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Perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol as ligands for the catalytic enantioselective addition of diethylzinc to aldehydes

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ABSTRACT

The catalytic potency of a series of perhydro-1,3-benzoxazines prepared from (−)-8-aminomenthol was examined in the enantioselective addition of diethylzinc to aldehydes. When (2*R*,3*S*,3a*S*,4a*R*,6*R*,8a*S*)-2-isopropyl-6,9,9-trimethyl-3-phenyldecahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ol **7b** was used as a chiral ligand, 1-substituted propanols with an (*R*)-configuration were obtained in high yields and enantiomeric excesses up to >99%. The catalyst can be recovered and used without any loss in its activity.

1. Introduction

Catalytic asymmetric carbon–carbon bond formation is known as one of the most important organic synthetic processes. In this field, considerable attention has been devoted to the enantioselective addition of dialkylzincs to aldehydes in the presence of catalytic amounts of a chiral ligand.[1] The process constitutes a fundamental and versatile method for obtaining optically active secondary alcohols, which are versatile and important chiral building blocks for the synthesis of natural products and biologically active compounds. In addition, the reaction of diethylzinc with aldehydes has also become a classical test in the design of new ligands for catalytic enantioselective synthesis.

Since Oguni and Omi reported the first addition of diethylzinc to aldehydes catalyzed by (*S*)-leucinol,[2] numerous chiral ligands such as sulfonamide and phosphoramide complexes, chiral amides, diamines, diols and BINOL derivatives, oxazolines, imino alcohols, and amino alcohols or amino thiols have been developed although β-amino alcohols hold a prominent position.[3] Other five-membered chiral heterocycles such as oxazolidines have been used less[4] despite being promising ligands in the asymmetric addition of alkynylzinc to aldehydes.[5]

Over the last few years, we have reported the utility of chiral perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol as stoichiometric chiral auxiliaries covalently attached to substrate in diastereoselective synthesis.[6,7]

Based on the results reported for oxazolidines, we thought that chiral perhydro-1,3-benzoxazines ligands could also catalyze the asymmetric addition of dialkylzinc to aldehydes. Herein we report the discovery of a new chiral perhydro-1,3-benzoxazine-based ligand for the asymmetric addition of diethylzinc to aldehydes with high ee values under mild conditions.

2. Results and discussion

We began by examining the behavior of zinc amides derived from perhydro-1,3-benzoxazines **2a**–**e** which essentially differ in the nature and size of the substituent at the *N*,*O*-ketalic carbon of the heterocycle, and the C-2 symmetric chiral bisperhydrobenzoxazine **2f**. These perhydro-1,3-benzoxazines were prepared, as single diastereomers, in good yields by condensation of (−)-8-aminomenthol **1**[8] with the corresponding aldehyde in refluxing toluene (Scheme 1).[9]

The catalytic potency of **2a**–**f** was examined using the reaction between Et_2Zn and 2-naphthaldehyde with 10 mol % of the catalyst in a toluene/hexane 2:1 mixture at room temperature for 24 h; the results are summarized in Table 1.

In general, the reactions occurred in good yields but the enantioselectivity induced by chiral perhydro-1,3-benzoxazines **2a**–**f** was not very high. The best result was obtained with bisperhydrobenzoxazine **2f**, but the enantioselectivity was just over 50%. In order to improve the observed enantiomeric excesses for this catalytic process, perhydro-1,3-benzoxazines **2g** and **2h** bearing a hydroxyl group were tested. Benzoxazine **2g** was prepared as a single diastereoisomer in excellent yield by the condensation of (−)-8-aminomenthol with phenylglyoxal and a subsequent addition of phenylmagnesium bromide to the resulting 2-benzoyl perhydro-1,3-benzoxazine in diethyl ether at 0 °C. As previously described,[10] the condensation of (−)-8-aminomenthol with the glycolaldehyde dimer in CH_2Cl_2 at room temperature yielded nearly quantitative benzoxazine **2h** (Scheme 1). Unfortunately both **2g** and **2h** provided poor enantioselectivities despite having the structure of a β-amino alcohol (Table 1, entries 7 and 8). It is interesting to note that the catalysts **2a**–**f** induced the formation of (*S*)-1-(naphthalen-2-yl)propan-1-ol, whereas benzoxazines **2g** and **2h** provided the (*R*)-enantiomer.

Generally, it was expected from the reports in the literature that the enantioselectivity would increase when the degree of *N*-alkyl substitution increased in β-amino alcohols.[1b] However, the

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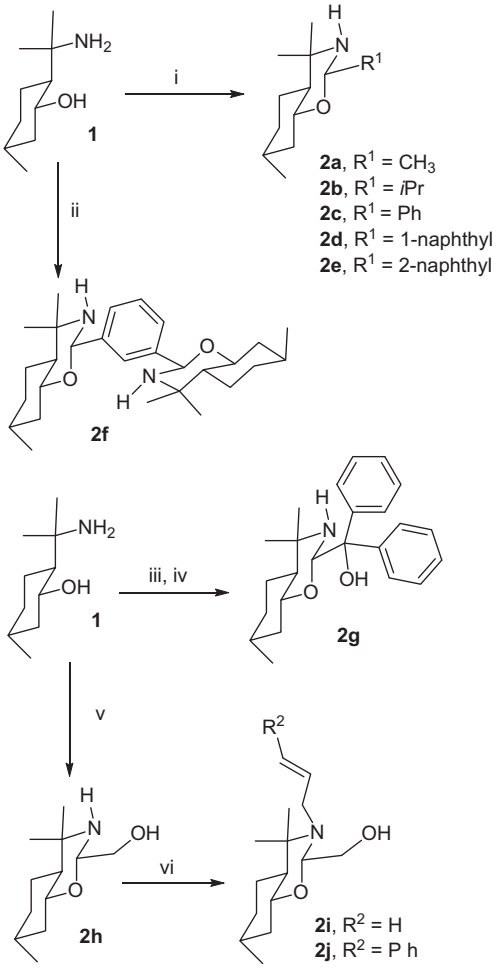


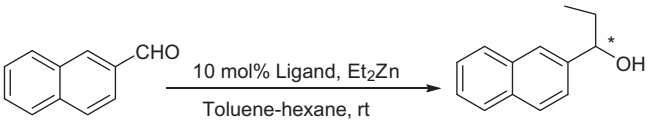
Scheme 1. Reagents and conditions: (i) R^1CHO, toluene, reflux, **2a** (98%), **2b** (88%), **2c** (99%), **2d** (96%), **2e** (98%); (ii) isophthalaldehyde, toluene, reflux, 86%; (iii) PhCOCHO, CH_2Cl_2, rt; (iv) PhMgBr, Et_2O, 0 °C, 83%; (v) glycolaldehyde dimer, CH_2Cl_2, rt, 99%; (vi) $R^2CH{=}CHCH_2Br$, K_2CO_3, CH_3CN, 80–90 °C, **2i** (80%), **2j** (88%).

N-substituted ligands **2i** and **2j** obtained by alkylation of **2h** with allyl and cinnamyl bromides in the presence of potassium carbonate in refluxing acetonitrile (Scheme 1),[10] resulted in only a modest improvement in the enantioselectivity of the reaction.

We have recently reported the utility of chiral perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol in the synthesis of *cis*-3,4-disubstituted pyrrolidines by thermally[11] or Lewis acid[12]-induced intramolecular carbonyl-ene cyclizations. The cyclization reaction of ketones **3a**–**e** gave a mixture of two *cis*-3-hydroxy-3,4-disubstituted pyrrolidines **4a**–**e** and **5a**–**e** fused with a perhydrobenzoxazine structure and both diastereomers can be obtained as the major products depending on the reaction conditions (Scheme 2).

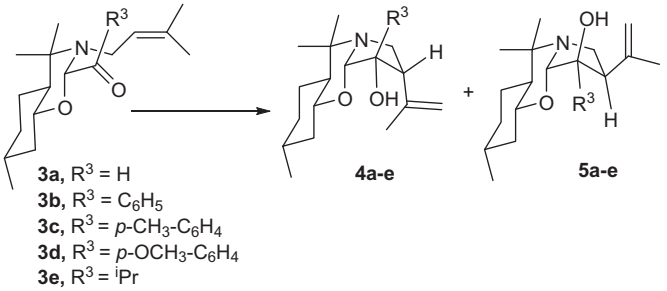
We believed that these more rigid structures might discriminate better between the two enantiotopic faces of the aldehyde within the transition state complex. Thus, we examined the catalytic potency of some of these decahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ols as chiral ligands in the asymmetric ethylation of naphthaldehyde. The data obtained are also summarized in Table 1. The results showed that both the chemical yield and the enantioselectivity of the products catalyzed by ligands **4** were low (<38% ee, entries 11–13). However, when ligands **5** were used, we found a great improvement not only in the enantioselectivity but also in the chemical yield (entries 14–18). The (*R*)-1-(2′-naphthyl)-1-propanol was obtained in 95% yield and 88% ee in the presence of **5a**

Table 1
Addition of Et_2Zn to 2-naphthaldehyde promoted by chiral perhydro-1,3-benzoxazines **2a**–**j**, **4b**, **4d**, **4e**, **5a**–**e**, **6b**, **6e**, **7a**, **7b** and **7e**



Entry[a]	Ligand	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**2a**	80	25	(*S*)
2	**2b**	50	6	(*S*)
3	**2c**	80	39	(*S*)
4	**2d**	79	17	(*S*)
5	**2e**	83	44	(*S*)
6	**2f**	80	54	(*S*)
7	**2g**	61	30	(*R*)
8	**2h**	52	21	(*R*)
9	**2i**	65	28	(*R*)
10	**2j**	38	25	(*R*)
11	**4b**	12	15	(*S*)
12	**4d**	48	9	(*S*)
13	**4e**	60	38	(*S*)
14	**5a**	95	88	(*R*)
15	**5b**	85	75	(*R*)
16	**5c**	85	76	(*R*)
17	**5d**	80	64	(*R*)
18	**5e**	90	52	(*R*)
19	**6b**	18	15	(*S*)
20	**6e**	68	21	(*S*)
21	**7a**	93	80	(*R*)
22	**7b**	95	97	(*R*)
23	**7e**	44	28	(*R*)

[a] All reactions were carried out for 24 h under argon.
[b] Yield refers to pure compounds after column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column.
[d] The absolute configuration was assigned by comparing the sign of the specific rotation and t_R of the HPLC analysis with that of the literature data.



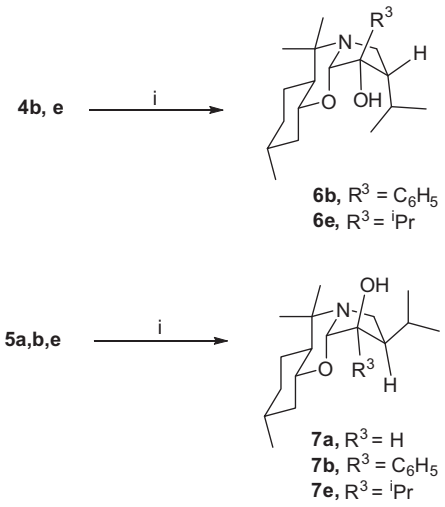
Scheme 2. Diastereoselective keto-ene cyclization of compounds **3a**–**e**.

(entry 14) and 85% yield and 75% ee in the presence of **5b** (entry 15). Encouraged by these results, we decided to increase the steric volume in the vicinity of the hydroxyl group by catalytic hydrogenation of the prenyl group to an isopropyl group using hydrogen and Pd/C catalyst in ethanol (Scheme 3).

The new ligands **6b**, **6e**, **7a**, and **7e** did not improve the ee in the ethylation of 2-naphthaldehyde (compare entries 11, 13, 14, and 18 vs entries 19, 20, 21, and 23). However, it was surprising that when ligand **7b** was used, both the enantioselectivity and the chemical yield were excellent (entry 22, 97% ee, 95% yield).

In order to better understand the applications and limitations of the ligand **7b**, different aldehydes were carefully examined. The results are summarized in Table 2.

Optically active secondary alcohols with >93% ee and excellent chemical yields were obtained in the enantioselective addition of diethylzinc to aromatic aldehydes. Aromatic aldehydes bearing electron-donating and electron-withdrawing groups behaved

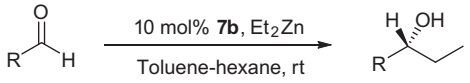


Scheme 3. Reagents and conditions: (i) 10 wt % Pd/C, H_2, EtOH, rt, **6b** (93%), **6e** (78%), **7a** (92%), **7b** (93%), **7e** (80%).

similarly. The best asymmetric induction was found when using *p*-trifluoromethylbenzaldehyde as the substrate with a strong electron-withdrawing $-CF_3$ group which gave up to 99% ee (Table 2, entry 12). The enantioselectivity was also excellent for heterocyclic aldehydes (Table 2, entries 15 and 16). Most gratifyingly, our ligand was also very effective in the enantioselective addition of diethylzinc to the aliphatic hydrocinnamaldehyde (entry 17) and α,β-unsaturated aldehydes (entries 13 and 14). Only in the case of cinnamaldehyde did the ee drop below 90%.[13] In addition to the high enantioselectivity, the reaction time decreased significantly. In all cases, the reactions were completed in less than 45 min.

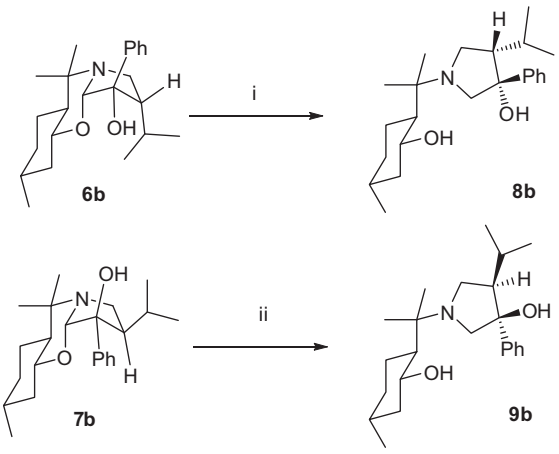
For the best catalyst **7b**, the relationship between the amount of the catalyst and the enantioselectivity observed was also examined. When the quantity of **7b** was decreased from 10 mol % to 1 mol %, the enantioselectivity in the ethylation of 2-naphtaldehyde remained at 96%, although it was necessary to increase the reaction time up to 12 h to obtain a 95% chemical yield. A lower amount of catalyst (0.2 mol % **7b**) led to a slight decrease of both the enantioselectivity (92% ee) and the yield of the reaction (90% yield).

Table 2
Addition of Et_2Zn to aldehydes promoted by chiral perhydro-1,3-benzoxazine **7b**



Entry[a]	Aldehyde	Yield[b] (%)	ee[c] (%)
1	2-Naphthaldehyde	95	97
2	1-Naphthaldehyde	89	96
3	Benzaldehyde	94	94
4	*o*-Tolylaldehyde	96	97
5	*o*-Anisaldehyde	97	95
6	*o*-Chlorobenzaldehyde	97	94
7	*o*-Bromobenzaldehyde	99	93
8	*m*-Chlorobenzaldehyde	87	96
9	*p*-Tolylaldehyde	98	97
10	*p*-Anisaldehyde	99	97
11	*p*-Chlorobenzaldehyde	98	97
12	*p*-Trifluoromethylbenzaldehyde	99	99
13	(*E*)-Cinnamaldehyde	93	88
14	(*E*)-α-Methylcinnamaldehyde	93	94
15	2-Furylcarboxaldehyde	83	95
16	2-Thiophenecarboxaldehyde	94	96
17	3-Phenylpropionaldehyde	90	93

[a] All reactions were processed for 30–45 min under argon.
[b] Yield refers to pure compounds after column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column.

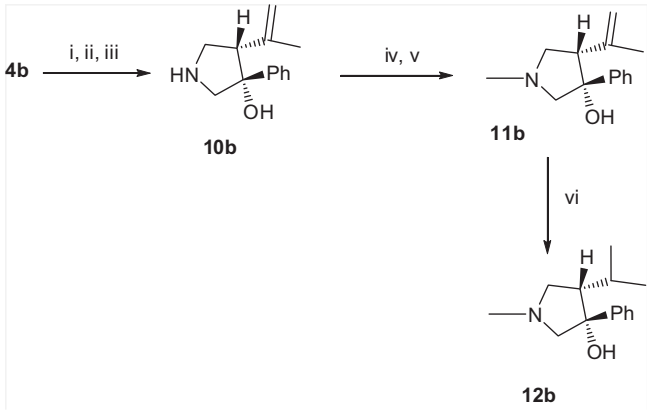


Scheme 4. Reagents and conditions: (i) $LiAlH_4$, $AlCl_3$, THF, −10 °C, 92%; (ii) $NaBH_3CN$, MeOH, HCl 0.1 M (pH ~4), 60 °C, 83%.

Table 3
Addition of Et_2Zn to aldehydes promoted by chiral perhydro-1,3-benzoxazines **8b** and **9b**, and pyrrolidines **11b** and **12b**

Entry[a]	Ligand	Aldehyde	Yield[b] (%)	ee[c,d] (%)
1	**8b**	2-Naphthaldehyde	84	53 (*S*)
2	**8b**	*p*-Anisaldehyde	66	40 (*S*)
3	**9b**	2-Naphthaldehyde	71[e]	9 (*S*)
4	**9b**	*p*-Chlorobenzaldehyde	67[e]	4 (*S*)
5	**9b**	*p*-Anisaldehyde	69[e]	7 (*S*)
6	**11b**	2-Naphthaldehyde	90	65 (*S*)
7	**11b**	*p*-Chlorobenzaldehyde	93	71 (*S*)
8	**11b**	*p*-Anisaldehyde	89	61 (*S*)
9	**11b**	1-Naphthaldehyde	83	62 (*S*)
10	**12b**	2-Naphthaldehyde	95	87 (*S*)
11	**12b**	*p*-Chlorobenzaldehyde	93	88 (*S*)
12	**12b**	*p*-Anisaldehyde	96	89 (*S*)
13	**12b**	1-Naphthaldehyde	91	86 (*S*)

[a] The reactions were processed for 24 h under argon.
[b] Yield refers to pure compounds after column chromatography.
[c] Enantiomeric excess was determined by HPLC analysis using a chiral column.
[d] The absolute configuration was assigned by comparing the sign of the specific rotation and t_R of the HPLC analysis with that of literature data.
[e] The reactions were processed for 48 h under argon.



Scheme 5. Reagents and conditions: (i) $LiAlH_4$, $AlCl_3$, THF, −10 °C; (ii) PCC, CH_2Cl_2, 4 Å molecular sieves, rt; (iii) KOH, H_2O–MeOH–THF, rt, 48% from **4b**; (iv) dimethyl pyrocarbonate, CH_2Cl_2, rt; (v) $LiAlH_4$, Et_2O, rt, 70%; (vi) 10 wt % Pd/C, H_2, EtOH, rt, 80%.

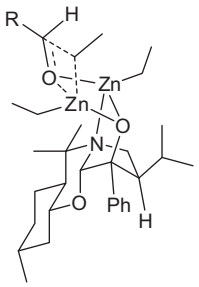


Figure 1. Proposed transition state for the asymmetric addition with **7b**.

On the other hand, ligand **7b** could be recovered in more than 80% yield after the reaction had been finished by quenching by the addition of an aqueous ammonium chloride solution, diethyl ether extraction, and chromatography purification. The recovered ligand **7b** could be reused in two subsequent cycles as the catalyst in the reaction of ethylation of 2-naphthaldehyde, giving the same results as freshly prepared catalyst without an obvious decrease in chemical yield or ee values (cycle 1, 95% yield, 95% ee and cycle 2, 95% yield, 94% ee).

With the aim of evaluating the influence and contribution exerted by the benzoxazine ring in the asymmetric induction, we tested the behavior as chiral ligands of the amino menthol derivatives **8b** and **9b**. Ligands **8b** and **9b** were obtained by the reductive ring opening of the 1,3-oxazine ring of **6b** and **7b** with aluminum hydride and sodium cyanoborohydride, respectively (Scheme 4). As shown in Table 3, the ethylation of aromatic aldehydes in the presence of **8b** gave (*S*)-alcohols in acceptable chemical yields but with modest enantioselectivity (entries 1 and 2) while negligible enantioselectivity was induced by **9b** (entries 3–5).

On the other hand, as previously described,[11] the reductive ring opening of the 1,3-oxazine ring of **4b** and elimination of the menthol appendage by oxidation with PCC followed by treatment with a 2.5 M solution of KOH in THF–MeOH–H_2O yielded the corresponding 3-hydroxypyrrolidine derivative **10b** which could be easily methylated by treatment with dimethyl pyrocarbonate, followed by LAH reduction of the resulting carbamate (Scheme 5). The resulting 3-hydroxypyrrolidinol **11b** was also tested as a chiral ligand in the addition of Et_2Zn to aldehydes. 1-Substituted propanols with an (*S*)-configuration were obtained in good yields but with moderate enantioselectivities (Table 3, entries 6–9). The yields and the enantioselectivities improved considerably when 3-hydroxypyrrolidinol **12b**, obtained by catalytic hydrogenation of the prenyl to an isopropyl group, was tested but the enantioselectivity remained below 90%.[14] These results suggest that the presence of the oxazine ring is crucial for getting good enantioselectivities.

We propose the transition state shown in Figure 1, in agreement with the *anti*-transition state structure proposed by Noyori,[15] to account for the stereoselectivity observed with chiral ligand **7b**. In this transition state, the transfer of the ethyl group occurs to the *re*-face of the aldehyde, leading to the (*R*)-enantiomer of the alcohols.

3. Conclusion

In conclusion, we have developed a highly effective, new perhydro-1,3-benzoxazine-based chiral ligand **7b** for the diethylzinc addition reaction to aldehydes under mild conditions. A wide variety of secondary alcohols have been obtained in up to 99% yields and 99% ee's. This catalyst is a stable crystalline solid and can be conveniently prepared on a gram scale from (−)-8-aminomenthol in four simple steps and with a good yield.[11] The catalytic effect of this ligand to other asymmetric reactions is currently under investigation in our laboratory and will be reported in due course.

4. Experimental

4.1. Materials and methods

All reactions were carried out in anhydrous solvents under an argon atmosphere and in oven-dried glasswares. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) were registered in $CDCl_3$ as solvent and chemical shifts are given relative to TMS as an internal reference. Specific rotations were determined on a digital polarimeter using a Na lamp and concentration is given in g per 100 mL. Melting points were determined in open capillary tubes and are uncorrected. Solvents were dried by standard methods. TLC was performed on glass-backed plates coated with silica gel 60 with F254 indicator; the chromatograms were visualized under UV light and/or by staining with a Ce/Mo reagent. Flash chromatography was carried out on silica gel 60 (230–240 mesh). Chiral HPLC analysis was performed using a Daicel Chiralcel OD column (250 × 4.6 mm), Chiralpak AS-H or Chiralpak AD-H column (250 × 4.6 mm). UV detection was monitored at 220 nm or at 254 nm.

Compounds **2a**,[16] **2c–e**,[9] **2h–j**,[10] **4b**,**e**,[11] **4d**,[12] **5a**,**b**,**e**[11] and **5c**,**d**[12] have been previously described.

4.2. Synthesis of octahydro-1,3-benzoxazines 2a–f

A solution of (−)-8-aminomenthol (2.0 g, 11.7 mmol) and the appropriate aldehyde (12.9 mmol) in toluene (50 mL) was refluxed until the reaction was complete (TLC 3–6 h). The solvent was evaporated under vacuum, and the residue was purified by recrystallization and/or by flash chromatography on silica gel using hexane/EtOAc 8:1 as eluent. For the preparation of bisperhydrobenzoxazine **2f**, only 6.45 mmol of isophthalaldehyde were used.

4.2.1. (2*S*,4a*S*,7*R*,8a*R*)-2-Isopropyl-4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine 2b

Yield: 88%. Colorless oil. $[\alpha]_D^{25} = +7.8$ (*c* 1.1, $CHCl_3$) .^{1}H NMR (δ): 0.85–1.05 (m, 4H); 0.90 (d, 3H, *J* = 6.5 Hz); 0.93 (d, 6H, *J* = 6.7 Hz); 1.05 (s, 3H); 1.06 (s, 3H); 1.18 (m, 1H); 1.48–1.75 (m, 4H); 1.91 (m, 1H); 3.34 (td, 1H, J_1 = 10.2 Hz, J_2 = 4.0 Hz); 4.00 (d, 1H, *J* = 5.2 Hz). ^{13}C NMR (δ): 17.4 (CH_3); 18.1 (CH_3); 19.6 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 29.6 (CH_3); 31.2 (CH); 32.8 (CH); 34.9 (CH_2); 41.6 (CH_2); 50.8 (C); 51.8 (CH); 74.7 (CH); 86.5 (CH). IR (Film): 3310, 1745, 760 cm^{-1}. HRMS: calcd for $C_{14}H_{28}NO$ $[M+H]^+$ 226.217, found 226.2169.

4.2.2. (2*S*,4a*S*,7*R*,8a*R*,2′*S*,4a′*S*,7′*R*,8a′*R*)-Benzene-1,3-diylbis(4,4,7-trimethyloctahydro-2*H*-1,3-benzoxazine) 2f

Yield: 86%. Colorless solid. Mp: 130–131 °C (from ethanol). $[\alpha]_D^{25} = +75.8$ (*c* 1.2, $CHCl_3$) ^{1}H NMR (δ): 0.86–1.07 (m, 4H); 0.95 (d, 6H, *J* = 6.5 Hz); 1.10–1.19 (m, 4H); 1.12 (s, 6H); 1.20 (s, 6H); 1.52 (m, 2H); 1.60 (m, 2H); 1.66–1.75 (m, 4H); 2.01 (m, 2H); 3.58 (td, 2H, J_1 = 10.3, Hz, J_2 = 4.2 Hz); 5.34 (s, 2H); 7.30 (m, 1H); 7.39 (m, 2H); 7.58 (s, 1H). ^{13}C NMR (δ): 19.6 (2 CH_3); 22.3 (2 CH_3); 25.6 (2 CH_2); 29.8 (2 CH_3); 31.4 (2 CH); 35.0 (2 CH_2); 41.6 (2 CH_2); 51.5 (2 CH); 51.7 (2 C); 75.2 (2 CH); 83.7 (2 CH); 123.6 (CH); 125.5 (2 CH); 128.3 (2 CH); 141.1 (C). IR (Nujol): 3300, 3050, 1720, 1605, 750, 705, 610 cm^{-1}. HRMS: calcd for $C_{28}H_{45}N_2O_2$ $[M+H]^+$ 441.3481, found 441.3463.

4.3. Preparation of benzoxazine 2g

A mixture of (−)-8-aminomenthol (2.5 g, 15 mmol) and phenylglyoxal (2.01 g, 15 mmol) in dichloromethane (75 mL) was stirred for 24 h at room temperature. The solvent was removed under vacuum, quantitatively yielding the 2-benzoyl perhydrobenzoxazine. This perhydrobenzoxazine was dissolved in anhydrous ethyl ether (50 mL), cooled to 0 °C, and a commercial (Aldrich) ether 3.0 M

solution of phenylmagnesium bromide (7.0 mL) was added dropwise, under an argon atmosphere. Stirring was continued until the disappearance of the starting ketone (TLC, 45 min). The reaction was quenched with a saturated aqueous solution of NH_4Cl (50 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated at reduced pressure, and the residue was purified by flash chromatography on silica gel, using hexanes/ethyl acetate 60:1 as eluent.

4.3.1. [(2*S*,4a*S*,7*R*,8a*R*)-4,4,7-Trimethyloctahydro-2*H*-1,3-benzoxazin-2-yl](diphenyl)methanol 2g

Yield: 83%. Colorless solid. Mp: 91–92 °C (from ethanol). $[\alpha]_D^{25} = +50.5$ (*c* 1.0, $CHCl_3$). ^1H NMR (δ): 0.73–1.08 (m, 4H); 0.81 (d, 3H, *J* = 6.6 Hz); 0.91 (s, 3H); 0.99 (s, 3H); 1.23 (m, 1H); 1.36 (m, 1H); 1.52–1.60 (m, 2H); 1.82 (m, 1H); 3.41 (td, 1H, J_1 = 10.3 Hz, J_2 = 4.0 Hz); 3.99 (s, 1H); 4.87 (s, 1H); 7.20–7.23 (m, 6H); 7.36–7.40 (m, 2H); 7.55–7.59 (m, 2H). ^{13}C NMR (δ): 19.6 (CH_3); 22.2 (CH_3); 25.4 (CH_2); 29.8 (CH_3); 31.3 (CH); 34.9 (CH_2); 41.4 (CH_2); 51.5 (C); 51.7 (CH); 75.6 (CH); 77.2 (C); 86.4 (CH); 126.8 (CH); 126.9 (CH); 127.0 (2 CH); 127.4 (2 CH); 127.6 (2 CH); 127.7 (2 CH); 144.1 (C); 144.2 (C). HRMS: calcd for $C_{24}H_{32}NO_2$ $[M+H]^+$ 366.2433, found 366.2413.

4.4. Synthesis of octahydro-1,3-benzoxazines 6b, 6e, 7a, 7b and 7e

A mixture of the corresponding 1,3-benzoxazine **4b**, **4e**, **5a**, **5b** or **5e** (4.0 mmol) and 10 wt % palladium on carbon (75 mg) in ethanol (30 mL) was stirred at room temperature under H_2 at atmospheric pressure until the reaction was completed (TLC, 24–48 h). The catalyst was separated by filtration over a pad of Celite. The solvent was eliminated on a rotavapor, and the residue was purified by flash chromatography on silica gel, using a mixture of hexane–ethyl acetate as eluent.

4.4.1. (2*S*,3*R*,3a*S*,4a*R*,6*R*,8a*S*)-2-Isopropyl-6,9,9-trimethyl-3-phenyldecahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ol 6b

Yield: 93%. Colorless oil. $[\alpha]_D^{25} = -52.2$ (*c* 1.0, $CHCl_3$). ^1H NMR (δ): 0.73 (d, 3H, *J* = 6.2 Hz), 0.86 (d, 3H, *J* = 6.2 Hz), 0.93 (d, 3H, *J* = 6.5 Hz), 0.89–1.18 (m, 3H), 1.14 (s, 3H), 1.21 (s, 3H), 1.42–1.52 (m, 2H), 1.66 (m, 1H), 1.72 (m, 1H), 1.87–2.06 (m, 3H), 2.96 (dd, 1H, J_1 = 8.7 Hz, J_2 = 8.1 Hz), 3.12 (dd, 1H, J_1 = 8.1 Hz, J_2 = 7.6 Hz), 3.45 (td, 1H, J_1 = 10.5 Hz, J_2 = 4.2 Hz), 3.75 (s, 1H), 4.55 (s, 1H), 7.19–7.24 (m, 1H), 7.27–7.36 (m, 2H); 7.67–7.68 (m, 2H). ^{13}C NMR (δ): 19.2 (CH_3), 21.7 (CH_3), 22.0 (CH_3), 22.2 (CH_3), 24.8 (CH_2), 27.0 (CH_3), 28.4 (CH), 31.2 (CH), 34.9 (CH_2), 41.1 (CH_2), 45.1 (CH), 48.7 (CH_2), 53.5 (C), 56.9 (CH), 75.0 (CH), 79.8 (C), 92.8 (CH), 124.6 (2 CH), 126.0 (CH), 127.7 (2 CH), 148.8 (C). IR (Film): 3510, 3060, 3025, 1605, 705, 670, 640 cm^{-1}. HRMS: calcd for $C_{23}H_{36}NO_2$ $[M+H]^+$ 358.2746, found 358.2744.

4.4.2. (2*S*,3*S*,3a*S*,4a*R*,6*R*,8a*S*)-2,3-Diisopropyl-6,9,9-trimethyldecahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ol 6e

Yield: 78%. Colorless oil. $[\alpha]_D^{25} = -36.8$ (*c* 0.9, $CHCl_3$). ^1H NMR (δ): 0.86 (d, 3H, *J* = 6.3 Hz), 0.90–1.11 (m, 3H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.92 (d, 3H, *J* = 6.5 Hz), 0.94 (d, 3H, *J* = 6.8 Hz), 0.98 (d, 3H, *J* = 6.3 Hz), 1.08 (s, 3H), 1.11 (s, 3H), 1.40–1.53 (m, 2H), 1.60 (m, 1H), 1.68–1.85 (m, 4H), 1.90 (m, 1H), 2.80–288 (m, 2H), 3.21 (s, 1H), 3.46 (td, 1H, J_1 = 10.5 Hz, J_2 = 4.2 Hz), 4.49 (s, 1H). ^{13}C NMR (δ): 17.5 (CH_3), 17.7 (CH_3), 20.8 (CH_3), 21.0 (CH_3), 22.3 (CH_3), 23.2 (CH_3), 24.9 (CH_2), 26.7 (CH_3), 28.2 (CH), 31.3 (CH), 35.1 (CH_2), 36.8 (CH), 41.3 (CH_2), 43.5 (CH), 47.9 (CH_2), 48.1 (CH), 53.0 (C), 74.9 (CH), 81.6 (C), 87.2 (CH). IR (Film): 3544, 3200, 2930, 1655, 1265, 710, 680 cm^{-1}. HRMS: calcd for $C_{20}H_{38}NO_2$ $[M+H]^+$ 324.2903, found 324.2891.

4.4.3. (2*R*,3*S*,3a*S*,4a*R*,6*R*,8a*S*)-2-Isopropyl-6,9,9-trimethyldecahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ol 7a

Yield: 92%. Colorless solid. Mp: 73–74 °C (from ethanol). $[\alpha]_D^{25} = -45.9$ (*c* 1.1, $CHCl_3$). ^1H NMR (δ): 0.86 (d, 3H, *J* = 6.7 Hz), 0.88 (d, 3H, *J* = 6.7 Hz), 0.88–1.03 (m, 3H), 0.96 (d, 3H, *J* = 6.5 Hz), 1.10 (s, 3H), 1.13 (s, 3H), 1.35–1.42 (m, 2H), 1.56 (m, 1H), 1.65–1.75 (m, 2H), 1.83 (m, 1H), 1.84–2.00 (m, 2H), 2.60 (dd, 1H, J_1 = 9.1 Hz, J_2 = 7.1 Hz), 3.10 (dd, 1H, J_1 = 9.7 Hz, J_2 = 9.1 Hz), 3.39 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.1 Hz), 3.89 (s, 1H), 4.65 (s, 1H). ^{13}C NMR (δ): 21.3 (CH_3), 21.7 (2 CH_3), 22.2 (CH_3), 24.7 (CH_2), 26.2 (CH_3), 27.8 (CH), 31.2 (CH), 35.0 (CH_2), 41.4 (CH_2), 43.2 (CH), 47.7 (CH_2, CH), 52.7 (C), 74.2 (CH), 74.5 (CH), 91.3 (CH). IR (Nujol): 3500 (br), 1735, 1030, 735, 710 cm^{-1}. HRMS: calcd for $C_{17}H_{32}NO_2$ $[M+H]^+$ 282.2433, found 282.2431.

4.4.4. (2*R*,3S,3a*S*,4a*R*,6*R*,8a*S*)-2-Isopropyl-6,9,9-trimethyl-3-phenyldecahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ol 7b

Yield: 93%. Colorless solid. Mp: 91–92 °C (from ethanol). $[\alpha]_D^{25} = -92.9$ (*c* 1.1, $CHCl_3$). ^1H NMR (δ): 0.47 (d, 3H, *J* = 6.5 Hz), 0.88 (d, 3H, *J* = 6.5 Hz), 0.89 (d, 3H, *J* = 6.5 Hz), 0.90–1.10 (m, 3H), 1.13 (s, 3H), 1.14 (s, 3H), 1.37 (m, 1H), 1.43–1.60 (m, 2H), 1.69 (m, 1H), 1.72–1.90 (m, 2H), 2.52 (td, 1H, J_1 = 9.9 Hz, J_2 = 6.0 Hz), 2.72 (dd, 1H, J_1 = 9.1 Hz, J_2 = 6.0 Hz), 2.89 (s, 1H), 3.22 (td, 1H, J_1 = 10.4 Hz, J_2 = 4.0 Hz), 3.39 (dd, 1H, J_1 = 9.9 Hz, J_2 = 9.1 Hz), 4.30 (s, 1H), 7.18–7.31 (m, 3H), 7.63–7.63 (m, 2H). ^{13}C NMR (δ): 22.3 (CH_3), 22.4 (CH_3); 22.5 (2 CH_3), 24.8 (CH_2), 26.2 (CH_3), 29.6 (CH), 31.2 (CH), 35.2 (CH_2), 41.2 (CH_2), 42.7 (CH), 49.0 (CH_2), 51.1 (CH), 53.1 (C), 74.4 (CH), 81.4 (C), 93.7 (CH), 126.4 (CH), 126.9 (2 CH), 127.0 (2 CH_3), 140.7 (C). IR (Nujol): 3505, 3060, 2935, 1500, 1035, 700 cm^{-1}. HRMS: calcd for $C_{23}H_{36}NO_2$ $[M+H]^+$ 358.2746, found 358.2741.

4.4.5. (2*R*,3*R*,3a*S*,4a*R*,6*R*,8a*S*)-2,3-Diisopropyl-6,9,9-trimethyldecahydro-4a*H*-pyrrolo[2,1-*b*][1,3]benzoxazin-3-ol 7e

Yield: 80%. Colorless oil. $[\alpha]_D^{25} = -51.5$ (*c* 0.7, $CHCl_3$). ^1H NMR (δ): 0.83–1.15 (m, 3H), 0.91 (d, 3H, *J* = 6.6 Hz), 0.94 (d, 3H, *J* = 6.6 Hz), 0.97 (d, 3H, *J* = 6.6 Hz), 1.01 (d, 3H, *J* = 6.9 Hz), 1.05 (d, 3H, *J* = 6.9 Hz), 1.09 (s, 3H), 1.13 (s, 3H), 1.39–1.42 (m, 2H); 1.48 (m, 1H); 1.71 (m, 1H), 1.88 (m, 1H), 1.90–210 (m, 3H), 2.13 (m, 1H), 2.68 (dd, 1H, J_1 = 8.9 Hz, J_2 = 5.3 Hz), 3.14 (dd, 1H, J_1 = 9.8 Hz, J_2 = 8.9 Hz), 3.29 (td, 1H, *J* = 10.4 Hz, J_2 = 4.1 Hz), 4.43 (s, 1H). ^{13}C NMR (δ): 17.7 (CH_3), 18.8 (CH_3), 20.8 (CH_3), 22.3 (CH_3), 22.4 (CH_3), 22.9 (CH_3), 24.9 (CH_2), 26.3 (CH_3), 28.2 (CH), 31.4 (CH), 32.7 (CH), 35.2 (CH_2), 41.4 (CH_2), 42.7 (CH), 46.2 (CH), 47.0 (CH_2), 52.9 (C), 74.4 (CH), 83.9 (C), 93.0 (CH). IR (Film): 3530, 2930, 760, 715 cm^{-1}. HRMS: calcd for $C_{20}H_{38}NO_2$ $[M+H]^+$ 324.2903, found 324.2894.

4.5. Preparation of amino alcohol 8b

Dry $AlCl_3$ (133 mg, 1.0 mmol) was added, in portions, to a suspension of $LiAlH_4$ (114 mg, 3.0 mmol) in anhydrous THF (15 mL) cooled to −10 °C. The mixture was stirred for 10 min and a solution of **6b** (215 mg, 0.6 mmol) in dry THF (10 mL) was added slowly. The reaction mixture was stirred for 8 min at −10 °C and the reaction was quenched by the addition of a 20% NaOH solution (1.5 mL). The resulting mixture was filtered. The solid was washed with EtOAc, and the organic layer was dried ($MgSO_4$). The solvent was eliminated under reduced pressure and the residue was chromatographed on silica gel with hexane/EtOAc 3:1 as eluent.

4.5.1. (3*R*,4*S*)-1-{2-[1*S*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl]-propan-2-yl}-4-isopropyl-3-phenylpyrrolidin-3-ol 8b

Yield: 92%. Colorless solid. Mp: 103–105 °C (from hexane/EtOAc 100:1). $[\alpha]_D^{25} = -52.9$ (*c* 1.1, $CHCl_3$). ^1H NMR (333 K) (δ): 0.48 (d,

3H, J = 6.6 Hz), 0.81–1.28 (m, 3H), 0.89 (d, 6H, J = 6.6 Hz), 1.02 (s, 3H), 1.17 (s, 3H), 1.39–1.48 (m, 2H), 1.56–1.68 (m, 2H), 1.82 (m, 1H), 1.93 (m, 1H), 2.12–2.23 (m, 2H), 2.92–3.00 (m, 2H), 3.14–3.20 (m, 2H), 3.65 (td, 1H, J_1 = 10.2 Hz, J_2 = 4.0 Hz), 7.19 (m, 1H), 7.26–7.33 (m, 2H), 7.46–7.50 (m, 2H), 8.38 (br s, 1H). ^{13}C NMR (333 K) (δ): 16.9 (CH_3), 21.4 (CH_3), 22.0 (CH_3), 22.1 (CH_3), 22.2 (CH_3), 25.8 (CH_2), 27.6 (CH), 31.1 (CH), 35.2 (CH_2), 44.4 (CH_2), 49.0 (CH), 49.9 (CH_2), 55.6 (CH), 59.6 (C), 64.3 (CH_2), 73.0 (CH), 80.8 (C), 125.1 (2 CH), 126.6 (CH), 128.1 (2 CH), 145.1 (C). IR (Nujol): 3300, 3060, 760, 700 cm^{-1}. HRMS: calcd for $C_{23}H_{38}NO_2$ $[M+H]^+$ 360.2903, found 360.2903.

4.6. Preparation of amino alcohol 9b

At first, $NaBH_3CN$ (113 mg, 1.8 mmol) was added to a solution of **7b** (215 mg, 0.6 mmol) in methanol (25 mL) cooled to 0 °C and acidified to pH ~4 by an aqueous solution of HCl 0.1 M. The mixture was heated at 60 °C and the pH was maintained at 4 by a periodic addition of 0.1 M HCl until the reaction was complete (TLC). The solvents were eliminated under reduced pressure. The residue was dissolved in CH_2Cl_2 (40 mL), and an aqueous solution of KOH 2.5 M (20 mL) was added. The mixture was stirred for 30 min, after which the organic layer was decanted, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic fractions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash chromatography on silica gel using a mixture of hexane/EtOAc 3:1 as eluent.

4.6.1. (3*S*,4*R*)-1-{2-[1*S*,2*R*,4*R*)-2-Hydroxy-4-methylcyclohexyl]-propan-2-yl}-4-isopropyl-3-phenylpyrrolidin-3-ol 9b

Yield: 83%. Colorless solid. Mp: 175–176 °C (from hexane/EtOAc 100:1). $[\alpha]_D^{25} = -12.2$ (c 0.90, $CHCl_3$). ^{1}H NMR (333 K) (δ): 0.57 (d, 3H, J = 5.7 Hz), 0.93–1.20 (m, 3H), 0.93 (d, 6H, J = 6.4 Hz), 1.02 (s, 3H), 1.17 (s, 3H), 1.46 (m, 1H), 1.58–1.75 (m, 3H), 1.83–2.13 (m, 3H), 2.20 (m, 1H), 2.77 (t, 1H, J = 9.3 Hz), 3.03–3.15 (m, 2H), 3.30 (t, 1H, J = 8.3 Hz), 3.68 (m, 1H), 7.21 (m, 1H), 7.28–7.34 (m, 2H), 7.49–7.52 (m, 2H), 8.19 (br s, OH). ^{13}C NMR (333 K) (δ): 17.6 (CH_3), 21.1 (CH_3), 22.0 (CH_3), 22.1 (CH_3), 22.2 (CH_3), 26.1 (CH_2), 27.5 (CH), 31.2 (CH), 35.4 (CH_2), 44.6 (CH_2), 48.8 (CH), 49.7 (CH_2), 56.3 (CH), 59.3 (C), 65.0 (CH_2), 73.1 (CH), 80.8 (C), 124.8 (2 CH), 126.6 (CH), 128.1 (2 CH), 146.5 (C). IR (Nujol): 3300, 3050, 760, 740, 700 cm^{-1}. HRMS: calcd for $C_{23}H_{38}NO_2$ $[M+H]^+$ 360.2903, found 360.2897.

4.7. Synthesis of pyrrolidine 10b

Dry $AlCl_3$ (334 mg, 2.5 mmol) was added, in portions, to a suspension of $LiAlH_4$ (285 mg, 7.5 mmol) in anhydrous THF (45 mL) cooled to −10 °C. The mixture was stirred for 10 min and a solution of **4b** (534 mg, 1.5 mmol) in dry THF (20 mL) was slowly added. The reaction mixture was stirred for 12 min at −10 °C and the reaction was quenched by the addition of a 20% NaOH solution (3 mL). The resulting mixture was filtered, after which the solid was washed with EtOAc, and the organic layer was dried ($MgSO_4$). The solvent was eliminated under reduced pressure and the residue was redissolved in CH_2Cl_2 (40 mL). Next, PCC (1.7 g, 8.0 mmol) and 4 Å molecular sieves (1.5 g) were added and the mixture was stirred at room temperature until the oxidation was finished (TCL, 6–8 h). The solvent was eliminated under reduced pressure, after which the residue was dissolved in a 15% aqueous solution of NaOH (25 mL), and the resulting solution was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. The solvents were eliminated under vacuum, after which the residue was taken up in a 2.5 M solution (16 mL) of KOH in THF/MeOH/H_2O (2:1:1), and the solution was stirred at room temperature for 5–6 h. After the elimination of the solvents under reduced pressure, the residue was dissolved in 50 mL of CH_2Cl_2 and washed with H_2O. The organic layer was dried over $MgSO_4$ and filtered, and the solvent was eliminated under vacuum to give an oily residue that was purified by flash chromatography on silica gel, using a mixture of MeOH/$CHCl_3$ 1:12 as eluent.

4.7.1. (3*R*,4*S*)-3-Phenyl-4-(prop-1-en-2-yl)pyrrolidin-3-ol 10b

Yield 48%. Colorless solid. Mp: 163–164 °C (from EtOAc). $[\alpha]_D^{25} = +94.9$ (c 0.7, MeOH). ^{1}H NMR (δ): 1.35 (s, 3H), 2.30 (br s, 2H), 3.12–3.32 (m, 5H), 4.90 (s, 1H), 5.05 (s, 1H), 7.24 (m, 1H), 7.32–7.37 (m, 2H), 7.50–7.52 (m, 2H). ^{13}C NMR (δ): 24.9 (CH_3), 50.4 (CH_2), 58.6 (CH), 63.6 (CH_2), 80.9 (C), 113.4 (CH_2), 125.1 (2 CH), 126.9 (CH), 128.3 (2 CH), 142.5 (C), 144.0 (C). IR (Nujol): 3300, 3100, 1640, 755, 710, 700, 670 cm^{-1}. HRMS: calcd for $C_{13}H_{18}NO$ $[M+H]^+$ 204.1388, found 204.1382.

4.8. Synthesis of pyrrolidine 11b

Dimethyl pyrocarbonate (198 mg, 1.5 mmol) was added to a solution of amine **10b** (203 mg, 1.0 mmol) in CH_2Cl_2 (16 mL) and the mixture was stirred for 20 min at room temperature. The solvent was removed by evaporation, after which the residue was dissolved in anhydrous diethyl ether (16 mL) and slowly added to a suspension of $LiAlH_4$ (213 mg, 5.6 mmol) in anhydrous diethyl ether (15 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction was quenched by addition of a 20% NaOH solution (2.0 mL). The mixture was then filtered off. The solids were washed with EtOAc and the solution was dried over anhydrous $MgSO_4$. The solvents were evaporated and the residue was purified by flash chromatography on silica gel with MeOH/$CHCl_3$ 1:12 as eluent.

4.8.1. (3*R*,4*S*)-1-Methyl-3-phenyl-4-(prop-1-en-2-yl)pyrrolidin-3-ol 11b

Yield: 70%. Colorless solid. Mp: 63–64 °C (from hexane). $[\alpha]_D^{25} = +78.5$ (c 0.3, $CHCl_3$). ^{1}H NMR (δ): 1.41 (s, 3H), 2.43 (s, 3H), 2.82 (d, 1H, J = 10.3 Hz), 2.87–3.05 (m, 3H), 3.13 (d, 1H, J = 10.3 Hz), 3.18 (t, 1H, J = 8.3 Hz), 4.86 (s, 1H), 4.99 (s, 1H), 7.27 (m, 1H), 7.24–7.39 (m, 2H), 7.54–7.57 (m, 2H). ^{13}C NMR (δ): 24.0 (CH_3), 42.4 (CH_3), 58.4 (CH), 58.8 (CH_2), 72.9 (CH_2), 80.5 (C), 113.1 (CH_2), 124.8 (2 CH), 126.5 (CH), 127.9 (2 CH), 142.3 (C), 145.4 (C). IR (Nujol): 3290, 3100, 1640, 760, 700 cm^{-1}. HRMS: calcd for $C_{14}H_{20}NO$ $[M+H]^+$ 218.1545, found 218.1532.

4.9. Synthesis of pyrrolidine 12b

A mixture of **11b** (130 mg, 0.60 mmol) and 10 wt % palladium on carbon (13 mg) in ethanol (15 mL) was stirred at room temperature under H_2 at atmospheric pressure until the reaction was complete (TLC, 24–48 h). The catalyst was separated by filtration over a pad of Celite, after which the solvent was eliminated on a rotavapor, and the residue was purified by flash chromatography on silica gel, using a mixture of MeOH/$CHCl_3$ 1:12 as eluent.

4.9.1. (3*R*,4*S*)-1-Methyl-4-isopropyl-3-phenylpyrrolidin-3-ol 12b

Yield: 80%. Colorless oil. $[\alpha]_D^{25} = -13.2$ (c 1.1,$CHCl_3$). ^{1}H NMR (δ): 0.56 (d, 3H, J = 6.5 Hz), 0.87 (d, 3H, J = 6.5 Hz), 1.88 (m, 1H), 2.26 (m, 1H), 2.39 (s, 3H), 2.70–2.79 (m, 3H), 2.88 (dd, 1H, J_1 = 9.5 Hz, J_2 = 7.3 Hz), 3.27 (br s, 1H), 7.22 (m, 1H), 7.29–7.34 (m, 2H), 7.53–7.56 (m, 2H). ^{13}C NMR (δ): 22.0 (CH_3), 22.3 (CH_3), 28.9 (CH), 42.2 (CH_3), 57.0 (CH), 59.8 (CH_2), 73.4 (CH_2), 81.3 (C), 124.9 (2CH), 126.3 (CH), 127.0 (2 CH), 144.7 (C). IR (Film): 3400, 3100, 3060, 3030, 1600, 765, 700, 640 cm^{-1}. HRMS: calcd for $C_{14}H_{22}NO$ $[M+H]^+$ 220.1701, found .220.1689.

4.10. General procedure for the addition of diethylzinc to aldehydes

To a flame-dried, argon-purged flask containing the ligand (0.2 mmol) and dry toluene (4 mL) was added a 1 M solution of diethylzinc in hexane (4 mL, 4 mmol, Aldrich) at room temperature. After being stirred for 10 min, a solution of the corresponding aldehyde (2.0 mmol) in dry toluene (4 mL) was added and allowed to react at room temperature until the reaction was complete (TLC, 30–45 min). The reaction was quenched with the dropwise addition of an aqueous ammonium chloride solution. The organic layer was separated and the aqueous phase was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, and dried over anhydrous $MgSO_4$. The solvents were eliminated under reduced pressure and the residue was purified by column chromatography on silica gel using mixtures of hexane/EtOAc as eluent. The ee values were determined by HPLC on a chiral stationary phase.

4.10.1. 1-(Naphthalen-2-yl)propan-1-ol

Chiracel OD; UV 254 nm; isopropanol/hexane = 10:90; flow 1 mL/min; t_R = 11.0 min for enantiomer (*S*), t_R = 12.1 min for enantiomer (*R*).

4.10.2. 1-(Naphthalen-1-y)propan-1-ol

Chiracel OD; UV 254 nm; isopropanol/hexane = 10:90; flow 1 mL/min; t_R = 9.4 min for enantiomer (*S*), t_R = 16.5 min for enantiomer (*R*).

4.10.3. 1-Phenylpropan-1-ol

Chiracel OD; UV 254 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 25.0 min for enantiomer (*R*), t_R = 28.8 min for enantiomer (*S*).

4.10.4. 1-(*o*-Tolyl)-1-propanol

Chiralpak AD-H; UV 220 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 14.5 min for enantiomer (*R*), t_R = 17.9 min for enantiomer (*S*).

4.10.5. 1-(*p*-Methoxyphenyl)propan-1-ol

Chiracel OD; UV 254 nm; isopropanol/hexane = 2:98; flow 1 mL/min; t_R = 21.0 min for enantiomer (*R*), t_R = 26.5 min for enantiomer (*S*).

4.10.6. 1-(*p*-Chlorophenyl)-1-propanol

Chiracel OD; UV 254 nm; isopropanol/hexane = 2:98; flow 1 mL/min; t_R = 14.7 min for enantiomer (*S*), t_R = 16.0 min for enantiomer (*R*).

4.10.7. 1-Phenyl-3-pentanol

Chiracel OD; UV 254 nm; isopropanol/hexane = 2:98; flow 1 mL/min; t_R = 20.6 min for enantiomer (*R*), t_R = 32.8 min for enantiomer (*S*).

4.10.8. (*E*)-1-Phenyl-1-penten-3-ol

Chiralpak AS-H; UV 254 nm; isopropanol/hexane = 2:98; flow 1 mL/min; t_R = 11.7 min for enantiomer (*R*), t_R = 13.9 min for enantiomer (*S*).

4.10.9. 1-(*o*-Bromophenyl)-1-propanol

Chiralpak AD-H; UV 220 nm;isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 18.5 min for enantiomer (*R*), t_R = 19.1 min for enantiomer (*S*).

4.10.10. 1-(*m*-Chlorophenyl)-1-propanol

Chiralpak AD-H; UV 254 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 21.5 min for enantiomer (*R*), t_R = 24.1 min for enantiomer (*S*).

4.10.11. 1-(*o*-Chlorophenyl)-1-propanol

Chiralpak AD-H; UV 254 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 16.7 min for enantiomer (*R*), t_R = 17.4 min for enantiomer (*S*).

4.10.12. 1-(*o*-Methoxyphenyl)-1-propanol

Chiralpak AD-H; UV 220 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 26.4 min for enantiomer (*S*), t_R = 34.5 min for enantiomer (*R*).

4.10.13. 1-(*p*-Tolyl)-1-propanol

Chiralpak AD-H; UV 220 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 19.5 min for enantiomer (*R*), t_R = 21.3 min for enantiomer (*S*).

4.10.14. 1-(*p*-Trifluoromethylphenyl)-1-propanol

Chiralpak AD-H; UV 254 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 17.4 min for enantiomer (*R*), t_R = 18.1 min for enantiomer (*S*).

4.10.15. 1-(2-Furyl)-1-propanol

Chiracel OD; UV 220 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 21.8 min for enantiomer (*R*), t_R = 25.0 min for enantiomer (*S*).

4.10.16. 1-(Thiophen-2-yl)-1-propanol

Chiracel OD; UV 220 nm; isopropanol/hexane = 1:99; flow 1 mL/min; t_R = 25.6 min for enantiomer (*R*), t_R = 28.5 min for enantiomer (*S*).

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