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Stereoselective synthesis of carane-based aminodiols as chiral ligands for the catalytic addition of diethylzinc to aldehydes

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ABSTRACT

Key intermediate epoxy alcohol **4** was prepared regio- and stereoselectively from (+)-3-carene **1** via carene oxide **2** and (−)-*trans*-allyl alcohol **3**. The lithium perchlorate-catalysed ring opening of **4** with secondary and primary achiral and chiral amines resulted in primary, secondary and tertiary aminodiols. Aminodiols **5**–**14** were applied as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde, resulting in (*R*)- and (*S*)-1-phenyl-1-propanol with moderate enantioselectivity. *N*-Benzyl, *N*-methyl, and (*S*)- and (*R*)-*N*-methylbenzyl derivatives **7** and **10**–**13** were transformed into 1,3-oxazines **17**–**21** via highly regioselective ring closures. When **17**–**21** were applied as chiral catalysts in the addition of diethylzinc to aromatic and aliphatic aldehydes, high chiral induction in the tricyclic catalysts was observed. The effects of the substituents on the nitrogen of the aminodiols and 1,3-oxazines were studied in detail; the best enantioselectivity was observed in the case of *N*-methylbenzyl-substituted oxazine **19**.

1. Introduction

Chiral synthons that can be applied successfully in asymmetric homogeneous and heterogeneous catalysis are of increasing importance in organic chemistry.[1–3] Some of these building blocks and chiral catalysts, such as monoterpene-based 1,2- and 1,3-amino alcohols derived from readily available chiral terpenes, and are widely used in enantioselective transformations.[4–6] Various amino alcohols obtained from monoterpenes, such as (+)-pulegone,[4] α- and β-pinene,[7,8] and fenchone-camphor,[9] have been used as catalytic ligands for various chemical transformations. Chiral aminodiols, which combine the chemical properties of 1,2- and 1,3-amino alcohols, have also proven to be excellent catalysts.[10–18] Aminodiols are similarly useful starting materials for the synthesis of 1,3-oxazines or oxazolidines, depending upon which hydroxy group undergoes ring closure with the amino group. Since the resulting heterobicycles contain a free hydroxy group, this extra coordinative functional group may possibly lead to higher rigidity within the transition state, and therefore to higher enantioselective induction in asymmetric addition reactions, for example, catalytic asymmetric carbon–carbon bond formation, as in the dialkylzinc addition to aldehydes, asymmetric allylic alkylation, and so on.[14,19–21] Furthermore, aminodiols may serve as useful starting materials for the synthesis of biologically active natural compounds,[22–25] for example, cytoxazone, a selective modulator of the secretion of T_H2 cytokine, a microbial metabolite isolated from *Streptomyces* species.[23,24]

We recently reported the transformations of enantiomerically pure α-pinene, δ-pinene, apopinene and myrtenal to β-amino acid derivatives, for example, amino esters and amino alcohols, which proved to be excellent building blocks for the synthesis of monoterpene-fused saturated 1,3-heterocycles with noteworthy MDR blocking and antitumour activity.[26] Pinane-based 1,3-amino alcohols were also applied as chiral auxiliaries in enantioselective reactions.[26d] As part of our systematic studies on 1,3-difunctional chiral monoterpenic building blocks,[26] we also recently reported the synthesis of (+)- and (−)-2-aminomethyl-6,6-dimethylbicyclo[3.1.1]heptane-2,3-diols from α-pinene enantiomers.[27] The resulting aminodiols were successfully applied as catalysts and as building blocks in the regioselective ring closures of aminodiols, to give chiral spiro 1,3-heterocycles.[27,28]

Herein, our aim was to build up an aminodiol library, starting from readily available (+)-3-carene, and to use the resulting aminodiols as chiral catalysts in the enantioselective addition of diethylzinc to aromatic and aliphatic aldehydes.

2. Results and discussion

2.1. Synthesis of carane-based aminodiols

The key-intermediate epoxy alcohol **4** was synthesised as shown in Scheme 1, by a combination of literature methods.[27,29,30] Starting from commercially available (+)-3-carene **1**, epoxidation

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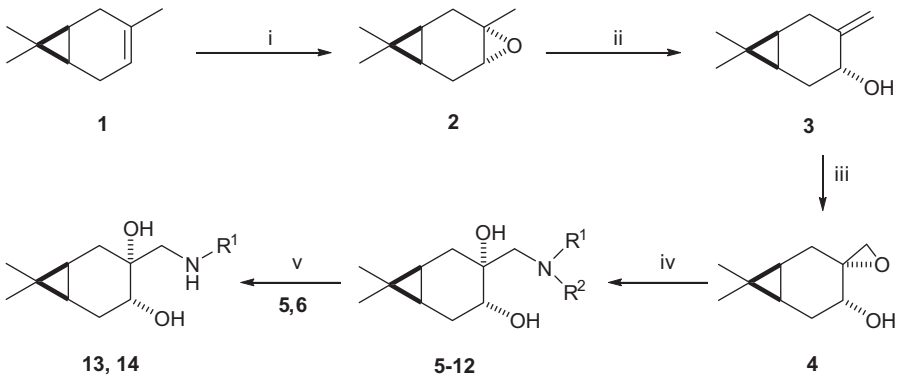


5: R^1 = Me, R^2 = CH_2Ph; **6**: R^1 = R^2 = CH_2Ph; **7**: R^1 = H, R^2 = CH_2Ph;
8: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*R*); **9**: R^1 = CH_2Ph, R^2 = CH(Me)Ph (*S*);
10: R^1 = H, R^2 = CH(Me)Ph (*R*); **11**: R^1 = H, R^2 = CH(Me)Ph (*S*);
12: R^1 = H, R^2 = *i*-Pr; **13**: R^1 = Me; **14:** R^1 = H

Scheme 1. Reagents and conditions: (i) MCPBA, $CHCl_3$, rt, 1 h, yield 60%; (ii) *n*-BuLi, 2,2,6,6-tetramethylpiperidine, Et_2AlCl, dry toluene, Ar atm, 0 °C, 2 h, yield 58%; (iii) MCPBA, DCM, Na_2HPO_4 buffer, rt, 1 h, yield 65%; (iv) 4 equiv HNR^1R^2, 1 equiv $LiClO_4$, MeCN, reflux, 6–40 h, yield 18–70%; (v) 10% Pd/C, MeOH, H_2, 1 atm, **13**: yield 37%, **14**: yield 63%.

with MCPBA furnished epoxide **2** in a stereospecific reaction.[29] 3-Carene oxide **2** underwent rearrangement to allyl alcohol **3** in dry toluene in the presence of tetramethylpiperidine diethylaluminate and *n*-butyllithium.[30] Epoxidation of allylic alcohol **3** with MCPBA resulted in epoxy alcohol **4** in a stereospecific reaction.[27]

Since our previous results clearly demonstrated that the N-substituents of 1,3-aminoalcohols and aminodiols when applied as catalysts, definitely influenced the enantioselectivity of their catalysed reactions,[26d,27] an eight-membered aminodiol library **5–12** was prepared by aminolysis of **4** with secondary and primary amines. The oxirane ring was opened with lithium perchlorate as a catalyst.[12,27,31] To study the effects of the bulky substituents, (*R*)- and (*S*)-1-phenylethylamine and (*R*)- and (*S*)-*N*-benzyl-1-phenylethylamine were utilised; the latter resulted in the expected tertiary aminodiol **11** only in low yield, probably because of the strong steric hindrance of the substituents (Scheme 1).

Secondary and primary aminodiols were obtained in two different ways: *N*-benzylaminodiol **5** was prepared by the reaction of **4** with benzylamine under similar conditions as applied for tertiary aminodiols, while the *N*-methyl derivative **13** and primary aminodiol **14** were synthesised by debenzylation of the corresponding *N,N*-dibenzyl- and *N*-benzyl-*N*-methylaminodiols **5** and **6** under standard conditions, by hydrogenation in the presence of a palladium-on-carbon catalyst (Scheme 1).

2.2. Application of aminodiols 5–14 as chiral ligands for the catalytic addition of diethylzinc to benzaldehyde

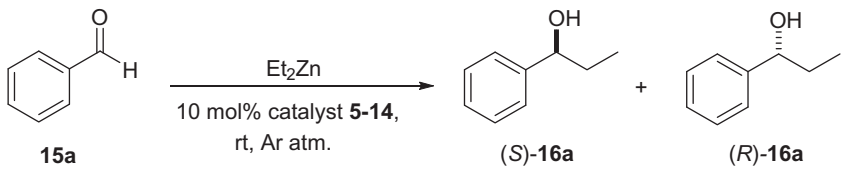
The aminodiol derivatives **5–14** were used as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde, resulting in chiral 1-phenyl-1-propanol (Scheme 2).

Our results are presented in Table 1. The enantiomeric purities of the 1-phenyl-1-propanols (*S*)-**16a** and (*R*)-**16a** obtained were determined by GC on a CHIRASIL-DEX CB column, according to literature methods.[26d] The observed enantioselectivities were low to moderate and, in cases of (*S*)-selectivity (using compounds **6**, **7**, **9**, **10**, **13** and **14**), were significantly lower than those involving (*R*)-selectivity (compounds **5**, **8**, **11** and **12**). The best, but still moderate, result was obtained with *N*-(*S*)-1-phenylethyl-substituted aminodiol **11**. When compared with the previous results using aminodiols,[27] it seems that tridentate carane-based aminodiols are less enantioselective catalysts than the tridentate pinane-based analogues, probably because of the weaker steric hindrance of the carane moiety as compared with the pinane ring system.

2.3. Regioselective synthesis of carane-fused 1,3-oxazines

Andrés et al. recently reported that tricyclic aminodiol derivatives with rigid structures had enhanced catalytic potential, discriminating better between the two enantiotopic faces of the aldehyde within the transition state complex.[21] To prepare conformationally more constrained structures, we attempted to incorporate one of the hydroxy groups of our aminodiols into a spiro-oxazolidine or a condensed 1,3-oxazine ring. When aminodiols **7** and **10**–**13** were reacted with formaldehyde under mild conditions, 1,3-oxazines **17**–**21** were obtained in highly regioselective ring closures, with opposite regioselectivities relative to those of the pinane-based analogues reported recently (Scheme 3).[27]

The excellent regioselectivity of the reaction could be explained by the extended bicyclo[4.1.0]heptane structure, which makes the equatorial 3-aminomethyl and 4-hydroxy groups preferable for the ring closure.

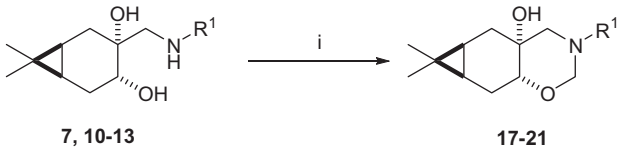


Scheme 2. Addition of diethylzinc to benzaldehyde.

Table 1
Addition of diethylzinc to benzaldehyde, catalysed by various types of aminodiols

Entry	Catalyst (10 mol %)	Yield[a] (%)	ee[b] (%)	Configuration of major product[c]
1	**5**	87	13	(*R*)
2	**6**	84	10	(*S*)
3	**7**	90	3	(*S*)
4	**8**	75	31	(*R*)
5	**9**	80	8	(*S*)
6	**10**	88	7	(*S*)
7	**11**	78	37	(*R*)
8	**12**	73	30	(*R*)
9	**13**	81	16	(*S*)
10	**14**	73	5	(*S*)

[a] Yields after silica column chromatography are given.
[b] Determined on the crude product by GC (Chirasil-DEX CB column).
[c] Determined by comparing the t_R of the GC analysis and the specific rotation with the literature data.



7, 10-13 **17-21**

17: $R^1 = CH_2Ph$; **18**: $R^1 = Me$; **19**: $R^1 = CH(Me)Ph$ (*R*);
20: $R^1 = CH(Me)Ph$ (*S*); **21**: $R^1 = i$-Pr

Scheme 3. Reagents and conditions: (i) CH_2O/H_2O, rt,1 h, yield 63–96%.

2.4. Application of 1,3-oxazines 17–21 as chiral ligands for the catalytic addition of diethylzinc to aldehydes

When oxazines **17–21** were applied as catalysts in the addition of diethylzinc, increased enantioselectivity was observed (Table 2). The best result (ee = 96%) was obtained on the use of *N*-(*R*)-1-phenylethyl-substituted 1,3-oxazine **19**.

Table 2
Addition of diethylzinc to benzaldehyde catalysed by various 1,3-oxazines

Entry	Catalyst (10 mol %)	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	**17**	74	94	(*S*)
2	**18**	72	92	(*S*)
3	**19**	77	96	(*S*)
4	**20**	71	62	(*S*)
5	**21**	83	38	(*S*)

[a] Yields after silica column chromatography are given.
[b] Determined on the crude product by GC (Chirasil-DEX CB column).
[c] Determined by comparing the t_R of the GC analysis and the specific rotation with literature data.

We propose the transition state shown in Figure 1 to account for the stereoselectivity observed with chiral ligand **17**. In this transition state, the transfer of the ethyl group occurs on the *si*-face of the aldehyde, leading to the (*S*)-enantiomer of the alcohols.

With the best catalyst **19**, the diethylzinc addition reaction was extended to other aromatic and aliphatic aldehydes (Scheme 4). Our results are presented in Table 3. The enantiomeric purities of the 1-aryl and 1-alkyl-1-propanols obtained were determined by GC on a CHIRASIL-DEX CB column or by chiral HPLC analysis on a Chiralcel OD-H column, according to literature methods.[19,21,26d,32–36]

The results presented in Table 3 clearly show that hydroxy-substituted 1,3-oxazine **19** proved to be an efficient catalyst in this model reaction. High chemical conversions and enantioselectivities were observed in the addition of diethylzinc to aromatic aldehydes catalysed by 1,3-oxazines **17**–**21**, while lower, but still good yields and selectivities were obtained when aliphatic aldehydes were applied.

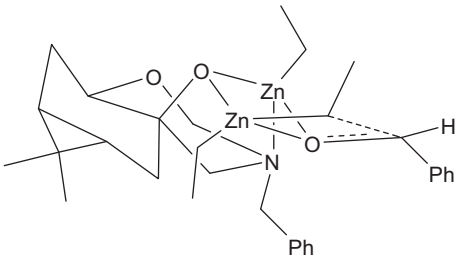
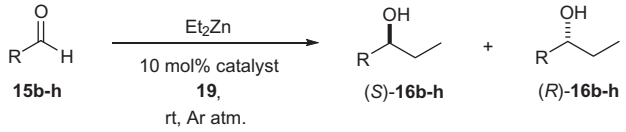


Figure 1. Proposed transition state for the asymmetric addition with **17**.



Scheme 4. Addition of diethylzinc to aldehydes.

Table 3
Addition of diethylzinc to aldehydes catalysed by ligand **19**

Entry	Product	R	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	**16b**	(4-MeO)C_6H_4	89	97	(*S*)
2	**16c**	(4-Me)C_6H_4	93	97	(*S*)
3	**16d**	(3-MeO)C_6H_4	91	96	(*S*)
4	**16e**	(3-Me)C_6H_4	90	93	(*S*)
5	**16f**	2-Naphthyl	86	96	(*S*)
6	**16g**	Cyclohexyl	80	92	(*S*)
7	**16h**	*n*-Butyl	87	77	(*S*)

[a] Yields after silica column chromatography are given.
[b] Determined on the crude product by HPLC (Chiracel OD-H).
[c] Determined by comparing the t_R of the HPLC analysis and the specific rotation with the literature data.

3. Conclusions

The new carane-based aminodiols prepared herein may serve as chiral building blocks in the asymmetric syntheses of potential drug candidates, and they can also be used as chiral auxiliaries and catalysts in enantioselective syntheses. Substituent-dependent enantioselectivity was observed in the sequence $NH_2 < NHR < NRR$. The ring closures of secondary aminodiols proceeded with high regioselectivity, resulting exclusively in monoterpene-condensed 1,3-oxazines. The 1,3-oxazines obtained proved to be excellent catalysts in the additions of diethylzinc to either aromatic or aliphatic aldehydes, probably as a consequence of their conformationally constrained structures.

4. Experimental

4.1. General experimental procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer (400 MHz and 100.6 MHz, δ = 0 (TMS)). Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given in Hertz. FT-IR spectra were recorded on a Perkin–Elmer Spectrum 100 instrument. Microanalyses were performed on a Perkin–Elmer 2400 elemental analyser. GC measurements were made on a Perkin–Elmer Autosystem XL GC, consisting of a Flame Ionisation Detector and a Turbochrom Workstation data system (Perkin–Elmer Corporation Norwalk, USA). The column used for the direct separation of enantiomers was a CHIRASIL-DEX CB column (2500 × 0.25 mm I.D.). Chiral HPLC analysis was performed on a Chiralcel OD-H column (250 × 4.6 mm). UV detection was monitored at 210 nm or at 254 nm.

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 of the chemicals and solvents were used as supplied. Compounds **2** and **3** were prepared from (1*S*,6*R*)-(+)-3-carene (Sigma–Alrich Co.) according to literature methods.[27,29,30]

4.2. (1*S*,2′*R*,4*R*,6*R*)-7,7-Dimethylspiro[bicyclo[4.1.0]heptane-3,2′-oxiran]-4-ol 4

To a solution of (−)-(1*R*,3*R*,6*S*)-4-methylene-7,7-dimethylbicyclo[4.1.0]-heptan-3-ol **3** (2.01 g, 13.2 mmol) in 50 mL CH_2Cl_2 and $Na_2HPO_4{\cdot}2H_2O$ (6.91 g, 44.3 mmol) in 130 mL water, *m*-chloroperbenzoic acid (75% purity, 23.7 mmol) was added at 0 °C and the mixture was stirred at room temperature. When the reaction was complete, as indicated by TLC (1 h), the mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The organic layer was washed with 5% KOH solution (3 × 50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by vacuum distillation (bp: 125 °C at 4 mbar), to afford **4**. Isolated compound: 1.44 g (65%); colourless crystals, mp: 23–25 °C, $[\alpha]_D^{20} = -48$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.76 (1H, dt, *J* = 3.7, 9.3 Hz), 0.93 (3H, s), 1.04 (3H, s), 1.04–1.05 (1H, m), 1.48 (1H, dd, *J* = 1.4, 15.2 Hz), 1.71 (1H, dt, *J* = 3.7, 15.3 Hz), 2.16–2.23 (2H, m), 2.33 (1H, dd, *J* = 8.4, 15.0 Hz), 2.60 (1H, d, *J* = 5.0 Hz), 2.75 (1H, dd, *J* = 0.8, 4.8 Hz), 3.29 (1H, *t*, *J* = 4.3 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.6, 16.7, 21.2, 24.3, 27.9, 28.7, 34.9, 54.6, 60.5, 69.7. IR (KBr, cm^{-1}) *v* = 3435, 2865, 1434, 1079, 856. Anal. Calcd for $C_{10}H_{16}O_2$ (168.23): C, 71.39; H, 9.59. Found: C, 71.28; H, 9.67.

4.3. General procedure for the epoxide ring opening with secondary and primary amines

To a solution of epoxy alcohol **4** (12.0 mmol, 2.00 g) in MeCN (150 mL) was added a solution of the appropriate amine (48.0 mmol) in MeCN (15 mL) and $LiClO_4$ (12 mmol, 1.30 g). The mixture was refluxed for 1–3 days. When the reaction was completed (indicated by TLC), 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 recrystallisation (**6**, **10**, **11** and **12**) or by column chromatography on silica gel with an appropriate solvent mixture (**5**, **7–9**), resulting in compounds **5–12.**

4.3.1. (1*S*,3*R*,4*R*,6*R*)-3-(Benzyl(methyl)amino)methyl)-7,7-dimethylbicyclo[4.1.0]heptane-3,4-diol 5

Prepared with *N*-benzyl-*N*-methylamine at reflux for 8 h. Compound **5** was purified by column chromatography on silica gel (toluene/EtOH = 9:1). Compound **5**: 2.26 g (65%); yellow crystals, mp 63–67 °C; $[\alpha]_D^{20} = +35$ (*c* 0.125, EtOH) ^{1}H NMR ($CDCl_3$) δ (ppm): 0.62 (1H, dt, *J* = 4.4, 9.5 Hz), 0.78–0.83 (1H, m), 0.82 (3H, s), 0.87 (1H, dd, *J* = 4.4, 15.1 Hz), 0.99 (3H, s), 1.73 (1H, dt, *J* = 8.9, 15.1 Hz), 1.95–2.07 (2H, m), 2.37 (3H, s), 2.60 (2H, s), 3.35–3.46 (2H, m), 3.87 (1H, br d, *J* = 12.7 Hz), 7.27–7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.9, 16.2, 20.7, 25.9, 28.8, 30.2, 44.8, 64.7, 67.4, 70.9, 73.5, 127.7, 128.8, 129.4, 138.3. IR (KBr, cm^{-1}) *v* = 3466, 2929, 1452, 1092, 738, 696. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84. Found: C, 74.59; H, 9.52; N, 4.94.

4.3.2. (1*S*,3*R*,4*R*,6*R*)-3-(Dibenzylamino)methyl)-7,7-dimethylbicyclo[4.1.0]heptane-3,4-diol 6

Prepared with dibenzylamine at reflux for 29 h. Compound **6** (2.98 g, 68%); colourless crystals, mp 149–151 °C (*n*-hexane); $[\alpha]_D^{20} = +31$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.45 (1H, dt, *J* = 4.1, 9.5 Hz), 0.60–0.66 (1H, m), 0.78 (3H, s), 0.93 (3H, s), 1.02 (1H, dd, *J* = 4.2, 15.3 Hz), 1.64–1.73 (2H, m), 1.77–1.85 (1H, m), 2.43 (1H, d, *J* = 14.2 Hz), 2.54 (1H, d, *J* = 14.2 Hz), 2.98–3.07 (1H, m), 3.61 (2H, d, *J* = 14.1 Hz), 3.67 (2H, d, *J* = 14.4 Hz), 3.80 (1H, s), 4.62 (1H, d, *J*= 5.3 Hz), 7.25–7.35 (10H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.1, 17.4, 22.3, 27.3, 29.7, 30.3, 59.8, 61,6, 70.9, 71.4, 72.3, 127.6, 129.0, 129.6, 140.2. IR (KBr, cm^{-1}) *v* = 3341, 2941, 1453, 741, 700. Anal. Calcd for $C_{24}H_{31}NO_2$ (365.51): C, 78.86; H, 8.55; N, 3.83. Found: C, 78.61; H, 8.79; N, 4.04.

4.3.3. (1*S*,3*R*,4*R*,6*R*)-3-(Benzylamino)methyl)-7,7-dimethylbicyclo[4.1.0]heptane-3,4-diol 7

Prepared with benzylamine at reflux for 14 h. Compound **7** was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 9:1). Compound **7**: 2.31 g (70%); yellow crystals, mp 49–54 °C; $[\alpha]_D^{20} = +23$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.52 (1H, dt, *J* = 4.5, 9.8 Hz), 0.64–0.70 (1H, m), 0.85 (3H, s), 0.95 (3H, s), 1.07 (1H, dd, *J* = 4.3, 15.2 Hz), 1.67–1.73 (2H, m), 1.84 (1H, dd, *J* = 9.8, 15.0 Hz), 2.47 (2H, d, *J* = 11.3 Hz), 2.53 (2H, d, *J* = 11.3 Hz), 3.21 (1H, *t*, *J* = 8.2 Hz), 3.69–3.78 (2H, m), 3.89 (1H, br s), 7.23–7.35 (5H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.2, 17.6, 22.2, 27.2, 29.7, 30.7, 34.9 54.4, 58.4, 70.8, 72.3, 127.4, 128.7, 129.1, 141.5. IR (KBr, cm^{-1}) *v* = 2839, 1944, 1454, 732, 698. Anal. Calcd for $C_{17}H_{25}NO_2$ (275.39): C, 74.14; H, 9.15; N, 5.09. Found: C, 73.98; H, 9.30; N, 5.23.

4.3.4. (1*S*,3*R*,4*R*,6*R*)-3-(Benzyl((*R*)-1-phenylethyl)amino)methyl-7,7-dimethylbicyclo[4.1.0]heptane-3,4-diol 8

Prepared with benzyl ((*R*)-1-phenylethyl)amine at reflux for 16 h. Compound **8** was purified by column chromatography on silica gel (Et_2O/AcOH = 99:1). Compound **8**: 1.73 g (38%); a yellow oil; $[\alpha]_D^{20} = +56$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.48 (1H, dt, *J* = 4.4, 9.8 Hz), 0.60–0.66 (1H, m), 0.74 (3H, s), 0.90 (1H, dd, *J* = 4.6, 15.4 Hz), 0.94 (3H, s), 1.35 (3H, d, *J* = 7.1 Hz), 1.60–1.76 (2H, m), 1.91 (1H, dd, *J* = 9.8, 15.4 Hz), 2.22 (1H, d *J* = 14.0 Hz), 2.66 (1H, d, *J* = 13.9 Hz), 2.88–2.99 (1H, m), 3.51 (1H, d, *J* = 14.3 Hz), 3.75 (1H, s), 3.82 (1H, d, *J* = 14.3 Hz), 4.95–4.05 (1H, m), 4.65 (1H, d, *J* = 5.8 Hz) 7.24–7.39 (10H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 15.6, 16.1, 17.4, 17.5, 22.2, 27.3, 29.7, 30.3, 56.3, 56.9, 57.7, 71,9, 72.1, 127.5, 127.6, 128.6, 129.0, 129.1, 129.2, 141.4, 142.5. IR (KBr, cm^{-1}) *v* = 3434, 2927, 1452, 731, 699. Anal. Calcd for $C_{25}H_{33}NO_2$ (379.25): C, 79.11; H, 8.76; N, 3.69. Found: C, 79.23; H, 8.63; N, 3.80.

4.3.5. (1*S*,3*R*,4*R*,6*R*)-3-(Benzyl((*S*)-1-phenylethyl)amino)methyl-7,7-dimethylbicyclo[4.1.0]heptane-3,4-diol 9

Prepared with benzyl ((*S*)-1-phenylethyl)amine at reflux for 40 h. Compound **9** was purified by column chromatography on sil-

ica gel (Et_2O/AcOH = 99:1). Compound **9**: 0.32 g (29%); a yellow oil; $[\alpha]_D^{20} = -8$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.39 (1H, dt, *J* = 4.2, 9.5 Hz), 0.58–0.63 (1H, m), 0.78 (3H, s), 0.91 (3H, s), 0.93 (1H, dd, *J* = 4.4, 14.6 Hz), 1.33 (3H, d, *J* = 6.4 Hz), 1.51 (1H, dd, *J* = 9.8, 15.1 Hz), 1.62–1.72 (2H, m), 2.29 (1H, d *J* = 13.9 Hz), 2.61 (1H, d, *J* = 14.1 Hz), 2.95–3.02 (1H, m), 3.63–3.72 (3H, m), 3.96–4.01 (1H, m), 4.53 (1H, d, *J* = 5.9 Hz), 7.22–7.31 (10H, m). ^{13}C NMR (DMSO-d_6) δ (ppm): 13.8, 16.2, 17.4, 17.5, 22.2, 27.3, 29.6, 30.1, 56.4, 56.9, 58.0, 71,1, 72.2, 127.5, 128.7, 129.0, 129.5, 141.4, 143.2. IR (KBr, cm^{-1}) ν = 3434, 2924, 1451, 749, 699. Anal. Calcd for $C_{25}H_{33}NO_2$ (379.25): C, 79.11; H, 8.76; N, 3.69. Found: C, 79.30; H, 8.60; N, 3.86.

4.3.6. (1*S*,3*R*,4*R*,6*R*)-7,7-Dimethyl-3-(((*R*)-1-phenylethylamino) methyl)bicyclo[4.1.0]heptane-3,4-diol 10

Prepared with benzyl (*R*)-1-phenylethylamine at reflux for 7 h. Compound **10** (1.63 g, 47%); colourless crystals, mp 102–104 °C (*n*-hexane); $[\alpha]_D^{20} = +65$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.39 (1H, dt, *J* = 4.3, 9.6 Hz), 0.62–0.69 (1H, m), 0.81 (3H, s), 0.94 (3H, s), 1.02 (1H, dd, *J* = 4.3, 15.1 Hz), 1.24 (3H, d, *J* = 6.5 Hz), 1.67–1.79 (3H, m), 2.22 (1H, d, *J* = 11.5 Hz), 2.46 (1H, d, *J* = 10.2 Hz), 3.15 (1H, *t*, *J* = 8.7 Hz), 3.29 (1H, d, *J* = 7.2 Hz), 3.64 (1H, *q*, *J* = 6.5, 12.9 Hz), 3.87 (1H, s), 5.20 (1H, br s), 7.18–7.33 (5H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.2, 17.4, 22.2, 25.3, 27.1, 29.7, 30.5, 57.1, 58.9, 70.6, 72.4, 127.26, 127.47, 129.2, 146.7. IR (KBr, cm^{-1}) ν = 3362, 2922, 1453, 1113, 1090, 851, 700. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84. Found: C, 74.56; H, 9.57; N, 4.99.

4.3.7. (1*S*,3*R*,4*R*,6*R*)-7,7-Dimethyl-3-(((*S*)-1-phenylethylamino) methyl)bicyclo[4.1.0]heptane-3,4-diol 11

Prepared with (*S*)-1-phenylethylamine at reflux for 7 h. Compound **11** (0.63 g, 18%); colourless crystals, mp 57–58 °C (*n*-hexane); $[\alpha]_D^{20} = -4$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.51 (1H, dt, *J* = 4.3, 9.6 Hz), 0.63–0.59 (1H, m), 0.84 (3H, s), 0.95 (3H, s), 0.97 (1H, dd, *J* = 4.4, 15.3 Hz), 1.28 (3H, d, *J* = 6.6 Hz), 1.65–1.70 (2H, m), 1.86 (1H, dd, *J* = 9.9, 15.2 Hz), 2.27 (1H, d, *J* = 11.8 Hz), 2.43 (1H, d, *J* = 11.6 Hz), 3.18 (1H, *t*, *J* = 8.12 Hz), 3.29 (1H, d, *J* = 7.2 Hz), 3.70 (1H, *q*, *J* = 6.4, 13.1 Hz), 3.89 (1H, br s), 7.23–7.37 (5H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 15.8, 17.0, 21.8, 24.7, 26.6, 29.5, 30.2, 56.5, 58.4, 70.8, 71.9, 126.9,128.2, 128.7, 146.0. IR (KBr, cm^{-1}) ν = 3309, 2928, 1452, 1114, 1040, 763, 697. Anal. Calcd for $C_{18}H_{27}NO_2$ (289.41): C, 74.70; H, 9.40; N, 4.84. Found: C, 74.59; H, 9.50; N, 4.97.

4.3.8. (1*S*,3*R*,4*R*,6*R*)-3-(Isopropylamino)methyl-7,7-dimethyl bicyclo[4.1.0]heptane-3,4-diol 12

Prepared with isopropylamine at reflux for 40 h. Compound **12** (0.85 g, 31%); colourless crystals, mp 96–99 °C (*n*-hexane); $[\alpha]_D^{20} = +44$ (*c* 0.125, EtOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.67 (1H, dt, *J* = 4.5, 9.5 Hz), 0.81–0.90 (4H, m), 1.00 (3H, s), 1.03 (1H, dd, *J* = 4.3, 15.5 Hz), 1.14 (3H, d, *J* = 4.3 Hz), 1.15 (3H, d, *J* = 4.3 Hz), 1.70–1.78 (1H, m), 1.94–2.05 (2H, m), 2.65 (1H, d, *J* = 12.2 Hz), 2.84–2.91 (2H, m), 3.49 (1H, dd, *J* = 7.6, 9.2 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.9, 16.5, 21.1, 22.4, 22.5, 26.0, 26.5, 29.1, 30.5, 50.2, 56.8, 70.2, 74.6. IR (KBr, cm^{-1}) ν = 3342, 2933, 2614, 1434, 1040, 867. Anal. Calcd for $C_{13}H_{25}NO_2$ (227.34): C, 68.68; H, 11.08; N, 6.16. Found: C, 68.56; H, 11.21; N, 6.29.

4.4. Preparation of aminodiols 13 and 14

To a suspension of palladium-on-carbon (5% Pd, 0.22 g) in MeOH (50 mL) was added aminodiol **5** or **6** (14.0 mmol) in MeOH (100 mL), and the mixture was stirred under a H_2 atmosphere at room temperature and normal pressure. When the reaction was completed (as monitored by TLC, 5 h), the mixture was filtered through a Celite pad and the solution was evaporated to dryness, resulting in **13** or **14**.

4.4.1. (1*S*,3*R*,4*R*,6*R*)-7,7-Dimethyl-3-((methylamino)methyl) bicyclo[4.1.0]heptane-3,4-diol 13

Compound **13** (0.15 g, 37%); colourless crystals, mp: 70–73 °C (*n*-hexane); $[\alpha]_D^{20} = +24$ (*c* 0.25, MeOH); ^{1}H NMR ($CDCl_3$) δ (ppm): 0.66 (1H, dt, *J* = 4.3, 9.5 Hz), 0.84–0.96 (4H, m), 0.95–1.09 (5H, m), 1.66–1.79 (1H, m), 1.94–2.06 (2H, m), 2.45 (3H, s), 2.55 (1H, d, *J* = 12.4 Hz), 2.82 (1H, d, *J* = 12.4 Hz), 3.18 (1H, s), 3.50–3.54 (1H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.8, 16.3, 21.0, 26.4, 29.0, 30.3, 34.9, 36.93, 62.3, 70.4, 74.5. IR (KBr, cm^{-1}) ν = 3326, 2951, 1629, 1461, 1088, 1061. Anal. Calcd for $C_{11}H_{21}NO_2$ (199.29): C, 66.29; H, 10.62; N, 7.03. Found: C, 66.01; H, 10.89; N, 7.30.

4.4.2. (1*S*,3*R*,4*R*,6*R*)-3-Aminomethyl-7,7-dimethylbicyclo [4.1.0]heptane-3,4-diol 14

Compound **14** (1.63 g, 63%); a colourless oil; $[\alpha]_D^{20} = -32$ (*c* 0.125, EtOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 0.53 (1H, dt, *J* = 4.3, 9.5 Hz), 0.63–0.69 (1H, m), 0.85 (3H, s), 0.95 (3H, s), 1.04 (1H, dd, *J* = 4.3, 15.1 Hz), 1.20–1.22 (1H, m), 1.66–1.70 (2H, m), 1.75–1.81 (1H, m), 3.19–3.23 (2H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.3, 17.6, 22.4, 27.4, 29.7, 29.9, 46.8, 50.8, 70.8, 71.6. IR (KBr, cm^{-1}) ν = 3378, 2935, 1572, 1456, 1049. Anal. Calcd for $C_{10}H_{19}NO_2$ (185.26): C, 64.83; H, 10.34; N, 7.56. Found: C, 64.60; H, 10.59; N, 7.76.

4.5. Preparation of 1,3-oxazines 17–21

At first, 20 mL 35% aqueous formaldehyde was added to the respective secondary aminodiol (1.8 mmol) solution in 5 mL Et_2O. The mixture was stirred at room temperature. After 1 h, it was made alkaline with 10% aqueous KOH and extracted with Et_2O (3 × 30 mL). The organic phase was dried (Na_2SO_4) and evaporated. The crude products **17–21** were purified by column chromatography.

4.5.1. (1a*R*,2a*R*,6a*R*,7a*S*)-5-Benzyl-1,1-dimethyl-6a-hydroxydecahydro-3-oxa-5-azacyclopropa[g]naphthalene 17

Compound **17** (0.49 g, 94%); colourless crystals, mp 60–68 °C (*n*-hexane); $[\alpha]_D^{20} = -61$ (*c* 0.125, EtOH); column chromatography on silica gel (n-hexane/EtOAc = 4:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.55 (1H, dt, *J* = 4.3, 9.6 Hz), 0.71 (1H, dt, *J* = 8.3 Hz), 0.88 (3H, s), 0.88–0.96 (1H, m), 0.97 (3H, s), 1.66–1.82 (3H, m), 2.23 (1H, d, *J* = 12.0 Hz), 2.65 (1H, dd, *J* = 2.0, 12.2 Hz), 3.03 (1H, dd, *J* = 7.3, 10.3 Hz), 3.66 (1H, d, *J* = 13.6 Hz), 3.78 (1H, d, *J* = 13.6 Hz), 3.76 (1H, s), 3.83 (1H, d, *J* = 8.8 Hz), 4.30 (1H, dd, *J* = 1.9, 8.6 Hz), 7.21–7.32 (5H, m), ^{13}C NMR (DMSO-d_6) δ (ppm): 16.2, 17.2, 17.5, 21.4, 22.9, 29.6, 29.8, 57.3, 61.5, 65.9, 79.3, 84.9, 127.7, 129.0, 129.4, 139.4. IR (KBr, cm^{-1}) ν = 3505, 2918, 1454, 1081, 742, 696. Anal. Calcd for $C_{18}H_{25}NO_2$ (287.40): C, 75.22; H, 8.77; N, 4.87. Found: C, 75.03; H, 8.99; N, 4.98.

4.5.2. (1a*R*,2a*R*,6a*R*,7a*S*)-6a-Hydroxy-1,1,5-trimethyldecahydro-3-oxa-5-azacyclopropa[g]naphthalene 18

Compound **18** (0.32 g, 84%); a colourless oil; $[\alpha]_D^{20} = -13$ (*c* 0.125, EtOH); column chromatography on silica gel (toluene/EtOH = 4:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.56 (1H, dt, *J* = 4.3, 9.6 Hz), 0.70 (1H, dt, *J* = 8.5 Hz), 0.88 (3H, s), 0.93–0.98 (4H, m), 1.64–1.82 (3H, m), 2.04 (1H, d, *J* = 11.6 Hz), 2.20 (3H, s), 2.61 (1H, dd, *J* = 1.7, 11.5 Hz), 2.94 (1H, dd, *J* = 7.6, 10.2 Hz), 3.58 (1H, d, *J* = 8.1 Hz), 3.62 (1H, d, *J* = 1.7 Hz), 4.25 (1H, dd, *J* = 1.8, 8.1 Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.2, 17.2, 17.5, 21.4, 22.8, 29.6, 29.7, 41.1, 64.4, 65.7, 78.6, 86.8. IR (KBr, cm^{-1}) ν = 3467, 2939, 1633, 1464, 1087, 895. Anal. Calcd for $C_{12}H_{21}NO_2$ (211.30): C, 68.21; H, 10.02; N, 6.63. Found: C, 68.01; H, 10.18, N, 6.84.

4.5.3. (1a*R*,2a*R*,6a*R*,7a*S*)-6a-Hydroxy-1,1-dimethyl-5-((*R*)-1-phenylethyl)decahydro-3-oxa-5-azacyclopropa[g]naphthalene 19

Compound **19** (0.52 g, 96%); colourless crystals, mp 61–65 °C (*n*-hexane); $[\alpha]_D^{20} = -18.0$ (*c* 0.125, EtOH); column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). ^{1}H NMR (DMSO-d_6) δ (ppm): 0.55 (1H, dt, *J* = 4.3, 9.5 Hz), 0.70 (1H, d, *J* = 8.1 Hz), 0.86 (3H, s), 0.92–0.96 (1H, m), 0.96–0.98 (3H, s), 1.26 (3H, d, *J* = 6.8 Hz), 1.66–1.81 (3H, m), 2.08 (1H, d, *J* = 11.5 Hz), 2.68 (1H, dd, *J* = 1.9, 11.4 Hz), 2.95 (1H, dd, *J* = 7.4, 10.1 Hz), 3.60 (1H, d, *J* = 1.5 Hz), 3.69 (1H, d, *J* = 8.4 Hz), 3.80 (1H, *q*, *J* = 7.2, 13.6 Hz), 4.39 (1H, dd, *J* = 1.9, 8.4 Hz), 7.23–7.38 (5H, m); ^{13}C NMR (DMSO-d_6) δ (ppm): 16.2, 17.2, 17.5, 20.3, 21.4, 22.9, 29.5, 29.7, 59.1, 59.4, 65.8, 79.2, 83.5, 129.0, 128.1, 127.7, 144.6. IR (KBr, cm^{-1}) ν = 3522, 2917, 1597, 1268, 885. Anal. Calcd for $C_{19}H_{27}NO_2$ (301.42): C, 75.71; H, 9.03; N, 4.65. Found: C, 75.57; H, 9.17; N, 4.81.

4.5.4. (1a*R*,2a*R*,6a*R*,7a*S*)-6a-Hydroxy-1,1-dimethyl-5-((*S*)-1-phenylethyl)decahydro-3-oxa-5-azacyclopropa[g]naphthalene 20

Compound **20** (0.44 g, 81%); a colourless oil; $[\alpha]_D^{20} = -44$ (*c* 0.125, EtOH); column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.71 (1H, dt, *J* = 4.4, 9.7 Hz), 0.84–0.91 (4H, m), 0.95–1.03 (4H, m), 1.42 (3H, d, *J* = 6.5 Hz), 1.85–1.95 (4H, m), 2.78 (1H, d, *J* = 10.8 Hz), 2.96 (1H, *t*, *J* = 8.6 Hz), 3.62–3.72 (2H, m), 4.65 (1H, dd, *J* = 1.9, 7.8 Hz), 7.23–7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ (ppm): 16.2, 17.2, 17.5, 20.3, 21.4, 22.9, 29.5, 29.7, 59.1, 59.4, 64.8, 79.3, 83.5, 127.7, 128.1, 129.0, 141.9. IR (KBr, cm^{-1}) ν = 3459, 2955, 1453, 1081, 700. Anal. Calcd for $C_{19}H_{27}NO_2$ (301.42): C, 75.71; H, 9.03; N, 4.65. Found: C, 75.60; H, 9.11; N, 4.77.

4.5.5. (1a*R*,2a*R*,6a*R*,7a*S*)-1,1-Dimethyl-6a-hydroxy-5-isopropyl decahydro-3-oxa-5-azacyclopropa[g]naphthalene 21

Compound **21** (0.27 g, 63%); a yellow oil; $[\alpha]_D^{20} = -22$ (*c* 0.125, MeOH); column chromatography on silica gel (*n*-hexane/EtOAc = 4:1). ^{1}H NMR ($CDCl_3$) δ (ppm): 0.75 (1H, dt, *J* = 4.4, 9.7 Hz), 0.83–0.91 (3H, m), 0.93 (3H, s), 0.99–1.07 (9H, m), 1.85–1.90 (2H, m), 1.99 (1H, dd, *J* = 9.8, 15.2 Hz), 2.16 (1H, d, *J* = 10.8 Hz), 2.72 (1H, dd, *J* = 2.2, 10.9 Hz), 2.79–2.89 (1H, m), 2.99 (1H, *t*, *J* = 8.9 Hz), 3.86 (1H, d, *J* = 7.7 Hz), 4.49 (1H, dd, *J* = 2.2, 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ (ppm): 15.8, 16.5, 17.5, 18.6, 19.9, 21.2, 22.8, 28.7, 29.2, 51.4, 57.9, 65.7, 79.4, 84.0. IR (KBr, cm^{-1}) ν = 3522, 2862, 1452, 1083, 890. Anal. Calcd for $C_{14}H_{25}NO_2$ (239.35): C, 70.25; H, 10.53; N, 5.85. Found: C, 70.02; H, 10.79; N, 5.99.

4.6. General experimental procedure for the reactions of aldehydes with diethylzinc in the presence of chiral catalyst 5–14 or 17–21

To the respective catalyst (0.1 mmol) **5–14** or **17–21**, 1 M Et_2Zn in *n*-hexane solution (3 mL, 3 mmol) was added under an Ar atmosphere at room temperature. The reaction was stirred for 25 min at room temperature, and the aldehyde (1 mmol) was then added to the solution, with subsequent stirring at room temperature for a further 20 h. The reaction was quenched with a saturated NH_4Cl solution (15 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with water (10 mL), dried (Na_2SO_4) and evaporated under vacuum. The crude secondary alcohols obtained were purified by flash column chromatography (*n*-hexane/EtOAc = 4:1). The enantiomeric excess and absolute configuration of the resulting alcohols were determined by chiral GC, using a chiral stationary phase (Chirasil-Dex CB column) at 90 °C for 1-phenyl-1-propanol **16a** [t_{R1} = 7.0 min for the (*S*)-isomer, t_{R2} = 8.1 min for the (*R*)-isomer],[35] 1-cyclohexyl-1-propanol **16g** [t_{R1} = 7.1 min for the (*S*)-isomer, t_{R2} = 8.7 min for the (*R*)-isomer][34] and 3-heptanol **16h** [t_{R1} = 3.3 min for the (*S*)-isomer, t_{R2} = 3.9 min for the (*R*)-isomer].[34] Identification of **16b** and **16d–f** was done by chiral HPLC analysis on a Chiralcel OD-H column and the data are as follows: 1-(4-methoxyphenyl)-1-propanol **16b**; *V*(*n*-hexane)/*V*(2-propanol) = 95:5, 0.7 mL/min, 210 nm, t_{R1} = 15.3 min for the (*R*)-isomer, t_{R2} = 16.9 min for the (*S*)-isomer.[21] 1-(4-Tolyl)-1-propanol **16c** *V*(*n*-hexane)/*V*(2-propanol) = 95:5, 0.5 mL/min, t_{R1} = 10.4 min for the (*R*)-isomer, t_{R2} = 14.9 min for the (*S*)-isomer.[21] 1-(3-Methoxyphenyl)-1-propanol **16d**; *V*(*n*-hexane)/*V*(2-propanol) = 98:2, 0.4 mL/min, 210 nm, t_{R1} = 64.7 min for the (*R*)-isomer, t_{R2} = 70.7 min for the (*S*)-isomer.[34] 1-(3-Tolyl)-1-propanol **16e**; *V*(*n*-hexane)/*V*(2-propanol) = 95:5, 0.7 mL/min, 210 nm, t_{R1} = 10.1 min for the (*R*)-isomer, t_{R2} = 11.5 min for the (*S*)-isomer.[36] 1-(Naphthyl)-1-propanol **16f**; *V*(*n*-hexane)/*V*(2-propanol) = 95:5, 0.4 mL/min, 210 nm, t_{R1} = 29.9 min for the (*S*)-isomer, t_{R2} = 33.1 min for the (*R*)-isomer.[21] The direction of the optical rotations of the products was also checked. The spectroscopic data on the alcohols prepared were, in all cases, similar to those reported in the literature.[19,21,26d,32–35]

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