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Synthesis and application of monoterpene-based chiral aminodiols

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Dedicated to Professor Csaba Szántay on the occasion of his 80th birthday

Abstract—Primary, secondary and tertiary aminodiols were synthetized regio- and stereoselectively from (−)-α-pinene **1** via α-pinene oxide **2**, (−)-*trans*-pinocarveol **3** and key intermediate epoxy alcohol **4**. *N*-Benzyl derivative **5** was transformed to spiro-fused oxazolidine **13** in a highly regioselective ring closure. Aminodiols and their derivatives **5**–**13** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde, resulting in chiral 1-phenyl-1-propanol. The substituent effect on the nitrogen was studied in detail and the best enantioselectivity was observed in the case of *N*-methyl-*N*-benzyl-substituted derivative **8**. The phenomenon was interpreted by using molecular modelling at an ab initio level.

1. Introduction

Aliphatic aminodiols play important roles in drug therapy and drug research.[1–7] For example, chloramphenicol, one of the earliest antibiotics, is an aminodiol derivative, other aminodiols have been found to act as HIV protease inhibitors,[1–3] and still others have been shown to exert renin inhibitor activity.[5,6] Furthermore, aminodiols may serve as useful starting materials for the synthesis of biologically active natural compounds, e.g., cytoxazone, a selective modulator of the secretion of T_H2 cytokine, a microbial metabolite isolated from *Streptomyces* species.[8,9] Apart from the pharmacological interest, aminodiols are also useful starting materials for the syntheses of oxazines or oxazolidines, depending upon which hydroxy group undergoes ring closure with the amino group.[10] Since the resulting heterobicycles contain a free hydroxy group, further ring closure can yield heterotricyclic structures. Moreover, alicyclic aminodiols are potentially excellent starting points for the development of new ring–chain tautomeric systems.[10]

The identification of new chiral ligands for asymmetric syntheses is of increasing importance in organic chemistry. The readily available chiral terpenes and their derivatives are widely used as chiral auxiliaries in enantioselective transformations. The syntheses of 1,2- and 1,3-amino alcohols and their application as chiral ligands and auxiliaries in enantioselective transformations are currently undergoing intensive investigation.[7,11] Various amino alcohol catalysts derived from monoterpenes, such as (+)-pulegone,[12] β-pinene,[13] fenchone–camphor[14] and limonene,[15] have been reported to have been used successfully in enantioselective syntheses. Chiral aminodiols and their derivatives also find excellent application as catalysts for enantioselective transformations.[16–20]

We recently reported the transformations of enantiomerically pure α-pinene and 3-carene to β-amino acid derivatives, such as amino esters and amino alcohols, which proved to be excellent building blocks for the syntheses of monoterpene-fused saturated 1,3-heterocycles and were also applied as chiral auxiliaries in enantioselective reactions of diethylzinc with aromatic aldehydes.[21–24] In the present work, our aim was to build up an aminodiol library, starting from readily available α-pinene, and to apply the resulting aminodiols as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes.

2. Results and discussion

2.1. Synthesis of aminodiols 5–13

The enantiomeric epoxy alcohol **4** was synthetized stereoselectively by a combination of literature methods.[25–27] The synthetic route for epoxy alcohol **4** is shown in Scheme 1.

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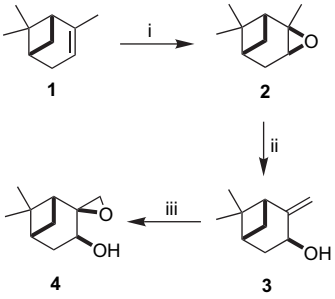
Starting from commercially available (−)-α-pinene **1**, epoxidation with MCPBA furnished epoxide **2** in a stereospecific reaction.[25] In the presence of 1 mol % of aluminium isopropoxide at 100–120 °C, α-pinene oxide rearranges to pinocarveol **3**.[27] Epoxidation of allylic alcohol **3** with MCPBA resulted in epoxy alcohol **4** in a stereospecific reaction.[26]

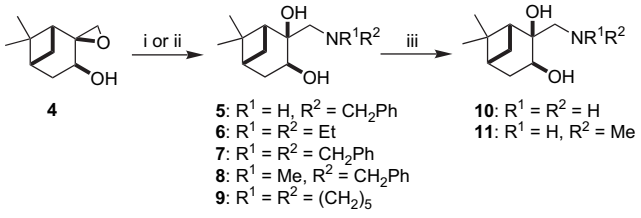


Scheme 1. Reaction conditions: (i) MCPBA, DCM, rt, 6 h, 82%; (ii) $Al(O^iPr)_3$, toluene, reflux, 2 h, 70%; (iii) MCPBA, DCM, Na_2HPO_4 buffer, rt, 12 h, 60%.

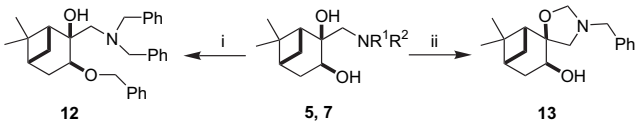
Aminolysis of epoxy alcohol **4** with secondary amines towards tertiary aminodiols **6–9** was performed in two different ways (Scheme 2). When mixtures of **4** and secondary amines were heated, long reaction times (7 days) and low yields were observed, probably because of the steric hindrance. Shorter reaction times (1–3 days) and better yields were achieved when lithium perchlorate was applied as catalyst for the ring-opening process.[16]

Secondary and primary aminodiols were obtained in two different ways: *N*-benzylaminodiol **5** was obtained by the reaction of **4** (Scheme 1) with benzylamine under similar conditions as applied for tertiary aminodiols, while the *N*-methyl derivative and primary aminodiol were prepared by debenzylation of the corresponding *N*,*N*-dibenzyl- and *N*-benzyl-*N*-methylaminodiols **7** and **8** under standard conditions by hydrogenation in the presence of palladium-on-carbon catalyst (Scheme 2).

Starting from the *N*,*N*-dibenzyl derivative **7**, *O*-benzyl derivative **12** was prepared. The reaction was accomplished by regioselective alkylation of **7** with benzyl bromide in the presence of sodium hydride. The quaternary hydroxy group was incorporated into a spiro-fused oxazoline **13** with formaldehyde by regioselective ring closure of *N*-benzyl derivative **5** (Scheme 3).



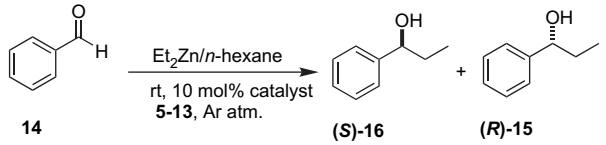
Scheme 2. Preparation of primary, secondary and tertiary aminodiols: (i) 4 equiv HNR^1R^2, MeOH, reflux, 7 days, 19–40%; (ii) 4 equiv HNR^1R^2, 1 equiv $LiClO_4$, MeOH, reflux, 1–3 days, 45–74%; (iii) 10% Pd/C, MeOH, H_2, 1 atm, 95%.



Scheme 3. Reaction conditions (i) NaH, $PhCH_2Br$, dry THF, rt, 24 h, 50% from **7**; (ii) CH_2O/H_2O, 1 h, rt, 80% from **5**.

2.2. Applications of aminodiols 5–13

The aminodiol derivatives **5–13** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde, resulting in chiral 1-phenyl-1-propanol (Scheme 4).



Scheme 4. Addition of diethylzinc to benzaldehyde.

Our results are presented in Table 1. The enantiomeric purities of the 1-phenyl-1-propanols **15** and **16** obtained were determined by GC on a CHIRASIL-DEX CB column, according to literature methods.[24,28,29] The observed enantioselectivities were low to good and in all cases predominantly the (*S*) enantiomer was formed. The best result was attained with *N*-benzyl-*N*-methyl-substituted aminodiol **8**. In the case of piperidine derivative **9**, no selectivity was achieved. It was also found that O-alkylation of any of the alcohol functional groups caused a decrease in enantioselectivity. As compared with the previous results on 1,3-amino alcohols,[24] it seems that tridentate monoterpene-based aminodiols are more successful catalysts than bidentate monoterpene-based 1,3-amino alcohols[24] in the reactions of diethylzinc with aromatic aldehydes.

For the best catalyst **8**, the relationship between the amount of the catalyst and the enantioselectivity observed was also examined. When the quantity of **8** was decreased from 10 to 5 mol %, the enantioselectivity remained at ee=84%. A lower amount of catalyst led to decreases both in the enantioselectivity and in the yield of the reaction (2.5 mol % **8**: ee=76%, 75% yield; 1 mol % **8**: ee=70%, 62% yield).

Table 1. Influence of catalyst loading on the yields and enantioselectivity according to Schemes 2 and 3

Entry	Ligand (10 mol %)	R^1	R^2	Yield[a] (%)	ee[b] (%)	Major enantiomer
1	**10**	H	H	88	54	*S*
2	**11**	H	Me	85	64	*S*
3	**5**	H	CH_2Ph	92	56	*S*
4	**6**	Et	Et	85	68	*S*
5	**7**	CH_2Ph	CH_2Ph	89	72	*S*
6	**8**	Me	CH_2Ph	87	84	*S*
7	**9**	$(CH_2)_5$		87	0	—
8	**12**[c]			60	32	*S*
9	**13**[c]			87	60	*S*

[a] Yields are given after silica gel column chromatography.
[b] Determined on the crude product by chiral GC (CHIRASIL-DEX CB column).
[c] See Scheme 3.

In order to interpret the *N*-substituent-induced difference in enantioselectivity, molecular modelling was performed for **8**. Although the arsenal used for such theoretical studies extends from the molecular mechanics force-field fine-tuned for transition states[30] to the ab initio methods at the DFT level,[31] it can be considered clear-cut that the modelling of the Noyori μ-oxo transition state following the QM/MM ONIOM approach[14,32,33] gives acceptably accurate results for design purposes at a reasonable computational cost. We therefore utilized the QM/MM ONIOM modelling protocol in this work. The inner cores of the transition structures were optimized ab initio (HF/LanL2DZ), while Rappe's universal force field (UFF) was employed for the ligands and the phenyl groups (Fig. 1). Ethyl groups were replaced by methyl groups to eliminate conformational freedom because this modification was not expected to cause significant errors in the trends of relative energies. The μ-oxo transition state possesses three stereogenic centres (Fig. 1); one of them is locked by the functional groups of aminodiol **8**, leading to four diastereomers, which were optimized by using the transition state-searching algorithm implemented in Gaussian03.

The diastereomers are designated by their absolute chirality on Zn, and on the carbon at the reaction centre. The geometries were preoptimized by using the PM3 semi-empirical method, and the final geometries were obtained at the ONIOM (HF/LanL2DZ:UFF). The final structures showed only a single imaginary frequency corresponding to the alkyl transfer. The relative stabilities of the transition state diastereomers calculated from the single-point energies at the full HF/LanL2DZ level are given in Table 2. It is clear from these results that the lowest-energy transition state diastereomers are in good accordance with the experimental enantioselectivity. The calculations suggest that the transalkylation most probably proceeds via diastereomer Zn-*S*, C-*S*, for **8** (Fig. 2).

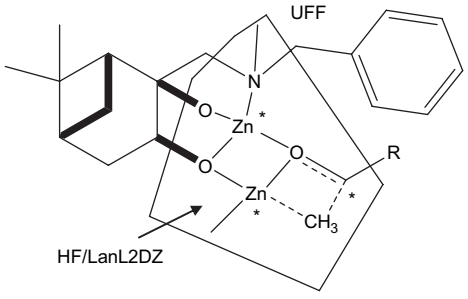


Figure 1. Favourable transition state proposed for Et_2Zn addition.

Table 2. Ab initio HF/LanL2DZ single-point energies calculated for μ-oxo complex of **8**

Zn	C	*E* (RHF)/au	($E-E_{min}$)/(kcal/mol)
R	*R*	−1449.052971	1.13
R	*S*	−1449.038909	9.95
S	*S*	−1449.054772	0.00
S	*R*	−1449.044227	6.62

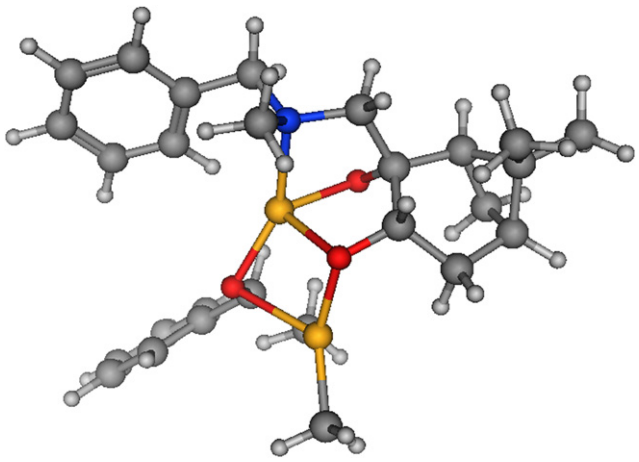


Figure 2. Lowest-energy structure (Zn-*S*, C-*S*) obtained for **8**.

3. Conclusion

The monoterpene-based aminodiols prepared may serve as chiral building blocks in the asymmetric syntheses of potential pharmacons, and they can also be used as chiral auxiliaries and catalysts in enantioselective syntheses. Substituent-dependent enantioselectivity was observed in the sequence NH_2<NHR<NRR, with the limitation that too large substituents can probably inhibit the formation of the transition complex. The theoretical calculations provided an explanation for the enantioselectivity and may serve as the starting point for the design of further enantioselective catalysts.

4. Experimental

4.1. General experimental procedures

^1H and ^{13}C NMR spectra were recorded on a Bruker AV 600 spectrometer (600 MHz, δ=0 (TMS)), in an appropriate solvent. Chemical shifts are expressed in parts per million (δ) relative to TMS as internal reference. *J* values are given in hertz. Microanalyzes were performed on a Perkin–Elmer 2400 elemental analyzer. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected. Chromatographic separations were carried out on Merck Kieselgel 60 (230–400 mesh, ASTM). Reactions were monitored with Merck Kieselgel 60 F_{254}-precoated TLC plates (0.25 mm thickness). All the chemicals and solvents were used as supplied.

GC measurements were made on a Chrompack CP-9002 system, consisting of a Flame Ionization detector 901A and a Maestro II Chromatography data system (Chrompack International B.V., Middelburg, The Netherlands). The column used for the direct separation of 1-phenyl-1-propanol and for the enantiomer excess determination in the case of epoxy alcohol was a CHIRASIL-DEX CB column (2500×0.25 mm I.D.) operated at 80 °C (**4**) or 120 °C (**15** and **16**), and 140 kPa.

Compounds **2**–**4** were prepared from (1*S*,5*S*)-(−)-α-pinene (Aldrich Co.) according to literature methods (ee for compound **4** was found by GC measurement to be >95%).[25–27]

4.2. General procedure for the synthesis of tertiary aminodiols 5–9

Method A: a solution of the appropriate amine (4.8 mmol) in MeOH (10 mL) was added to a solution of epoxy alcohol **4** (0.20 g, 1.2 mmol) in MeOH (15 mL) and the mixture was refluxed for 7 days (the reaction was monitored by means of TLC). Removal of the solvent provided yellow, oily products. The crude products were purified by flash chromatography on silica gel (toluene/EtOH=4:1), resulting in compounds **5**–**9**.

Method B: a solution of the appropriate amine (48 mmol) in MeCN (15 mL) and $LiClO_4$ (1.28 g, 12 mmol) was added to a solution of epoxy alcohol **4** (2.00 g, 12 mmol) in MeCN (150 mL) and the mixture was refluxed for 1–3 days (the reaction was monitored by means of TLC). When the reaction was completed, the mixture was evaporated to dryness, and the residue was dissolved in water (50 mL) and extracted with $CHCl_3$ (3×50 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (toluene/EtOH=4:1), resulting in compounds **5**–**9**.

4.2.1. (1*R*,2*S*,3*S*,5*R*)-2-Benzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (5). Compound **5** was prepared according to the general procedure given in Section 4.2.

Compound **5** (Method A: 40% yield; Method B: 63% yield (reaction time: 72 h)); mp 53–55 °C; $[\alpha]_D^{20}$ −11.0 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.84 (3H, *s*), 1.23 (3H, *s*), 1.45 (1H, *d*, *J*=10.3 Hz), 1.65 (1H, *ddd*, *J*=2.2, 5.9, 13.9 Hz), 1.87–1.92 (1H, *m*), 1.96 (1H, *t*, *J*=5.9 Hz), 2.16–2.22 (1H, *m*), 2.38–2.45 (1H, *m*), 2.67 (2H, *dd*, *J*=1.0, 12.3 Hz), 3.25 (1H, *br s*), 3.82 (2H, *dd*, *J*=13.2, 19.9 Hz), 4.10 (2H, *dd*, *J*=5.9, 9.4 Hz), 7.23–7.35 (5H, *m*); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.2, 28.0, 28.1, 37.1, 38.7, 40.6, 51.3, 54.2, 59.0, 67.7, 74.6, 127.2, 128.2, 128.5, 139.8. Anal. Calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.09%. Found: C, 73.82; H, 9.09; N, 5.41%.

4.2.2. (1*R*,2*S*,3*S*,5*R*)-2-Diethylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (6). Compound **6** was prepared according to the general procedure given in Section 4.2.

Compound **6** (Method A: 25% yield; Method B: 74% yield (reaction time: 60 h)); an oil; $[\alpha]_D^{20}$ −10.0 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.92 (3H, *s*), 1.03 (6H, *t*, *J*=7.1 Hz), 1.25 (3H, *s*), 1.47 (1H, *d*, *J*=10.2 Hz), 1.73 (1H, *ddd*, *J*=2.7, 4.8, 13.9 Hz), 1.88–1.93 (1H, *m*), 1.96 (1H, *t*, *J*=5.9 Hz), 2.14–2.22 (1H, *m*), 2.36–2.45 (1H, *m*), 2.62 (1H, *d*, *J*=10.5 Hz), 2.64 (4H, *dd*, *J*=7.1, 17.6 Hz), 3.92 (1H, *dd*, *J*=4.9, 9.1 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 12.0, 24.2, 27.7, 27.8, 37.9, 38.7, 40.4, 48.5, 53.3, 64.4, 68.9, 72.8. Anal. Calcd for $C_{14}H_{27}NO_2$ (241.37): C, 69.66; H, 11.27; N, 5.80%. Found: C, 69.43; H, 11.33; N, 6.27%.

4.2.3. (1*R*,2*S*,3*S*,5*R*)-2-Dibenzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (7). Compound **7** was prepared according to the general procedure given in Section 4.2.

Compound **7** (Method A: 32% yield; Method B: 55% yield (reaction time: 48 h)); mp 62–63 °C; $[\alpha]_D^{20}$ −10.5 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.56 (3H, *s*), 1.14 (3H, *s*), 1.39 (1H, *d*, *J*=10.3 Hz), 1.54–1.61 (1H, *m*), 1.78–1.86 (2H, *m*), 2.07–2.15 (1H, *m*), 2.19–2.28 (1H, *m*), 2.58 (1H, *d*, *J*=13.6 Hz), 2.68 (1H, *d*, *J*=13.6 Hz), 3.41 (1H, *br s*), 3.56 (2H, *d*, *J*=13.2 Hz), 3.75 (1H, *dd*, *J*=6.0, 9.3 Hz), 3.87 (2H, *d*, *J*=13.2 Hz), 4.41 (1H, *br s*), 7.23–7.37 (10H, *m*); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.8, 27.9, 28.0, 36.7, 38.5, 40.4, 52.3, 60.6, 63.3, 67.8, 74.6, 127.4, 128.5, 129.2, 138.8. Anal. Calcd for $C_{24}H_{31}NO_2$ (365.51): C, 78.86; H, 8.55; N, 3.83%. Found: C, 79.02; H, 8.29; N, 3.95%.

4.2.4. (1*R*,2*S*,3*S*,5*R*)-2-[(Benzylmethylamino)methyl]-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (8). Compound **8** was prepared according to the general procedure given in Section 4.2.

Compound **8** (Method A: 30% yield; Method B: 50% yield (reaction time: 24 h)); an oil; $[\alpha]_D^{20}$ −18.0 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.79 (3H, *s*), 1.21 (3H, *s*), 1.46 (1H, *d*, *J*=10.3 Hz), 1.64–1.73 (1H, *m*), 1.84–1.91 (1H, *m*), 1.93 (1H, *t*, *J*=5.7 Hz), 2.12–2.21 (1H, *m*), 2.31–2.35 (1H, *m*), 2.38 (3H, *s*), 2.53 (1H, *d*, *J*=13.1 Hz), 2.64 (1H, *d*, *J*=13.1 Hz), 3.58 (1H, *d*, *J*=13.1 Hz), 3.67 (1H, *d*, *J*=13.1 Hz), 3.92 (1H, *dd*, *J*=5.3, 9.1 Hz), 7.23–7.37 (5H, *m*); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.1, 27.8, 37.3, 38.7, 40.4, 44.8, 52.8, 64.3, 67.4, 68.2, 74.0, 127.4, 128.4, 129.1, 138.4. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84%. Found: C, 74.38; H, 9.46; N, 5.19%.

4.2.5. (1*R*,2*S*,3*S*,5*R*)-6,6-Dimethyl-2-piperidin-1-ylmethylbicyclo[3.1.1]heptane-2,3-diol hydrochloride (9). Compound **9** was prepared according to the general procedure given in Section 4.2, with the modification that it was purified as the hydrochloride. The base liberated for catalytic usage was a viscous oil.

Compound **9** (Method A: 19% yield; Method B: 74% yield (reaction time: 24 h)); mp 233–234 °C; $[\alpha]_D^{20}$ −3.0 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.90 (3H, *s*), 1.27 (3H, *s*), 1.39 (1H, *d*, *J*=10.9 Hz), 1.43–1.51 (1H, *m*), 1.76–1.86 (4H, *m*), 1.90–1.94 (1H, *m*), 2.02 (1H, *t*, *J*=5.6 Hz), 2.16–2.27 (2H, *m*), 2.40–2.54 (2H, *m*), 2.81–2.90 (2H, *m*), 2.92 (1H, *dd*, *J*=7.7, 13.5 Hz), 3.12 (1H, *d*, *J*=13.6 Hz), 3.58 (1H, *d*, *J*=12.0 Hz), 4.15 (1H, *d*, *J*=12.0 Hz), 4.29–4.34 (1H, *m*), 5.11 (1H, *s*), 6.27 (1H, *d*, *J*=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 21.8, 22.0, 22.2, 24.3, 26.4, 27.3, 36.9, 38.1, 39.8, 53.4, 27.2, 27.7, 64.9, 73.8. Anal. Calcd for $C_{15}H_{28}ClNO_2$ (289.84): C, 62.16; H, 9.74; N, 4.83%. Found: C, 62.46; H, 9.83; N, 5.00%.

4.3. General procedure for the synthesis of aminodiols 10 and 11

To a suspension of palladium-on-carbon (10%, 0.10 g) in MeOH (10 mL) was added aminodiol **7** or **8** (1.3 mmol) in

MeOH (15 mL), and the resulting mixture was stirred under a H_2 atmosphere at room temperature. When the reaction was complete, as indicated by TLC, the solution was filtered through a Celite pad and the solvent was removed, affording a colourless oily product **10** or **11**, which crystallized upon standing at ca. 4 °C. The crystalline product was recrystallized from *n*-hexane.

4.3.1. (1*R*,2*S*,3*S*,5*R*)-2-Aminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (10). Compound **10** was prepared according to the general procedure given in Section 4.3.

Compound **10** (0.35 g, 70% yield); mp 62–64 °C; $[\alpha]_D^{20}$ −7.0 (*c* 0.25, EtOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.91 (3H, *s*), 1.24 (3H, *s*), 1.44 (1H, *d*, *J*=10.3 Hz), 1.66 (1H, *ddd*, *J*=2.5, 5.5, 13.9 Hz), 1.87–1.93 (1H, *m*), 1.98 (1H, *t*, *J*=5.8 Hz), 2.20 (1H, *dtd*, *J*=2.2, 6.0, 14.6 Hz), 2.39–2.49 (1H, *m*), 2.67 (1H, *d*, *J*=12.5 Hz), 2.72 (1H, *d*, *J*=12.5 Hz), 3.29 (2H, *br s*), 4.06 (2H, *dd*, *J*=5.6, 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.3, 27.9, 28.0, 37.6, 38.7, 40.6, 50.4, 51.3, 66.8, 74.8. Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56%. Found: C, 65.21; H, 9.98; N, 7.36%.

4.3.2. (1*R*,2*S*,3*S*,5*R*)-6,6-Dimethyl-2-methylaminomethylbicyclo[3.1.1]heptane-2,3-diol (11). Compound **11** was prepared according to the general procedure given in Section 4.3.

Compound **11** (0.60 g, 86% yield); mp 78–79 °C; $[\alpha]_D^{20}$ −4.0 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.95 (3H, *s*), 1.26 (3H, *s*), 1.45 (1H, *d*, *J*=10.4 Hz), 1.65–1.75 (1H, *m*), 1.86–2.05 (3H, *m*), 2.14–2.26 (1H, *m*), 2.66 (3H, *s*), 2.72 (1H, *d*, *J*=12.0 Hz), 3.04 (1H, *d*, *J*=12.0 Hz), 3.46 (1H, *s*), 4.36 (1H, *dd*, *J*=4.9, 9.0 Hz), 5.60 (1H, *s*); ^{13}C NMR ($CDCl_3$) δ (ppm): 24.3, 27.5, 27.6, 34.8, 37.5, 38.3, 40.4, 51.9, 60.6, 64.9, 73.5. Anal. Calcd for $C_{11}H_{21}NO_2$ (199.29): C, 66.29; H, 10.62; N, 7.03%. Found: C, 66.60; H, 10.49; N, 7.35%.

4.4. (1*R*,2*S*,3*S*,5*R*)-3-Benzyl-2-dibenzylaminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diol (12)

To a stirred suspension of NaH (2.46 mmol) in 16 mL of dry THF was added 3 mL of a THF solution of aminodiol **7** (0.30 g, 0.82 mmol). After 30 min, a solution of benzyl bromide (0.15 g, 0.90 mmol) in 3 mL of THF was added via a syringe and the mixture was stirred at room temperature for 24 h. The reaction was quenched by the addition of 1 mL of water. The THF was removed under reduced pressure and the residue was extracted with $CHCl_3$ (3× 30 mL). The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc=2:1, R_f=0.40), resulting in compound **12**.

Compound **12** (0.20 g, 54% yield); an oil; $[\alpha]_D^{20}$ −4.5 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.28 (3H, *s*), 1.14 (3H, *s*), 1.49–1.53 (1H, *m*), 1.76–1.81 (1H, *m*), 1.82–1.86 (1H, *m*), 2.16–2.20 (1H, *m*), 2.23–2.29 (1H, *m*), 2.45 (1H, *d*, *J*= 13.8 Hz), 2.63 (1H, *d*, *J*=13.8 Hz), 3.66 (2H, *d*, *J*=13.5 Hz), 3.69 (1H, *dd*, *J*=4.5, 9.0 Hz), 3.88 (2H, *d*, *J*=13.5 Hz), 4.67 (1H, *d*, *J*=11.3 Hz), 4.75 (1H, *d*, *J*=11.3 Hz), 7.23–7.43 (15H, *m*); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.5, 27.4, 27.5, 35.5, 38.0, 40.4, 50.7, 60.8, 62.3, 71.2, 73.4, 12.8, 127.7, 127.8, 128.1, 128.4, 129.6, 140.0. Anal. Calcd for $C_{31}H_{37}NO_2$ (455.63): C, 81.72; H, 8.19; N, 3.07%. Found: C, 81.55; H, 8.37; N, 3.41%.

4.5. (1*R*,2*S*,3*S*,5*R*)-3′-Benzyl-6,6-dimethylspiro-[bicyclo[3.1.1]heptane-2,5′-oxazolidin]-3-ol (13)

Amino alcohol **5** (0.25 g, 0.9 mmol) was stirred with 10 mL of 35% aqueous formaldehyde at room temperature for 1 h. The mixture was made alkaline with 10% aqueous KOH and extracted with Et_2O (3×30 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to give an almost colourless oil, which was purified by flash chromatography on silica gel (*n*-hexane/EtOAc=3:2, R_f=0.45), resulting in compound **13**.

Compound **13** (0.24 g, 93% yield); an oil; $[\alpha]_D^{20}$ +6.0 (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.80 (3H, *s*), 1.26 (3H, *s*), 1.54 (1H, *d*, *J*=10.3 Hz), 1.86 (1H, *td*, *J*=3.2, 14.2 Hz), 1.90–1.96 (1H, *m*), 2.12 (1H, *t*, *J*=5.6 Hz), 2.18–2.25 (1H, *m*), 2.30–2.39 (1H, *m*), 2.82 (1H, *d*, *J*=11.0 Hz), 2.96 (1H, *d*, *J*=11.0 Hz), 3.66 (1H, *d*, *J*=4.8 Hz), 3.76 (1H, *d*, *J*=13.1 Hz), 3.82 (2H, *d*, *J*=13.1 Hz), 3.98–4.04 (1H, *m*), 4.32 (1H, *d*, *J*=4.4 Hz), 4.38 (1H, *d*, *J*=4.4 Hz), 7.23–7.35 (5H, *m*); ^{13}C NMR ($CDCl_3$) δ (ppm): 23.2, 26.7, 27.0, 37.1, 38.9, 39.8, 51.6, 57.5, 65.3, 69.4, 85.2, 85.5, 127.3, 128.4, 128.5, 138.5. Anal. Calcd for $C_{18}H_{25}NO_2$ (287.40): C, 75.22; H, 8.77; N, 4.87%. Found: C, 75.23; H, 8.39; N, 5.30%.

4.6. Typical experimental procedure for the reaction of aldehydes with diethylzinc in the presence of chiral catalyst 5–14

To a solution of **5** (41 mg, 0.15 mmol) in dry *n*-hexane (2 mL), 1 M Et_2Zn in *n*-hexane solution (4.5 mL, 4.5 mmol) was added under an Ar atmosphere at room temperature. The reaction mixture was stirred for 25 min at room temperature, and benzaldehyde (0.16 g, 1.5 mmol) in dry toluene was then added to it for 5 min. The reaction mixture was next stirred at room temperature for a further 20 h. The reaction was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (2×30 mL). The combined organic phase was washed with water (20 mL), dried (Na_2SO_4) and evaporated under vacuum. The crude alcohol obtained was purified by flash column chromatography (*n*-hexane/EtOAc=4:1), resulting in pure 1-phenyl-1-propanol. The enantiomeric excess and absolute configuration were determined by chiral GC, using a chiral stationary phase (Chirasil-Dex CB column), and the direction of the optical rotation of the products was checked. The spectroscopic data on the alcohols prepared were in all cases similar to those in the literature.[24,28,29]

4.7. Computational details

All transition structures were fully optimized without constraints, using Morokuma's ONIOM method implemented in Gaussian03, combining ab initio levels (HF/LanL2DZ) with Rappe's universal force field (UFF) on an FSC PRIMERGY system: 19×2×2 (dual-core dual-processor

RX220 boards) AMD Opteron computing nodes, 19×4 GB standard system memory PRIMERGY TX200 S2 head-node with Intel Xeon processor. Hydrogen atoms were used as link atoms between the two layers (HF/LanL2DZ: UFF). All transition structures were analyzed by frequency computations and showed one imaginary frequency of the methyl transfer mode.

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