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Enantioselective addition of diethylzinc to aldehydes catalyzed by γ-amino alcohols derived from (+)- and (−)-α-pinene

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Dedicated to Professor Géza Stájer on the occasion of his 70th birthday

Abstract—Primary, secondary and tertiary γ-amino alcohols **4**, **5**, **7** and **9** and 1,3-diamine **6** were synthesized from (+)- and (−)-α-pinene **1** via chiral *N*-Boc β-amino ester **3a** and carboxamide **3b**. The amino alcohols and diamine obtained were applied as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes, resulting in chiral 1-aryl-1-propanols. The first evidence of the substituent-dependent enantioselectivity of 1,3-amino alcohol catalysts was observed, and the phenomenon interpreted by using molecular modelling at the ab initio level.

1. Introduction

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.[1] Various amino alcohol catalysts derived from monoterpenes, such as (+)-pulegone,[2] β-pinene,[3] fenchone-camphor,[4] and limonene,[5] have been reported to have been used successfully in enantioselective syntheses. Monoterpene-fused 1,3-oxazines have also been applied as catalysts in enantioselective allylic substitutions.[6,7] 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.[8–10]

The enantioselective addition of organometallic reagents to aldehydes is one of the most effective methods for the synthesis of chiral secondary alcohols.[11] Since the discovery that amino alcohols, and especially β-amino alcohols, are excellent ligands for the enantioselective catalysis of the above-mentioned addition,[12–15] a great number of β-amino alcohols have been investigated,[16–19] though less attention has been paid to the application of γ-amino alcohols.[20–23] 1,3-Amino alcohols derived from (+)-pulegone,[24,25] camphor, (−)-fenchone[22] and (−)-menthone[23] have successfully been applied as chiral catalysts, but their application is limited, as in most cases, only one of the enantiomers of the starting material is available commercially.

Herein, we report the synthesis of new chiral 1,3-amino alcohols and diamines starting from (+)- and (−)-α-pinene, and their application in the enantioselective addition of diethylzinc to aromatic aldehydes.

2. Results and discussion

The synthetic route to the novel chiral γ-amino alcohols **4**, **5**, **7** and **9** and diamine **6** is shown in Scheme 1. Although both enantiomers were prepared, only the compounds derived from (−)-α-pinene are presented in Scheme 1. β-Amino ester **3a** and carboxamide **3b** were prepared regio- and stereoselectively according to the literature methods, starting from (+)- and (−)-α-pinene.[8,9] Deprotection of *N*-Boc amino ester **3a** with TFA, followed by lithium aluminium hydride reduction, resulted in the formation of primary amino alcohol **4**. *N*-Benzylamino alcohol **5** was synthesized through the reaction of compound **4** with benzaldehyde, followed by reduction of the in situ formed Schiff base with sodium borohydride. When carboxamide **3b** was reduced with lithium aluminium hydride, 1,3-diamine **6** was obtained.

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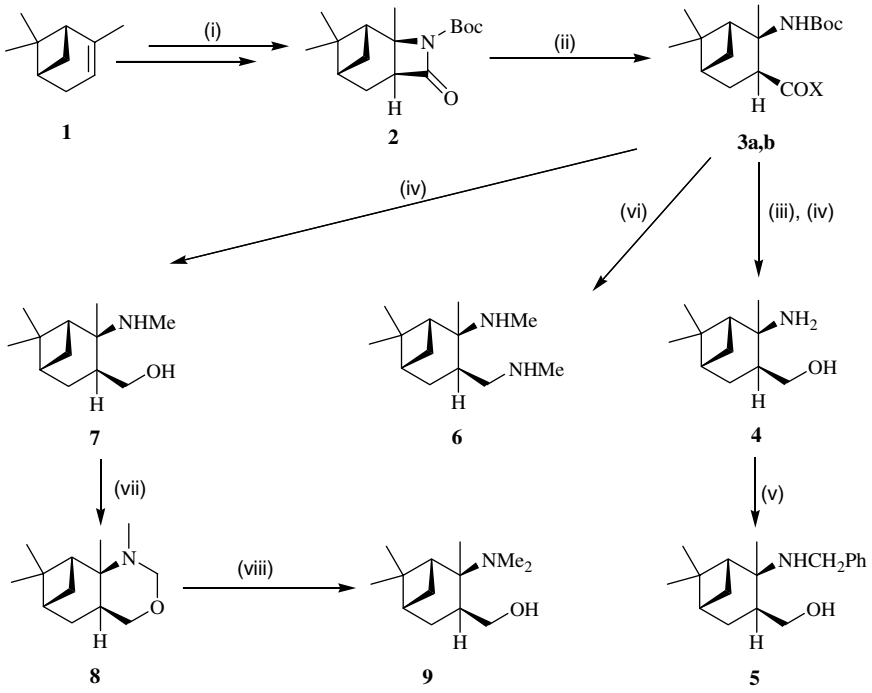


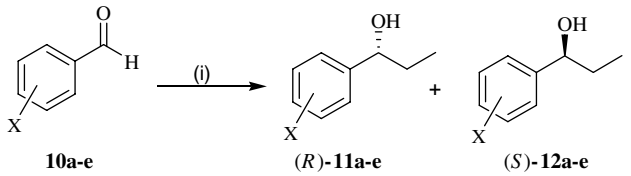
Scheme 1. Reagents and conditions: (i) CSI, Et_2O, 1 h, rt, then Boc_2O, Et_3N, DMAP/THF, rt, 4 h (lit.[8,9]); (ii) **3a**: NaOMe/MeOH; **3b**: $MeNH_2$/MeOH (lit.[9]); (iii) TFA, CH_2Cl_2, rt, 2 h (lit.[9]); (iv) LAH/THF, rt, 2 h, 85%; (v) PhCHO/EtOH, then $NaBH_4$, EtOH, rt, 12 h, 70%; (vi) LAH/THF, reflux, 4 h, 81%; (vii) CH_2O/H_2O, rt, 1 h, 90% (lit.[8]); (viii) LAH/THF, reflux, 24 h, 85%; **3a**: X = OMe, **3b**: X = NHMe.

Similarly, the reduction of *N*-Boc amino ester **3a** resulted in *N*-methylamino alcohol **7** (Scheme 1).

N,*N*-Dimethylamino alcohol **9** was prepared in two steps from **7**. *N*-Methylamino alcohol **7** was stirred with aqueous formaldehyde, and the resulting *N*-methyl-1,3-oxazine[8] reduced to compound **9** with lithium aluminium hydride. The enantiomeric excesses of **2** and **3a** (ee >99%) were determined by GC analysis on a CHIRASIL-DEX CB column.[8,9] Since there was no sign of the presence of any other diastereomer in the NMR spectra of the crude products **4**–**9**, the high enantiomeric excesses of **4**–**9** can be regarded as proved.

The amino alcohols **4**, **5**, **7** and **9** and diamine **6** were then applied as chiral catalysts in the enantioselective addition of diethylzinc to aromatic aldehydes, resulting in chiral 1-aryl-1-propanols (Scheme 2).

Our results are presented in Table 1. The enantiomeric purities of the 1-aryl-1-propanols **11a**–**e** and **12a**–**e** obtained were determined by GC analysis on a CHIRASIL-DEX CB column, according to the literature methods.[26,16] It was found that diamine **6** had no effect



Scheme 2. Reagents and conditions: (i) 3 equiv Et_2Zn/*n*-hexane, rt, 10 mol % catalyst **5**–**7** or **9**, argon atm.; X = **a**: H, **b**: 4-Me, **c**: 3-Me, **d**: 4-Br, **e**: 3-MeO.

Table 1. Influence of catalyst loading on the reaction yield and enantioselectivity according to Scheme 2

Entry	X	Ligand	Yield (%)[a]	ee (%)[b]	Major config. of 1-aryl-1-propanols
1	H	**6**	88	—	—
2	H	**4**	85	40	*R*
3	4-Me	**4**	92	21	*R*
4	3-Me	**4**	81	39	*R*
5	4-Br	**4**	89	32	*R*
6	3-MeO	**4**	70	22	*R*
7	H	**5**	87	13	*S*
8	4-Me	**5**	91	49	*S*
9	3-Me	**5**	87	40	*S*
10	4-Br	**5**	91	40	*S*
11	3-MeO	**5**	78	32	*S*
12	H	**7**	83	53	*R*
13	4-Me	**7**	85	36	*R*
14	3-Me	**7**	78	31	*R*
15	4-Br	**7**	87	10	*R*
16	3-MeO	**7**	75	20	*R*
17	H	**9**	91	62	*S*
18	4-Me	**9**	94	62	*S*
19	3-Me	**9**	85	58	*S*
20	4-Br	**9**	92	70	*S*
21	3-MeO	**9**	83	72	*S*

[a] Yields after silica gel column chromatography.
[b] Determined from the crude product by chiral GC (CHIRASIL-DEX CB column).

on the enantioselectivity in the diethylzinc addition (entry 1). When amino alcohol **4** or **7** was applied in an amount of 10 mol %, moderate asymmetric induction with *R* selectivity was observed. By changing the *N*-methyl substituent to *N*-Me_2 **9** or *N*-benzyl **5**, the direction of the enantioselectivity turned dramatically from *R*

to *S*. As far as we are aware, this is the first example of the usage of 1,3-amino alcohol catalysts for a change in asymmetric induction through the substituents on the nitrogen.

In order to interpret the *N*-substituent-induced difference in enantioselectivity, molecular modelling was performed for **4** and **9**. Although the arsenal used for such theoretical studies extends from the molecular mechanics force-field fine tuned for transition states[15] to the ab initio methods at the DFT level,[27] it can be considered as a consensus that the modelling of the Noyori μ-oxo transition state following the QM/MM ONIOM approach[4,28,29] gives acceptably accurate results for design purposes at a reasonable computational cost. We, therefore, utilized the QM/MM ONIOM modelling protocol in this work. 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), leading to eight diastereomers, which were optimized by using the transition state-searching algorithm implemented in Gaussian03. The diastereomers are designated by their absolute chirality on Zn1 in the heterocyclic ring, and on the carbon at the reaction centre, and by the *syn* or *anti* position of the transferring Zn2-attached alkyl group relative to the alkyl on Zn1. The geometries were preoptimized by using the PM3 semi-empirical method, and the final geometries were obtained at the ONIOM (RHF/LanL2DZ:UFF) level. The final structures showed only a single imaginary frequency corresponding to the alkyl transfer. The setup of the QM/MM layers is depicted in Figure 2.

The relative stabilities of the transition state diastereomers calculated from the single-point energies at the full

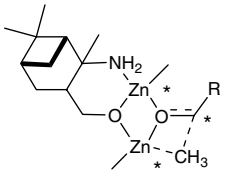


Figure 1.

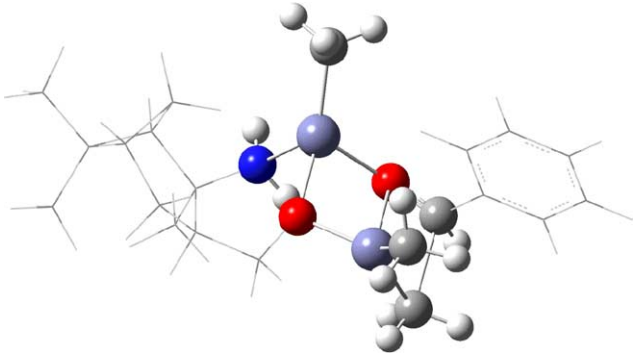


Figure 2. Setup for the QM/MM layers depicted for Zn-*R*, C-*R*, *anti*. Wireframe: UFF, ball-and-stick: RHF/LanL2DZ.

Table 2. Ab initio RHF/LanL2DZ single-point energies calculated for μ-oxo complexes of **4** and **9**

Ligand	Zn1	C	Zn2-alkyl	*E*(RHF)/a.u.	$(E - E_{min})$ (kcal/mol)
4	*R*	*R*	*anti*	−1146.45718888	6.55
4	*R*	*R*	*syn*	−1146.46590700	1.08
4	*R*	*S*	*anti*	−1146.46357861	2.54
4	*R*	*S*	*syn*	−1146.46443859	2.00
4	*S*	*R*	*anti*	−1146.46750248	0.07
4	*S*	*R*	*syn*	−1146.46762142	0.00
4	*S*	*S*	*anti*	−1146.45804927	6.01
4	*S*	*S*	*syn*	−1146.46699412	0.39
9	*R*	*R*	*anti*	−1224.44460798	9.88
9	*R*	*R*	*syn*	−1224.44913203	7.04
9	*R*	*S*	*anti*	−1224.44846000	7.46
9	*R*	*S*	*syn*	−1224.46035522	0.00
9	*S*	*R*	*anti*	−1224.44928128	6.95
9	*S*	*R*	*syn*	−1224.44831070	7.56
9	*S*	*S*	*anti*	−1224.44724215	8.23
9	*S*	*S*	*syn*	−1224.44936755	6.89

RHF/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 enantioselectivities. The calculations suggest that the transalkylation most likely proceeds via diastereomers Zn1-*S*, C-*R*, *syn* and Zn1-*R*, C-*S*, *syn* for **4** and **9**, respectively (Figs. 3 and 4). The energy differences between the transition states for **4** are less pronounced than those for **9**, which is also in line with the higher enantioselectivities observed in the case of **9**. The resulting geometries allow the determination for the possible

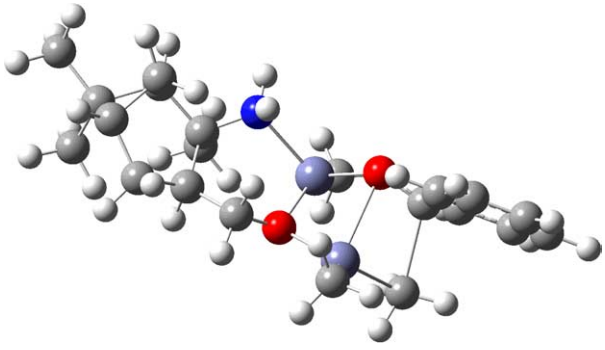


Figure 3. Lowest-energy structure (Zn1-*S*, C-*R*, *syn*) obtained for **4**.

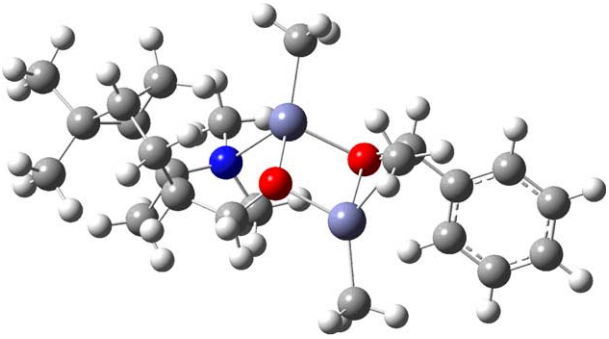


Figure 4. Lowest-energy structure (Zn1-*R*, C-*S*, *syn*) obtained for **9**.

reason of inverted enantioselectivity. For **4**, the transition state geometry is stable in a boat heterocyclic ring conformation, where the bridging methylene of the pinene is situated above the ring. This geometry facilitates the Zn1-*S* configuration and there is no steric repulsion in the absence of any *N*-substituent. In **9**, the disubstitution causes a steric clash between the bridging methylene and the *N*-Me group, which in turn prevents the Zn1-*S* configuration, and thereby results in an inverted configuration at the reaction centre.

3. Conclusion

The γ-amino alcohols prepared may serve as chiral building blocks in the asymmetric syntheses of potential pharmaceutical agents, and can also be used as chiral auxiliaries and catalysts in enantioselective syntheses. The theoretical calculations provided an explanation for the substituent-dependent enantioselectivity and may serve as a starting point for the design of further enantioselective catalysts.

4. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer [400 MHz, $\delta = 0$ (TMS)], in an appropriate solvent. Chemical shifts are expressed in ppm (δ) relative to TMS as the internal reference. *J* values are given in Hz. FT-IR spectra recordings were performed on a Perkin–Elmer model 1000 spectrophotometer, microanalyses on a Perkin–Elmer 2400 elemental analyzer, and GC measurements on a Crompack 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-aryl-1-propanols was a CHIRASIL-DEX CB column (2500 × 0.25 mm I.D.) operated at 110, 115 and 120 °C, and 140 kPa. Optical rotations were obtained with a Perkin–Elmer 341 polarimeter. Melting points were determined on a Kofler apparatus and are uncorrected.

Compounds **2**, **3a** and **3b**, amino alcohol **4** and 1,3-oxazine **8** were prepared from (1*S*,5*S*)-(−)- and (1*R*,5*R*)-(+)-α-pinene according to the literature methods.[8,9]

4.1. (1*R*,2*R*,3*S*,5*R*)-(2-Benzylamino-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methanol hydrochloride 5

Amino alcohol **4** (0.73 g, 4 mmol) and benzaldehyde (0.42 g, 4 mmol) were dissolved in dry ethanol (30 mL), and the solution stirred for 1 h at room temperature and then evaporated to dryness. The residual oily product was dissolved in dry ethanol, and $NaBH_4$ (0.45 g, 12 mmol) added in small portions to the stirred solution under ice cooling. The mixture was stirred for a further 12 h at room temperature, and the excess of $NaBH_4$ was then decomposed with 5% acetic acid solution. After the solution had turned clear, the reaction mixture was evaporated to half-volume, basified with 1 M NaOH and extracted with chloroform (3 × 30 mL). The combined organic phase was dried over Na_2SO_4 and evaporated, giving compound **5** as a yellow oil, which was purified as the hydrochloride. The base liberated for application as a catalyst was a colourless oil.

Compound **5** (0.85 g, 70% yield); mp 202–205 °C; $[\alpha]_D^{20} = -14.1$ (*c* 0.5, MeOH); ^{1}H NMR (DMSO-d_6) δ (ppm): 1.07 (3H, s), 1.31 (3H, s), 1.36 (1H, d, $J = 9.6$ Hz), 1.53 (3H, s), 1.65–1.73 (1H, m), 1.92–2.01 (2H, m), 2.25–2.33 (2H, m), 2.35–2.42 (1H, m), 3.72 (1H, dd, $J = 6.0$, 11.1 Hz), 3.82 (1H, dd, $J = 4.0$, 11.1 Hz), 3.86–3.94 (1H, m), 4.17–4.26 (1H, m), 5.84 (1H, br s), 7.39–7.55 (5H, m), 8.53 (1H, br s); ^{13}C NMR ($CDCl_3$) δ (ppm): 22.5, 24.1, 26.1, 27.4, 29.0, 38.1, 38.5, 39.6, 44.1, 48.3, 60.1, 67.2, 128.5, 128.7, 129.6. Anal. Calcd for $C_{18}H_{28}ClNO$ (309.87): C, 69.77; H, 9.11; N, 4.52. Found: C, 69.83; H, 9.02; N, 4.74.

The (1*S*,2*S*,3*R*,5*S*)-enantiomer of **5** was prepared as described above; mp 201–203 °C; $[\alpha]_D^{20} = +13.2$ ($c = 0.5$, MeOH); the spectroscopic data and mp were similar to those for **5**. Analysis: found: C, 69.71; H, 9.23; N, 4.82.

4.2. (1*R*,2*R*,3*R*,5*R*)-Methyl-(2,6,6-trimethyl-3-methylaminomethylbicyclo[3.1.1]hept-2-yl)amine hydrochloride 6

To a slurry of $LiAlH_4$ (1.31 g, 34.8 mmol) in dry THF (100 mL), carboxamide **3b** (2.69 g, 8.7 mmol) in THF (20 mL) was added dropwise at 0 °C. After stirring and refluxing for 4 h (the reduction was monitored by means of TLC), the mixture was decomposed with water (2.6 mL) in THF (20 mL) under ice cooling. The inorganic material was filtered off and washed with THF (3 × 50 mL). Drying over Na_2SO_4 and evaporation gave the base of **6** as a yellow oil, which was purified as the hydrochloride. Compound **6** (1.73 g, 81% yield); mp 190–192 °C; $[\alpha]_D^{20} = -11.7$ (*c* 0.5, MeOH); ^{1}H NMR (D_2O) δ (ppm): 1.04 (1H, d, $J = 10.6$ Hz), 1.13 (3H, s), 1.36 (3H, s), 1.39 (3H, s), 1.51–1.62 (1H, m), 2.05–2.12 (1H, m), 2.21–2.30 (2H, m), 2.36–2.44 (1H, m), 2.39 (3H, s), 2.50–2.59 (1H, m), 2.54 (3H, s), 2.85 (1H, dd, $J = 8.6$, 12.1 Hz), 2.94 (1H, dd, $J = 6.5$, 12.4 Hz); ^{13}C NMR (D_2O) δ (ppm): 23.0, 23.8, 26.8, 28.0, 32.1, 34.6, 37.1, 38.1, 39.8, 49.0, 53.2, 62.9. Anal. Calcd for $C_{13}H_{27}ClN_2$ (246.82): C, 63.26; H, 11.03; N, 11.35. Found: C, 63.45; H, 10.86; N, 11.51. The (1*S*,2*S*,3*S*,5*S*)-enantiomer of **6** was prepared as described above; mp 192–194 °C; $[\alpha]_D^{20} = +12.8$ (*c* 0.5, MeOH); the spectroscopic data were similar to those for **6**. Analysis: found: C, 62.97; H, 11.34; N, 11.58.

4.3. (1*R*,2*R*,3*S*,5*R*)-(2-Methylamino-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methanol hydrochloride 7

To a slurry of $LiAlH_4$ (3.41 g, 89.4 mmol) in dry THF (150 mL), *N*-Boc-amino ester **3a** (7.5 g, 24.1 mmol) in THF (40 mL) was added dropwise at room temperature. After stirring for 2 h (the reduction was monitored by means of TLC), the mixture was decomposed with water

(3.8 mL) in THF (30 mL) under ice cooling. The inorganic material was filtered off and washed with THF (3×100 mL). Drying over Na_2SO_4 and evaporation gave the base of **7** as pale-yellow crystals, which were recrystallized from *n*-hexane. Compound **7** (3.9 g, 82% yield); mp 45–47 °C; $[\alpha]_D^{20} = -11.6$ (*c* 0.2, MeOH). Anal. Calcd for $C_{12}H_{23}NO$ (197.32): C, 73.04; H, 11.75; N, 7.10. Found: C, 72.83; H, 11.39; N, 7.31. The spectroscopic data were similar to the literature data.[8] The (1*S*,2*S*,3*R*,5*S*)-enantiomer of **7** was prepared as described above; mp 44–45 °C; $[\alpha]_D^{20} = +12.5$ (*c* 0.2, MeOH); the spectroscopic data were similar to those for **7**. Analysis: found: C, 72.95; H, 11.87; N, 7.43.

4.4. (1*R*,2*R*,3*S*,5*R*)-(2-Dimethylamino-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl)methanol hydrochloride 9

Amino alcohol **6** (0.96 g, 4.86 mmol) was stirred with 20 mL of 33% aqueous formaldehyde at room temperature for 1 h. The mixture was made alkaline with 10% aqueous KOH and extracted with diethyl ether (3×50 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to give an almost colourless oil. The crude product was purified on a silica gel column (toluene/ethanol = 9:1, $R_f = 0.45$), resulting in 0.92 g (4.4 mmol, 90%) of a colourless oily product, which was used in the next step without further purification. To a slurry of $LiAlH_4$ (0.50 g, 13.2 mmol) in 60 mL of dry THF, oxazine **3** (0.92 g, 4.4 mmol) in 10 mL of dry THF was added dropwise at room temperature. After stirring and refluxing for 24 h (the reduction was monitored by means of TLC), the mixture was decomposed with 1.5 mL of water under ice cooling. After stirring for 1 h, the inorganic material was filtered off and washed with THF. After drying over Na_2SO_4 and evaporation, a pale-yellow oil was obtained. Amino alcohol **9** was purified as the hydrochloride. The base liberated for catalytic usage was a viscous oil. Compound **9** (0.93 g, 85% yield); mp 173–175 °C; $[\alpha]_D^{20} = -31.8$ (*c* 0.5, MeOH); ^{1}H NMR (D_2O) δ (ppm): 1.06 (1H, d, $J = 11.1$ Hz), 1.18 (3H, s), 1.38 (3H, s), 1.47 (3H, s), 1.85–1.93 (1H, m), 2.05–2.21 (2H, m), 2.35 (1H, t, $J = 5.5$ Hz), 2.49–2.57 (2H, m), 2.68 (3H, s), 3.02 (3H, s), 3.79 (1H, dd, $J = 5.0$, 12.6 Hz), 4.12 (1H, dd, $J = 3.0$, 12.6 Hz); ^{13}C NMR (D_2O) δ (ppm): 19.8, 22.4, 28.1, 28.5, 32.0, 38.2, 39.0, 39.4, 40.1, 40.4, 41.4, 51.3, 61.7, 73.9. Anal. Calcd for $C_{13}H_{26}ClNO$ (247.80): C, 63.01; H, 10.58; N, 5.65. Found: C, 63.35; H, 10.29; N, 5.84. The (1*S*,2*S*,3*R*,5*S*)-enantiomer of **9** was prepared as described above; mp 175–176 °C; $[\alpha]_D^{20} = +30.1$ (*c* 0.5, MeOH); the spectroscopic data were similar to those for **9**. Analysis: found: C, 63.57; H, 10.46; N, 5.65.

4.5. Typical experimental procedure for the reaction of aldehydes with diethylzinc in the presence of chiral catalyst 4–7 and 9

To a solution of **9** (0.032 g, 0.15 mmol) in dry *n*-hexane (2 mL), 1 M diethylzinc in *n*-hexane solution (4.5 mL, 4.5 mmol) was added under an argon atmosphere at room temperature. The reaction mixture was stirred for 25 min at room temperature, after which benzaldehyde (0.16 g, 1.5 mmol) in dry toluene was added over 5 min. The reaction mixture was then stirred at room temperature for a further 20 h. The reaction mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with ethyl acetate (2×30 mL). The combined organic phase was washed with 0.1 M HCl solution (20 mL), dried over Na_2SO_4 and evaporated under vacuum. The crude alcohol obtained was purified by flash column chromatography (*n*-hexane/ethyl acetate = 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.[26,16]

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