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Enantioselective addition of diethylzinc to aldehydes using 1,4-aminoalcohols as chiral ligands

Dina Scarpi, Fabrizio Lo Galbo, Ernesto G. Occhiato and Antonio Guarna*

Dipartimento di Chimica Organica 'U. Schiff', Università di Firenze, Via della Lastruccia 13, 50019 Sesto Fiorentino, Italy

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Abstract—Conformationally constrained, optically active 1,4-aminoalcohols have been used as chiral ligands in the addition of diethylzinc to aromatic aldehydes. The enantioselectivity was strongly influenced by the *N*-alkyl group: the best results were achieved with *N*-ethyl- and *N*-benzyl-aminoalcohols (ees up to 95% and 81%, respectively). One example of addition to an aliphatic aldehyde is also reported (best ee 61%).

1. Introduction

The formation of C–C bonds has always been one of the most challenging goods in organic synthesis. Among current methods, the enantioselective addition of dialkylzinc compounds to aldehydes in the presence of chiral ligands has been widely explored since the first reports by Noyori and co-workers[1,2] The chiral ligands employed for this purpose include mainly aminoalcohols, with a few examples of aminothiols, amines, diols, disulfides and diselenides.[3] 1,2-Aminoalcohols have mostly been used as chiral ligands in the addition of dialkylzinc to aldehydes, whereas there are only a few examples of 1,4-aminoalcohols similarly employed (Fig. 1).[4–7] In these cases the ligand structure is formed by a rigid camphor or camphor-like core bearing the hydroxyl group. The amino group is normally bound to the core through an aliphatic chain (Fig. 1, compounds **2**–**6**). The only exception is represented by compound **1** (Fig. 1), whose core structure is a functionalised cyclohexane. Depending on the ligand structure and the aldehyde, the addition of dialkylzinc provides alcohols with ees from 3% to 95%.

We recently reported the facile synthesis of new enantiopure 1,4-aminoalcohols obtained by combining glycine and an arabinose derivative[8] (Fig. 2, **7**) or an α-aminoacid and a tartaric acid derivative[9] (Fig. 2, **8**). Because these conformationally constrained molecular structures have three potential sites for metal coordination, they seemed to us very promising as potential chiral ligands for metal-catalysed reactions. The addition of diethylzinc to aldehydes is a well known reaction and lots of mechanistic information is available. For this reason it was chosen as a benchmark for these potential metal ligands. Moreover, further interest was stimulated by the fact that only very few examples of 1,4-aminoalcohols have been employed so far as zinc ligands in this reaction.

2. Results and discussion

The synthesis of the Fmoc protected aminoalcohol **7** (Scheme 1) was performed as already described.[8] Deprotection with Et_2NH (12 h) in THF afforded **9a** in 50% yield after crystallisation. The subsequent reductive amination was carried out in MeOH at pH 6 with $NaBH_3CN$. *N*-Alkyl 1,4-aminoalcohols **9b**–**e** were thus obtained in good yields (76–82%) after chromatography.

Alkylation of benzaldehyde using diethylzinc in the presence of *N*-alkyl substituted 1,4-aminoalcohols **9b**–**e** was performed in anhydrous toluene at room temperature (Scheme 2). The use of aminoalcohol **9a** was hampered by its low solubility in toluene. We first carried out the reaction by employing 5 mol% of chiral ligand and stopping the reaction after 24 h (Table 1).

Under these conditions, we observed in all cases also the formation of a small amount of primary alcohol **12** that derives from β-H elimination and carbonyl reduction.[2]

* Corresponding author. Tel.: +39-055-4573481; fax: +39-055-45735-31; e-mail: antonio.guarna@unifi.it

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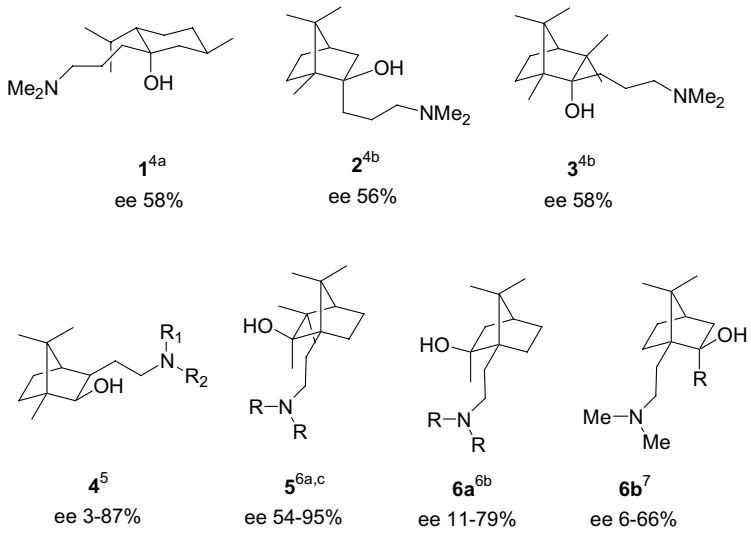


Figure 1. 1,4-Aminoalcohols ligands and best ee in the Et_2Zn catalysed addition to aldehydes.

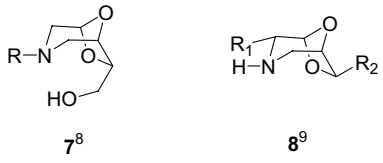
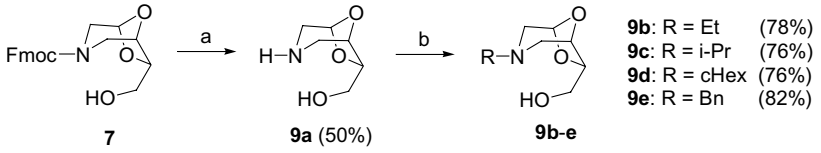


Figure 2. General structure of chiral 1,4-aminoalcohols deriving from glycine and an arabinose derivative **7** or from D-α-aminoacids and a tartaric acid derivative **8**.

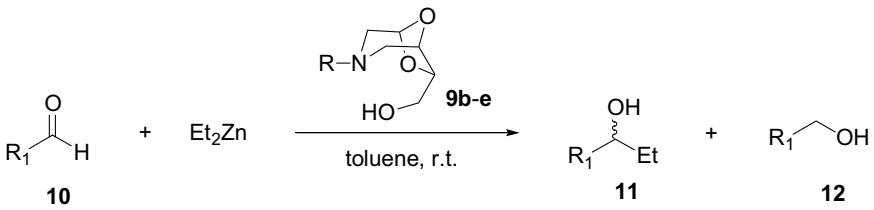
The best results were achieved when ligands **9b** and **9e** were used (entries 1 and 4, ee 82% and 65%, respectively), although the conversion was not complete in the latter case. These ligands were further investigated by varying reaction times and amount of catalyst (Table 2).

The addition of diethylzinc to benzaldehyde was carried out by using 5 and 20 mol% **9e** and stopping the reaction at 24, 48 and 120 h. Using 5 mol% the reaction was almost complete only after 120 h at room temperature (entry 3), affording (*S*)-alcohol with 71% ee. A comparable result was obtained after 48 h when 20 mol% catalyst was used (entry 5).

Compound **9b** was instead a better ligand, since carrying out the reaction with 5 mol% of **9b** allowed complete conversion to (*S*)-alcohol **12** in 24 h and with 82% ee (entry 7). When the reaction was performed with 10 and 20 mol% of ligand **9b**, we observed a progressive increase in enantioselectivity (entries 8 and 9) up to 94% ee. A similar result was obtained with ligand **9e** (compare entries 1 and 4). We attributed this ee increase to the diminished competition of a noncatalysed addition of diethylzinc to the benzaldehyde[10] that occurs under our conditions. This was verified by performing the reaction without ligand, either under nitrogen or argon atmosphere, which afforded racemic alcohol **11** in 14% yield after 24 h. For this reason, we decided to carry out all subsequent experiments with different aldehydes using 20 mol% of ligands **9b** and **9e** (Table 3).



Scheme 1. (a) Et_2NH, THF, room temperature, 12 h; (b) RCHO or $R_2C{=}O$, $NaBH_3CN$, MeOH pH 6, room temperature, 12 h.



Scheme 2. Catalysed addition of diethylzinc to aldehydes.

Table 1. Distribution of products obtained by diethylzinc addition to benzaldehyde **10** (R_1=Ph) in the presence of 5 mol% of chiral ligand **9b–e**; reaction time is 24 h

Entry	L*	R	**10**[a]	**11**[a]	**12**[a]	Ee (%)[b]	Configuration of **11**[c]
1	**9b**	Et	1	97	2	82	*S*
2	**9c**	*i*-Pr	5	89	6	37	*S*
3	**9d**	cHex	5	92	3	48	*S*
4	**9e**	Bn	27	70	3	65	*S*

[a] Determined by GC.
[b] Determined by GC using β DEX™ 120 column.
[c] Determined by the sign of the specific rotation.

Table 2. Distribution of products obtained by diethylzinc addition on benzaldehyde **10** (R_1=Ph) in the presence of chiral ligand **9b** (R=Et) or **9e** (R=Bn)

Entry	L*	Mol%	Time (h)	**10**[a]	**11**[a]	**12**[a]	Ee (%)[b]	Configuration of **11**[c]
1	**9e**	5	24	27	70	3	65	*S*
2	**9e**		48	11	85	4	69	*S*
3	**9e**		120	2	93	5	71	*S*
4	**9e**	20	24	10	86	4	76	*S*
5	**9e**		48	5	92	3	77	*S*
6	**9e**		120	0	97	3	81	*S*
7	**9b**	5	24	1	97	2	82	*S*
8	**9b**	10	24	0	98	2	90	*S*
9	**9b**	20	24	0	97	3	94	*S*

[a] Determined by GC.
[b] Determined by GC using β DEX™ 120 column.
[c] Determined by the sign of the specific rotation.

The reaction, carried out in the presence of ligand **9b**, was highly enantioselective (entries 2–6, 90–95% ee), with chloro and methyl substituted benzaldehydes. In the case of 4-methoxybenzaldehyde (entry 7), the conversion was complete, although water elimination during the work-up formed 1-methoxy-4-propenyl-benzene (14%) as by-product. Moreover the ee was lower than in the previous examples (84%), which could be due to the decreased rate of the catalysed reaction. In all cases, conversions were quantitative and the corresponding primary alcohols **12** were formed in low yields (0–5%).

Table 3. Distribution of products obtained by diethylzinc addition on aromatic aldehydes **10** in the presence of 20 mol% of chiral ligand **9b** (R=Et) and **9e** (R=Bn); the reaction was stopped after 24 h

Entry	L*	R_1	**10**[a]	**11**[a]	**12**[a]	Ee (%)[b]	Configuration of **11**[c]
1	**9b**	C_6H_5	0	97	3	94	*S*
2	**9b**	2-Cl–C_6H_4	0	95	5	90	*S*
3	**9b**	3-Cl–C_6H_4	0	96	4	91	*S*
4	**9b**	4-Cl–C_6H_4	0	98	2	94	*S*
5	**9b**	3-Me–C_6H_4	0	98	2	95	*S*
6	**9b**	4-Me–C_6H_4	0	97	3	93	*S*
7	**9b**	4-MeO–C_6H_4	0	86[d]	0	84	*S*
8	**9b**	$CH_3(CH_2)_5$	—	55[e]	—	61	*S*
9	**9e**	C_6H_5	10	86	4	76	*S*
10	**9e**	2-Cl–C_6H_4	0	87	13	63	*S*
11	**9e**	3-Cl–C_6H_4	0	82	18	64	*S*
12	**9e**	4-Cl–C_6H_4	7	93	0	81	*S*
13	**9e**	3-Me–C_6H_4	8	87	5	63	*S*
14	**9e**	4-Me–C_6H_4	18	65	17	54	*S*
15	**9e**	4-MeO–C_6H_4	41	47[f]	0	46	*S*
16	**9e**	$CH_3(CH_2)_5$	—	29[e]	—	44	*S*

[a] Determined by GC.
[b] Determined by GC using β DEX™ 120 column.
[c] Determined by the sign of the specific rotation.
[d] 1-Methoxy-4-propenyl-benzene is formed during the reaction (14%).
[e] Yield after chromatography.
[f] 1-Methoxy-4-propenyl-benzene is formed during the reaction (12%).

When ligand **9e** was employed, the reaction rate and ee decreased, as in the alkylation of benzaldehyde, and after 24 h at room temperature, quantitative conversion was reached only with 2- and 3-chloro substituted benzaldehydes (entries 10 and 11), although a significant amount of primary alcohol **12** was formed (13–18%). The variation of the amount of **12** obtained in all the experiments is difficult to rationalise and seems to be independent of the conversion to chiral alcohol **11** (compare entries 10 with 13 and 14 with 15). The best result was achieved in the formation of 1-(4-chlorophenyl)-propan-1-ol that was obtained in 81% ee (entry 12) and no primary alcohol **12** was detected.

The worst results in terms of conversions and ee (46–54%) were obtained with 4-methyl and 4-methoxy substituted benzaldehydes. In particular, in the case of 4-methoxybenzaldehyde (entry 15) the reaction rate further decreased by the electron donor group, resulting in an overall 59% conversion to alcohol **11** (47%) and to 1-methoxy-4-propenyl-benzene (12%).

Analogous results were obtained by employing heptanal as a substrate for the addition: the ee of the alcohol **11** was higher when ligand **9b** was used (61%, entry 8) than in the case of ligand **9e** (44%, entry 16), whereas the *S* configuration was maintained. The lower ees recorded are consistent with the results reported in the literature for nonaromatic aldehydes.

The stereochemical outcome of the reaction can be explained by using the transition state model proposed by Noyori and Yamakawa[11] for β-aminoalcohols in which two Zn ions are present in different coordination spheres, one of them being formed by the ligand–Zn complex. This model has been used and adapted to γ- and δ-aminoalcohols.[6a,12] For 1,4-aminoalcohols, the corresponding tricyclic transition state structure is formed by a fused 7/4/4 ring system (Fig. 3). In the case of ligands **9b** and **9e**, zinc aminoalkoxide **A**, formed in situ, can reasonably undergo the subsequent coordination only on the more accessible *Si*-face of the zinc atom (the *Re*-face is in fact more sterically hindered by the bicyclic structure of the ligand). Once the second zinc and aldehyde coordinated, there are four possible forms of the tricyclic transition states (**B**–**E**). Transition states of the *syn* type (**B** and **C**) should be less likely because of steric hindrance between the two nonreacting ethyl groups on the zinc atoms. Between the transition states of the *anti* type (**D** and **E**), the most energetically favourite should be the *anti* **D**, in which the aromatic ring of the benzaldehyde is oriented far from the hindered ligand 'cage', and (*S*)-alcohol is thus preferentially formed.

Referring to the addition of Et_2Zn to benzaldehyde as a model substrate, conversions and ee obtained with our best ligand **9b** are generally comparable with those reported in the literature for 1,4-aminoalcohols **1**–**6**. The

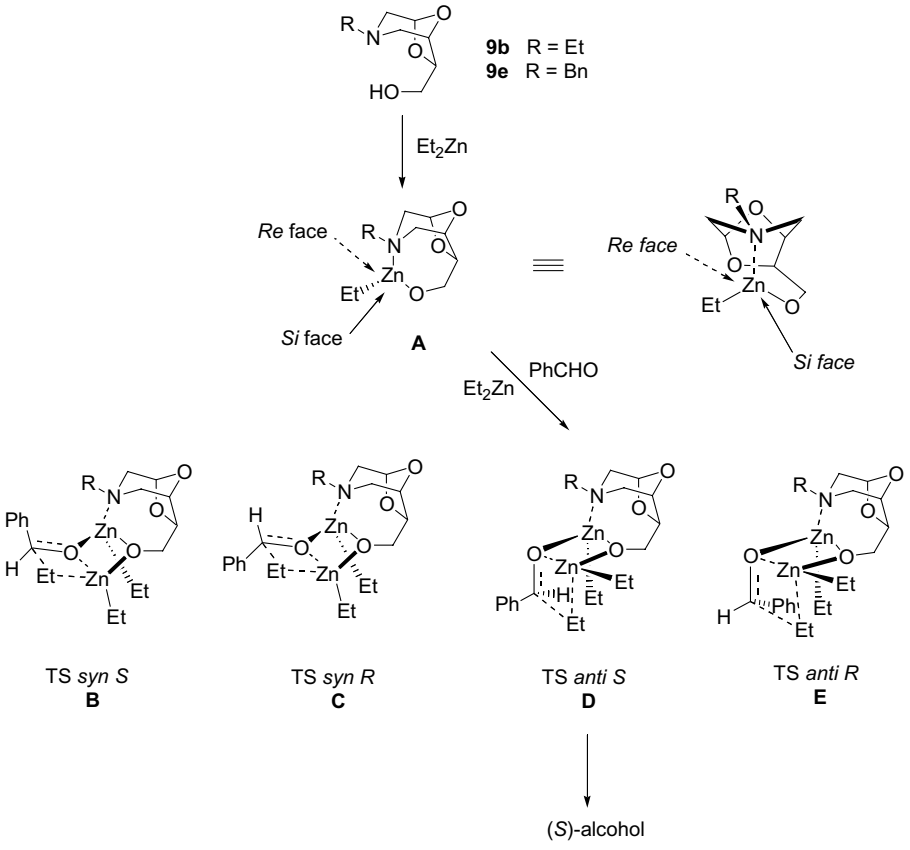


Figure 3. Model of transition states.

reported yields of the chiral alcohol **11** are usually above 90% after 24 h with 3–10 mol% of the ligand and enantiomeric excesses range from 64% to 95%.[4–6] Only in one case[6a] has a reported catalyst been superior to **9b** only in terms of reaction rate, being complete after 2 h with 5% ligand. In our case, a competitive zinc coordination by the acetal O-6 and O-8 atoms of ligands **9** could account for the slower reaction rates.[13] Despite the low degree of substitution on the structural core of our ligands **9** compared to **1**–**6**, the high ees obtained in the Et_2Zn addition to aldehydes are noteworthy. This could be attributed to the rigid structure of **9**.

In conclusion, we have shown that chiral 1,4-aminoalcohols **9** exhibit high asymmetric induction in the addition of diethyl zinc to aldehydes. Further investigations on their use as chiral ligands in other catalysed reactions and evaluation of the effect of substituents on the scaffold on the asymmetric induction are currently in progress and results will be reported in due course.

3. Experimental

Melting points are uncorrected. Chromatographic separations were performed under pressure on silica gel by flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel plates (Merck F254), with the same eluent as indicated for the column chromatography. ^{1}H NMR (200 MHz) and ^{13}C NMR (50.33 MHz) spectra were recorded with a Varian XL 200 instrument in $CDCl_3$ solution. Mass spectra were carried out by EI at 70 eV, unless otherwise stated, on QMD 1000 Carlo Erba instruments. GC analysis were performed on a HP5890 Series II instrument supported with a Supelco β DEX™ 120, 30 m × 0.25 mm, 0.25 μm film column. Microanalyses were carried out with a Perkin–Elmer 2400/2 elemental analyser. Optical rotations were determined with a JASCO DIP-370 instrument. 7-Hydroxymethyl-6,8-dioxa-3-aza-bicyclo[3.2.1]octane-3-carboxylic acid 9*H*-fluoren-9-ylmethyl ester **7** was synthesised as reported.[8]

3.1. (1*S*,5*S*,7*R*)-(6,8-Dioxa-3-aza-bicyclo[3.2.1]oct-7-yl)-methanol 9a

Et_2NH (31 mL, 300 mmol) is added to a solution of **7** (15.8 g, 43 mmol) in THF (250 mL) and the mixture stirred at room temperature. After 12 h, solvent and Et_2NH were removed under vacuum and crude **9a** was crystallised from *n*-hexane, affording pure **9a** as white crystals (3.1 g, 50%). Mp 70–71 °C. $[\alpha]_D^{20} = -70.1$ (*c* 0.96, $CHCl_3$). ^{1}H NMR δ (ppm): 5.48 (s, 1H), 4.28–4.25 (m, 1H), 4.20–4.07 (m, 2H), 3.87 (d, $J = 10.6$ Hz, 1H), 3.29–3.21 (m, 1H), 3.06–2.86 (m, 3H). ^{13}C NMR δ (ppm): 99.7 (d), 78.5 (d), 74.9 (d), 59.3 (t), 48.8 (t), 45.7 (t). MS *m*/*z* (%) 144 (M^+-1, 3), 114 (M^+-CH_2OH, 8), 99 (100). Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.33; H, 7.58; N, 9.56.

3.2. (1*S*,5*S*,7*R*)-(3-Ethyl-6,8-dioxa-3-aza-bicyclo-[3.2.1]oct-7-yl)-methanol 9b

CH_3CHO (771 μL, 5 equiv, 13.7 mmol) was added to a solution cooled at 0 °C of amino alcohol **9a** (398 mg, 2.74 mmol) and $NaBH_3CN$ (189 mg, 1.1 equiv, 3.01 mmol) in methanol (10 mL) at pH 6 by acetic acid. The solution was allowed to warm to rt and stirred for 12 h. Water (10 mL) and $Na_2CO_3{\cdot}10H_2O$ (s) up to pH 9–10 were added, the product extracted with $CHCl_3$ (3 × 15 mL) and the combined organic layers dried over Na_2SO_4. After filtration and evaporation of the solvent crude **9b** was obtained. Purification by chromatography (eluent: EtOAc–petroleum ether, 4:1, 1% Et_3N, $R_f = 0.13$) afforded pure **9b** (370 mg, 78%) as colourless oil. $[\alpha]_D^{22} = -88.5$ (*c* 0.58, $CHCl_3$). ^{1}H NMR δ (ppm): 7.20 (br s, 1H), 5.52 (s, 1H), 4.36–4.34 (m, 1H), 4.22–4.09 (m, 2H), 3.85 (d, $J = 12.0$ Hz, 1H), 3.07–2.99 (m, 2H), 2.64–2.56 (m, 1H), 2.47 (q, $J = 7.2$ Hz, 2H), 2.35 (d, $J = 11.4$ Hz, 1H), 1.07 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR δ (ppm): 99.0 (d), 78.4 (d), 74.8 (d), 59.1 (t), 55.8 (t), 52.6 (t), 50.9 (t), 11.2 (q). MS *m*/*z* (%) 173 (M^+, 11), 158 (7), 128 (75), 72 (100). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.51; H, 8.69; N, 8.33.

3.3. (1*S*,5*S*,7*R*)-(3-Isopropyl-6,8-dioxa-3-aza-bicyclo-[3.2.1]oct-7-yl)-methanol 9c

Prepared as described for **9b**, starting from **9a** (92 mg, 0.63 mmol), acetone (139 μL, 3 equiv, 1.89 mmol) and $NaBH_3CN$ (1.1 equiv). Purification by chromatography (eluent: EtOAc–CH_2Cl_2, 3:1, 1% Et_3N, $R_f = 0.25$) afforded pure **9c** (80 mg, 76%) as colourless oil. $[\alpha]_D^{27} = -72.5$ (*c* 0.96, $CHCl_3$). ^{1}H NMR δ (ppm): 7.17 (s, 1H), 5.54 (s, 1H), 4.36 (dd, $J = 4.4$, 2.2 Hz, 1H), 4.21–4.08 (m, 2H), 3.84 (d, $J = 12.2$ Hz, 1H), 2.95 (dd, $J = 10.6$, 3.6 Hz, 2H), 2.78 (dd, $J = 11.8$, 2.2 Hz, 1H), 2.68 (sept, $J = 6.6$ Hz, 1H), 2.50 (d, $J = 11.2$ Hz, 1H), 1.06 (d, $J = 6.6$ Hz, 3H), 1.04 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR δ (ppm): 99.0 (d), 78.1 (d), 74.6 (d), 59.0 (t), 53.4 (d), 51.3 (t), 48.8 (t), 18.2 (q), 17.2 (q). MS *m*/*z* (%) 187 (M^+, 8), 172 (M^+-CH_3), 56 (100). Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.83; H, 9.31; N, 7.69.

3.4. (1*S*,5*S*,7*R*)-(3-Cyclohexyl-6,8-dioxa-3-aza-bicyclo-[3.2.1]oct-7-yl)-methanol 9d

Prepared as described for **9b**, starting from **9a** (94 mg, 0.65 mmol), cyclohexanone (76 μL, 1.1 equiv, 0.71 mmol) and $NaBH_3CN$ (1.1 equiv). Purification by chromatography (eluent: EtOAc–petroleum ether, 5:1, 1% Et_3N, $R_f = 0.33$) afforded pure **9d** (113 mg, 76%) as colourless oil. $[\alpha]_D^{27} = -73.7$ (*c* 1.37, $CHCl_3$). ^{1}H NMR δ (ppm): 7.30–7.20 (br s, 1H), 5.53 (s, 1H), 4.37–4.34 (m, 1H), 4.21–4.06 (m, 2H), 3.83 (d, $J = 12.0$ Hz, 1H), 3.00–2.95 (m, 2H), 2.82 (dd, $J = 12.2$, 2.2 Hz, 1H), 2.54 (d, $J = 11.4$ Hz, 1H), 2.35–2.20 (m, 1H), 1.90–1.70 (m, 4 H), 1.30–1.08 (m, 6 H). ^{13}C NMR δ (ppm): 99.2 (d), 78.3 (d), 74.9 (d), 62.4 (d), 59.1 (t), 52.0 (t), 49.2 (t), 28.7 (t), 27.8

(t), 25.9 (t), 25.5 (t), 25.4 (t). MS m/z (%) 227 (M^+, 4), 184 (25), 55 (100). Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.37; H, 9.31; N, 6.25.

3.5. (1*S*,5*S*,7*R*)-(3-Benzyl-6,8-dioxa-3-aza-bicyclo-[3.2.1]oct-7-yl)-methanol 9e

Prepared as described for **9b**, starting from **9a** (172 mg, 1.18 mmol), benzaldehyde (132 μL, 1.1 equiv, 1.30 mmol) and $NaBH_3CN$ (1.1 equiv). Purification by chromatography (eluent: EtOAc–petroleum ether, 2:1, 1% Et_3N, $R_f = 0.32$) afforded pure **9e** (227 mg, 82%) as colourless oil. $[\alpha]_D^{27} = -92.3$ (c 0.88, $CHCl_3$). ^1H NMR δ (ppm): 7.38–7.22 (m, 5H), 6.66 (s, 1H), 5.48 (s, 1H), 4.36–4.33 (m, 1H), 4.21–4.09 (m, 2H), 3.89 (d, $J = 11.2$ Hz, 1H), 3.69 (d, $J = 12.4$ Hz, 1H), 3.43 (d, $J = 12.4$ Hz, 1H), 3.06 (d, $J = 12.2$ Hz, 1H), 2.87 (d, $J = 10.2$ Hz, 1H), 2.77–2.69 (m, 1H), 2.32 (d, $J = 11.4$ Hz, 1H). ^{13}C NMR δ (ppm): 135.2 (s), 129.4 (d, 2C), 128.5 (d, 2C), 127.8 (d), 99.0 (d), 78.4 (d), 74.4 (d), 61.8 (t), 59.2 (t), 55.7 (t), 53.4 (t). MS m/z (%) 234 (M^+-1, 9), 91 (100), 143 (5). Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.44; H, 7.22; N, 5.91.

3.6. General procedure for addition reaction of diethylzinc to aldehydes

Diethylzinc (1.0 M solution in hexane, 2 mmol) was added to a solution of ligand **9** (0.05–0.20 mmol) in anhydrous toluene (2 mL). After 30 min, aldehyde **10** (1 mmol) was added dropwise and the resulting mixture stirred for 24 h. The reaction was quenched by 1 M aqueous HCl solution (5 mL) and the product extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude alcohol **11** was obtained and directly analysed by GC to determine product composition and ee. In the case of chiral 3-nonanol, the ee was determined by polarimetric measurement after purification of the crude by chromatography (eluent: petroleum ether–EtOAc, 10:1, $R_f = 0.31$).

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