_6H_5, m).

^{13}C-NMR (63 MHz, $CDCl_3$): δ 14.0 (CH_3); 39.1, 41.6 (2xCH); 53.0 (NH-<u>C</u>H_2-COOR); 60.6 (<u>C</u>H_2OCO); 65.7, 71.6 (2 x CH_2-OBn); 72.6, 72.9 (2 x Ph<u>C</u>H_2-OR); 127.4, 127.5, 128.2, 137.5, 138.0 (2 x C_6H_5); 170.7 ppm (COOR).

IR($CDCl_3$) υ: 2984, 2865 (C H, m), 1735 (CO, s), 1454, 1376 (C H, m), 1202, 1098 (C-O-C, s).

Anal.: Calcd. for $C_{22}H_{27}NO_4$ C, 71.52; H, 7.37; N, 3.79. Found: C, 71.75; H, 7.41; N, 3.76.

(*ii*) A solution of freshly prepared phenylmagnesium bromide (6.64 mmol) in THF (20 mL) was cooled to 0 °C. A solution of **19** (1.00 g, 2.71 mmol) in THF (15 mL) was added slowly and the reaction mixture was reheated to room temperature. After 20 minutes sat. NH_4Cl(aq) (9 mL) was added slowly at 0 °C. The phases were separated and the aqueous phase were extracted with Et_2O (4 x 25 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure giving a pale yellow oil. The oil was further purified by flash chromatography furnishing an oil (1.29 g, 99.2%).

$[\alpha]_D$ = -46.8 (*c* 0.5 in $CHCl_3$)

^{1}H-NMR (250 MHz, $CDCl_3$): δ 1.85, 2.2 (2H, 2xCH, br); 2.77 (1H, N-C<u>H</u>H', d, J = 12.5); 2.9, 3.3, (2H, CH_2-OBn, 2xm); 3.5, 3.7 (2H, CH_2-OBn, 2xm); 3.77 (1H, N-CH<u>H</u>', d, J = 12.5); 4.4-4.6 (4H, 2xPh<u>C</u>H_2-OR, m); 7.1-7.53 ppm (20 H, 4xC_6H_5, m).

^{13}C-NMR (126 MHz, $CDCl_3$): δ 38.5, 43.4 (2xCH); 61.0 (N-CH_2); 66.5, 71.7 (2xCH_2-OBn); 72.9 (2xPh-<u>C</u>H_2-OR); 77.8 (Ph_2C-OH); 125.8, 126.5, 127.6, 127.9, 128.3, 137.6, 145.9 ppm (4xC_6H_5).

IR($CDCl_3$) υ: 3200-3600 (OH, br); 3031, 3064 (CH); 2866 (C H, s); 1453, 1378 (CH); 1095 (C-O-C, s).

Anal.: Calcd. for $C_{32}H_{33}NO_3$ C, 80.40; H, 6.93; N, 2.92. Found: C, 80.00; H, 7.02; N, 2.91.

General procedure for catalytic enantioselective addition of alkyl zincs to aldehydes. Addition of diethyl zinc to benzaldehyde in the presence of ligand **4c**.

Ligand **4c** (17.4 mg, 0.057 mmol) was suspended in dry toluene (1 mL) and cooled under nitrogen to 0 °C. A solution of diethyl zinc (1.0 M in hexane, 2.1 mL, 2.1 mmol) was added, and the resultant mixture was stirred for 30 min. before being cooled to -23 °C. Freshly distilled benzaldehyde (0.10 mL, 0.98 mmol) was added, and the mixture was stirred at -23 °C for 60 h. The reaction was quenched by addition of saturated aqueous ammonium chloride solution (2 mL), the layers were separated, and the aqueous phase was extracted with ether. The combined organics were washed with brine, dried over $MgSO_4$ and the solvents were removed *in vacuo*. The crude product was purified by flash chromatography to give the product as an oil (0.12 g, 92%). The *ee* was determined by means of chiral HPLC (Chiral OD-H column) and the absolute configuration was assigned by measurement of the specific optical rotation [19]. (In control experiments, it was found that the *ee* value measured on the crude product did not differ significantly from that measured on the purified material.)

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