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(+)-Camphor-derived amino alcohols as ligands for the catalytic enantioselective addition of diethylzinc to benzaldehydes

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Abstract—1,7,7-Trimethyl-3-(pyrid-2-ylmethyl)bicyclo[2.2.1]heptan-2-ol **4** and its 2-phenyl, 2-methyl and 2-butyl analogs **5**–**7** were synthesized, characterized and used as ligands for the addition of diethylzinc to benzaldehydes. Best results were attained with 5 mol% of amino alcohol *trans*-**4** (2-*exo*,3-*endo*), in hexane/toluene at rt. Thus, (1*S*)-1-phenylpropanol was obtained in 96% yield and 89% e.e. An increase of the size of the 2-substituent had a dramatic effect on enantioselectivity and yield. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Oguni and Omi first reported[1] the ability of chiral 2-amino alcohols to catalyze the enantioselective addition of diethylzinc to benzaldehyde. After that report, a wide variety of related reactions have been described in the literature and excellent levels of enantioselection have been achieved.[2–8] 2-Amino alcohols are particularly suitable ligands for this reaction as they react with dialkylzinc to give a zinc alkoxide. The zinc atom of the zinc alkoxide then coordinates to the nitrogen of the 2-amino group, leading to the formation of a five-membered chelate. Both of the reaction mechanisms suggested[4] for the addition of alkylzinc reagents to aldehydes are based on the formation of a Zn-chelate.

Although the catalytic properties of 2-amino alcohols have been extensively studied,[4] the utility of 3- or 4-amino alcohols[2] as ligands for the addition of diethylzinc to aldehydes is clearly less well understood. Some 3- and 4-amino alcohols with rigid structures have been reported to efficiently catalyze[4–6] this reaction. In those cases, the zinc atom is potentially part of a six- or seven-membered ring. Such chelates seem to be sufficiently stable due to the rigidity of the ligand that limits the conformational freedom of the *O*- and *N*-atoms.

The rigidity of camphor-based 1,4-amino alcohols has been proven to efficiently control the addition of organozinc reagents to aldehydes.[6] As a continuation of our ongoing research on the design and synthesis of new and inexpensive chiral ligands for catalytic enantioselective reactions,[7] we decided to synthesize new amino alcohols with the camphor skeleton. Herein, we report the synthesis and characterization of a series of 2-(pyridylmethyl)borneols and isoborneols[8] and their use as precursors of chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde.

2. Results and discussion

The installation of a pyridylmethyl group at the alpha position of the carbonyl group of (+)-camphor was attained following the method described in the literature.[9] Thus, the sodium enolate of camphor was reacted with pyridine-2-carbaldehyde to give enone **2**[9d] (Scheme 1). Hydrogenation of **2** on Pd/C in ethanol rendered ketone **3** as a 2:1 *exo*/*endo* mixture of diastereoisomers (Scheme 1). That mixture can be isomerized to the *endo* diastereoisomer by treatment with sodium methoxide in methanol, as reported for the benzylidene analog of **3**.[9a]

Reduction of a 7.5:1 *endo*/*exo* mixture of ketone **3** with $LiAlH_4$ in THF afforded alcohol **4** as a ca. 1:1 mixture of *cis*-/*trans*-diastereoisomers. The relative stereochemistry of the newly formed stereocenter was assigned on the basis of coupling constants ($J_{H2,H3}$), taking the benzylidene analog of **4** as a model.[9a] Thus, $J_{H2,H3}$ is 13.6 Hz for 2-*endo*,3-*endo*, 12.4 Hz for 2-*exo*,3-*exo* and

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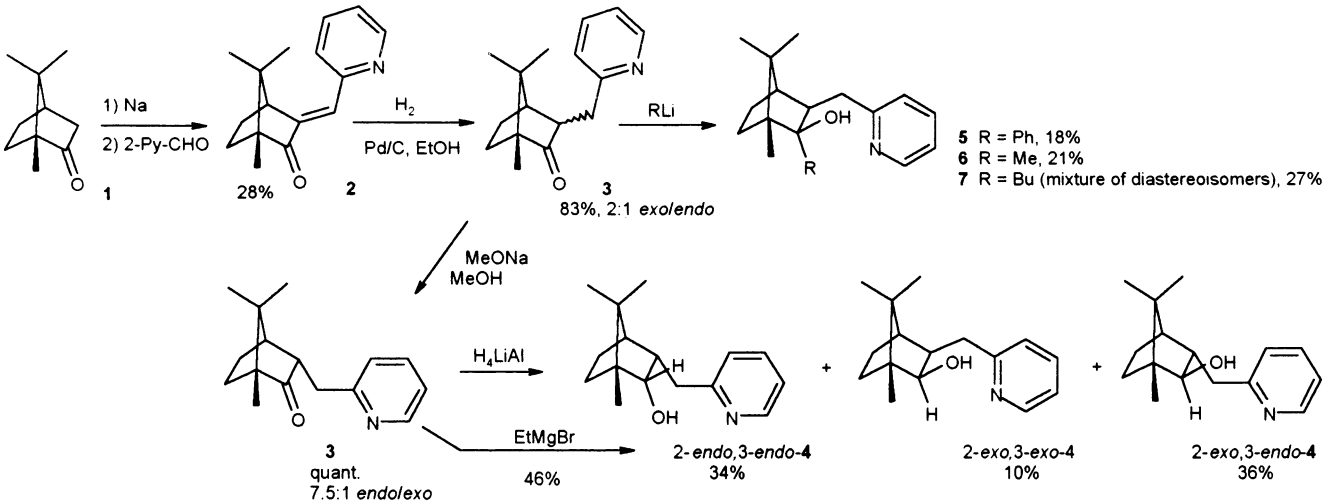


Scheme 1. Synthesis of 3-(2-pyridylmethyl)borneols and -isoborneols **4**–**7**.

4.0 Hz for 2-*exo*,3-*endo*. Separation of that mixture by flash chromatography rendered *cis*-**4** as a 3.2:1 mixture of 2-*endo*,3-*endo*/2-*exo*,3-*exo* diastereoisomeric alcohols, and *trans*-**4** (2-*exo*,3-*endo*) as a pure isomer (Scheme 1).

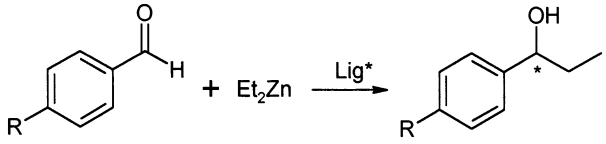
The small size of hydride allows both the *endo* and *exo* diastereomers of *endo*-**3** to be formed, the addition of more bulky nucleophiles such as PhLi or MeLi failed. However, the mentioned organometallic reagents added to ketone *exo*-**3** in polar solvents on the less hindered *endo* side,[10] affording alcohols **5** and **6** (Scheme 1). The yields of these additions were low as expected,[10] due to steric hindrance on the carbonyl group. Moreover, a competing base-promoted enolization takes place, as indicated by the deep red colors of the reaction mixtures. In contrast to those results, the addition of BuLi to a 2:1 *exo*/*endo* mixture of **3** in hexane provided an inseparable mixture of diastereomeric alcohols **7**. Probably, the *exo* attack was in that case possible as a result of the increased nucleophilicity of BuLi in an apolar solvent. When a 7.5:1 *endo*/*exo* mixture of **3** was treated with EtMgBr in THF no ethyl addition product was formed. Instead, *cis*-**4** was obtained as a 6:1 mixture of 2-*endo*,3-*endo*/2-*exo*,3-*exo* alcohols. Similar reductions of hindered ketones have been described in the literature.[11] It is interesting to note that EtMgBr is a more facially selective reducing agent than $LiAlH_4$ for the preparation of 2-*endo*,3-*endo*-**4** via reduction of **3**.

Ligands **4**–**7** were subsequently used in the catalytic addition of diethylzinc to benzaldehyde. The conditions used and the results obtained are summarized in Table 1.

When *trans*-**4** (2-*exo*,3-*endo*) (5 mol%) was used to catalyze the addition of diethylzinc to benzaldehyde at 22°C, (*S*)-1-phenylpropanol was formed in 96% yield and 89% e.e. (entry 1, Table 1). Those results did not improve either by lowering (entry 9), nor by increasing (entry 10) the temperature. This steady performance of the catalyst at various temperatures indicates that the active center of the catalyst is conformationally stable. In that light we conclude that fixing the conformation of three bonds of a seven-membered Zn-chelate provides enough rigidity to achieve good catalytic performance. A similar tolerance towards variations of reaction parameters was observed with the catalyst loading. Indeed, when the reaction was carried out at 40°C with only 1 mol% of ligand (entry 11), the decrease in the yield and e.e. was almost negligible. Lowering the amount of catalyst even further (to a level of 0.1 mol%) had a negative effect on those parameters (entry 12). However, the enantioselectivity of the reaction decreased only by about 10%. A similar catalyst behavior was observed by Hanyu et al.[6f] with their camphane-based 1,4-amino alcohols, and by Knollmuller et al.[6d] with their (2-*exo*,3-*exo*)-2-hydroxy-3-(2-aminoethyl) derivatives of (+)-camphor, in which the amino group was not aromatic.

Ligand *cis*-**4** showed a much poorer performance than the *trans* isomer. Indeed, under the best reaction conditions determined for *trans*-**4** (2-*exo*,3-*endo*) (entry 1), *cis*-**4** (3.2:1 2-*endo*,3-*endo*/2-*exo*,3-*exo* mixture) provided (*R*)-1-phenylpropanol in 84% yield and 52% e.e. (entry 2). When a 6:1 mixture of 2-*endo*,3-*endo*/2-*exo*,3-*exo*-**4** was used, the e.e. improved only slightly (entry 3). This result seems to indicate that 2-*endo*,3-*endo*-**4** (less crowded) is significantly more active than the 2-*exo*,3-*exo* isomer (more crowded). Because 2-*exo*-OH and 2-*endo*-OH derivatives of camphor are known to produce opposite enantiomers of 1-phenylpropanol,[4b,6d] and if 2-*exo*,3-*exo*-**4** would be contributing to the e.e., a clear change in enantioselectivity could be expected as a result of lowering the amount of that ligand. (*R*)-1-Phenylpropanol was obtained with ligand *cis*-**4** (2-*endo*,3-*endo*) [the opposite enantiomer was attained with *trans*-**4** (2-*exo*,3-*endo*)] probably because the side of the C(2)–O–Zn plane exposed by the Zn-chelate to the reagents for coordination is the opposite to that

Table 1. Enantioselective synthesis of 1-phenylpropanol via addition of diethylzinc to benzaldehyde catalyzed by the Zn-chelates of ligands **4**–**7**



Entry	R	Ligand (mol%)	T (°C)	t (h)	Solvent	Yield[a] (%)	Ee[b] (%)
1	H	*trans*-**4**[c] (5)	22	4	Hex./Tol.[d]	96	89 (*S*)
2	H	*cis*-**4**[e] (5)	22	12	Tol.	84	52 (*R*)
3	H	*cis*-**4**[f] (5)	22	12	Tol.	80	56 (*R*)
4	H	**5** (5)	22	24	Tol.	40 (1.3:1)[g]	8 (*R*)
5	H	**6** (5)	22	24	Tol.	52 (2.7:1)[g]	8 (*S*)
6	H	**7** (5)	22	24	Tol.	32 (1:1)[g]	14 (*R*)
7	H	*trans*-**4**[c] (2.5)	22	12	Tol.	86	87 (*S*)
8	H	*trans*-**4**[c] (10)	22	0.5	Hex./Tol.[d]	98	88 (*S*)
9	H	*trans*-**4**[c] (5)	−22	24	Hex./Tol.[d]	93	87 (*S*)
10	H	*trans*-**4**[c] (5)	35	1	Hex./Tol.[d]	98	87 (*S*)
11	H	*trans*-**4**[c] (1)	40	1	Hex./Tol.[d]	97	86 (*S*)
12	H	*trans*-**4**[c] (0.1)	40	1	Hex./Tol.[d]	81	76 (*S*)
13	MeO	*trans*-**4**[c] (5)	22	4	Hex./Tol.[d]	90	78 (*S*)
14	MeO	*cis*-**4**[f] (5)	22	6	Hex./Tol.[d]	79	22 (*R*)
15	Cl	*trans*-**4**[c] (5)	22	8	Hex./Tol.[d]	92	87 (*S*)
16	Cl	*cis*-**4**[f] (5)	22	10	Hex./Tol.[d]	88	54 (*R*)

[a] Isolated yield.
[b] Determined by HPLC (Chiralcel OD, hex./IPA 95:5, 1.0 mL/min, 254 nm; 1-phenylpropanol: $t_{R\ (R)}=11.3$ min, $t_{R\ (S)}=12.2$ min; 1-(*p*-MeO-phenyl)propanol: $t_{R\ (R)}=13.7$ min, $t_{R\ (S)}=14.9$ min; 1-(*p*-Cl-phenyl)propanol: $t_{R\ (R)}=11.5$ min, $t_{R\ (S)}=10.7$ min).[3e]
[c] 2-*exo*,3-*endo*
[d] 1:1 mixture.
[e] 3.2:1 2-*endo*,3-*endo*/2-*exo*,3-*exo* mixture.
[f] 6:1 2-*endo*,3-*endo*/2-*exo*,3-*exo* mixture.
[g] Ratio 1-phenylpropanol/benzyl alcohol.

exposed in the case of ligand *trans*-**4** (2-*exo*,3-*endo*). This hypothesis is supported by the observed chirality transfer from ligands *cis*- and *trans*-**4**, which is in agreement with that reported for DAIB[4a,b,c] and other (+)-camphor based catalysts.[6d,e] (−)-DAIB (*exo*-OH) as well as *trans*-**4** (2-*exo*,3-*endo*) catalyze the formation of (*S*)-1-phenylpropanol as the major enantiomer, meanwhile (+)-DAIB (*endo*-OH) and 2-*endo*,3-*endo*-*cis*-**4** favor the (*R*)-enantiomer.

The results obtained with ligands **5**–**7**, which contain a bulkier group (Ph, Me and Bu; entries 4–6, Table 1) on C(2) are consistent with the poor performance of 2-*exo*,3-*exo*-**4** discussed above. When the Zn-chelates derived from **5**–**7** were used as catalysts, both the reaction yield and the enantioselectivity decreased dramatically. Furthermore, the bigger the 2-substituent, the more benzyl alcohol formed (see Table 1). This indicates that the active metal center of the catalyst is too crowded and, therefore, it cannot coordinate simultaneously the reagent and the substrate. This conclusion is in agreement with the observation made by Hanyu et al.,[6f] that 2-*endo*-methyl,2-*exo*-hydroxyl substituted camphor 1,4-amino alcohol derivatives exhibit a poor catalytic performance.

3-(Pyridylmethyl)borneols **4** were used also to catalyze the addition of diethylzinc to *p*-MeO and *p*-Cl benzaldehyde. The presence of the electron donating methoxy group did not alter the reaction yield, but decreased the enantioselectivity of the reaction when both *trans*- and *cis*-**4** were used (entry 13 versus 1, and 14 versus 2). A chlorine atom at the 4-position of the benzene ring had no effect on the yield or in the selectivity of the reaction (entry 15 versus 1, and 16 versus 2).

3. Conclusion

In summary, we have synthesized 5 new (+)-camphor-based amino alcohols [*cis*- and *trans*-**4** (2-*exo*,3-*endo*), **5**–**7**, Scheme 1], and used them as ligands for the enantioselective addition of diethylzinc to benzaldehydes (Table 1). The seven-membered Zn-chelate derived from 2-*exo*,3-*endo*-**4** gave the best chemical yield and highest enantioselectivity (96 and 89%, respectively), among the compounds studied. Because 1,4-amino alcohols **4**–**7** might serve as useful chiral ligands for other types of enantioselective reactions, further studies on those ligands for the purposes of catalytic enantioselective synthesis are in progress. A computational study on the properties of intermediates of the reactions catalyzed by the diastereomeric Zn-chelates discussed above will be published in due course.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian spectrometer at 400 MHz and are reported in ppm downfield from $SiMe_4$. *J* values are given in Hz. ^{13}C NMR spectra were recorded on a Varian spectrometer at 100 MHz. HRMS were conducted on a Bruker BioApex 47e Fourier transform ion cyclotron resonance mass spectrometer (ES+). Optical rotations were measured on a Perkin–Elmer polarimeter at rt, using a cell of 1 dm of length and $\lambda = 598$ nm. Data are reported as follows: $[\alpha]_D^{temp}$ (solvent, concentration in g/100 mL). HPLC analyses were performed using a Waters system with UV detector. The column, detector wavelength, flow rate and solvents were as denoted. The retention times (t_R) for the enantiomers are reported. Melting points (mp) were performed on a Gallenkamp apparatus, using open capillary tubes. Values are given in degrees Celsius (uncorrected). Analytical thin layer chromatography (TLC) was performed on Merck silica gel plates with QF-254 indicator. Visualization was accomplished with UV light. Flash chromatography was performed using Merck silica gel 60 (40–63 μm).

Solvents were dried using standard procedures.[12] Camphor and diethylzinc (1.1 M in tol.) were purchased from Fluka. 2-pyridylcarbaldehyde and benzaldehyde were obtained from Fluka and were distilled/purified previous to use. Butyllithium (1.6 M in hexanes), methyllithium (1.6 M in Et_2O), EtMgBr (1.0 M in THF) were purchased from Aldrich. All moisture-sensitive reactions were performed in oven-dried glassware (12 h, 120°C), which was allowed to cool to rt over phosphorous pentoxide in a dessicator.

4.2. 1,7,7-Trimethyl-3-(pyrid-2-ylmethylidene)bicyclo-[2.2.1]heptan-2-one 2[9d]

In a 1 L three-necked round-bottomed flask under Ar was placed camphor (30.0 g, 0.20 mol) in dry benzene (300 mL). Sodium (5.0 g, 0.22 mol) was added and the resulting mixture was heated under reflux for 18 h, cooled to rt and the excess of sodium removed. The reaction mixture was cooled to 0°C, 2-pyridylcarbaldehyde (28 mL, 0.29 mol) was added dropwise, stirring was continued for 3 h at rt and then the dark red solution was poured into water (500 mL). The layers were separated and the aqueous phase extracted with AcOEt (4×200 mL). The combined organic extracts were washed with water (3×200 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude was purified by flash chromatography (silica, hex./AcOEt 7:1 and 3.2:1) to render a yellowish semi-solid, which was dissolved in Et_2O (200 mL) and extracted with 3% HCl (4×50 mL). The acidic phase was washed with Et_2O (50 mL), basified with 5% NaOH (200 mL) and extracted with Et_2O (3×50 mL), which was washed with H_2O (3×50 mL), dried ($MgSO_4$), filtered and the solvent evaporated in vacuum. 1,7,7-Trimethyl-3-(pyrid-2-ylmethylidene)-bicyclo[2.2.1]heptan-2-one was obtained as a yellow liquid (13.3 g, 55.0 mmol, 28%). $R_f = 0.32$ (silica, hex./AcOEt 6:1). $[\alpha]_D^{20} = +267$ (*c* 1.17, $CHCl_3$) (Lit.[9d] +208 *c* M/100, dioxan). ^{1}H NMR ($CDCl_3$): δ 8.67 (m, 1H), 7.68 (ddd, $J = 7.6$ Hz, $J = 7.6$ Hz, $J = 1.6$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.18 (m, 1H), 7.17 (s, 1H), 3.75 (d, $J = 4.4$ Hz, 1H), 2.21–2.12 (m, 1H), 1.82–1.74 (m, 1H), 1.52 (m, 2H), 1.04 (m, 3H), 1.02 (m, 3H), 0.83 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 208.9, 152.2, 149.9, 145.8, 136.1, 126.0, 125.6, 122.5, 57.3, 49.4, 46.1, 30.7, 26.1, 20.8, 18.2, 9.3. HRMS calcd for M^++H ($C_{16}H_{20}NO$) 242.1543; found 242.1539.

4.3. 1,7,7-Trimethyl-3-(pyrid-2-ylmethyl)bicyclo[2.2.1]-heptan-2-one 3

In a 250 mL 3-necked round-bottomed flask under argon was suspended 5% Pd/C (600 mg) in EtOH (150 mL). Enone **2** (6.0 g, 24.9 mmol) in EtOH (10 mL) was added, argon was replaced by hydrogen and the mixture was stirred at rt (balloon pressure) for 24 h. The suspension was then filtered through a short pad of Celite with the aid of EtOH (2×50 mL), and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (silica, hex./AcOEt 8:1 and 4:1). A clear oil was obtained (5.0 g, 20.6 mmol, 83%), which corresponded to the title compound as a 2:1 *exo*:*endo* mixture of diastereoisomers. $R_f = 0.11$ (silica, hex./AcOEt 8:1). $[\alpha]_D^{20} = +45.9$ (*c* 1.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.54 (m, 1H), 7.60 (m, 1H), 7.17 (m, 1H), 7.12 (m, 1H), 7.17 (s, 1H), 3.35 and 3.26 (2dd, $J = 14.4$ Hz, $J = 4.4$ Hz and $J = 14.4$ Hz, $J = 5.2$ Hz, 1H), 3.01 and 2.48 (m and dd, $J = 9.6$ Hz, $J = 4.0$ Hz, 1H), 2.79–2.68 (m, 1H), 2.05–1.91 (m, 2H), 1.80–1.46 (m, 2H), 1.41–1.31 (m, 1H), 0.97, 0.95, 0.94, 0.93, 0.89 (5s, 9H). ^{13}C NMR ($CDCl_3$): δ 220.6, 160.9, 160.3, 149.3, 136.3, 136.2, 123.1, 121.2, 58.7, 57.6, 54.6, 50.2, 47.1, 46.8, 46.3, 45.8, 39.8, 35.6, 31.2, 29.2, 29.3, 21.8, 20.4, 20.4, 19.6, 19.2, 9.5, 9.4. HRMS calcd for M^++H ($C_{16}H_{22}NO$) 244.1705; found 244.1695.

4.4. Isomerization to the *endo* product

In a 250 mL round-bottomed flask under argon was dissolved sodium (0.85 g, 37.0 mmol) in dry MeOH (75 mL). Ketone **3** (2:1 *exo*:*endo* mixture) (2.0 g, 8.2 mmol) in dry MeOH (5 mL) was added and the resulting mixture was heated under reflux (bath temperature: 80°C) for 24 h, cooled to rt, poured into a saturated NH_4Cl solution (400 mL) and extracted with Et_2O (4×150 mL). The combined organic extracts were washed with H_2O (3×100 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The target was obtained as a clear oil (2.0 g, 8.2 mmol, quant.) (7.5:1 *endo*:*exo* mixture). $[\alpha]_D^{20} = +82.6$ (*c* 1.38, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 8.53 (m, 1H), 7.60 (ddd, $J = 7.6$ Hz, $J = 7.6$ Hz, $J = 2.0$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.12 (m, 1H), 3.26 (dd, $J = 14.4$ Hz, $J = 5.2$ Hz, 1H), 3.02 (m, 1H), 2.72 (dd, $J = 14.4$ Hz, $J = 10.0$ Hz, 1H), 1.96 (m, 1H), 1.80–1.67 (m, 2H), 1.41–1.34 (m, 1H), 0.97 (s, 3H), 0.93 (s, 3H), 0.89 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 220.5, 160.3, 149.3, 136.2, 123.1, 121.2, 58.7, 50.2, 46.3, 45.8, 35.6, 31.2, 20.4, 19.6, 19.2, 9.5.

4.5. 1,7,7-Trimethyl-3-(pyrid-2-ylmethyl)bicyclo[2.2.1]-heptan-2-ol 4

In a 100 mL 3-necked round-bottomed flask under argon was suspended $LiAlH_4$ (0.5 g, 13.2 mmol) in dry THF (15 mL). 1,7,7-Trimethyl-*endo*-3-(pyrid-2-ylmethyl)-bicyclo[2.2.1]heptan-2-one (**3**, 750 mg, 3.1 mmol) in dry THF (10 mL) was added dropwise, the resulting mixture was stirred overnight at rt, cooled to 0°C, quenched slowly with 5% NaOH (30 mL), diluted with Et_2O (30 mL) and saturated with Na_2SO_4. The resulting heterogeneous mixture was stirred for 15 min, filtered with the aid of Et_2O (3×10 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (silica, hex./AcOEt 4:1 and 2:1). The *cis* isomer was obtained as an oil (330 mg, 1.3 mmol, 44%) and a mixture 3.2:1 2-*endo*,3-*endo*/2-*exo*,3-*exo*. The *trans* isomer (2-*exo*,3-*endo*) was obtained as white waxy solid (270 mg, 1.1 mmol, 36%).

cis-**4** (2-*endo*,3-*endo*): $R_f=0.31$ (silica, hex./AcOEt 2:1). $[\alpha]_D^{20}$ +18.0 (*c* 0.82, MeOH). ^1H NMR ($CDCl_3$): δ 8.45–8.42 (m, 1H), 7.64–7.59 (m, 1H), 7.17–7.10 (m, 2H), 6.50–6.20 (bs, 1H), 3.93 and 3.73 (dd and d, $J=9.6$ Hz, $J=1.6$ Hz, and $J=7.6$ Hz, 1H), 3.51 and 3.29 (t, $J=13.6$ Hz and $J=12.4$ Hz, 1H), 2.79 and 2.44 (dd, $J=13.6$ Hz, $J=2.4$ Hz and $J=13.2$ Hz, $J=2.0$ Hz, 1H), 2.39–2.30 and 1.94–1.88 (m and ddd, $J=12.8$ Hz, $J=8.0$ Hz and $J=2.8$ Hz, 1H), 2.17–2.11 and 1.75–1.68 (2m, 1H), 1.65–1.62 and 1.59–1.53 (2m, 2H), 1.28–1.14 and 1.08–0.96 (2m, 2H), 1.02, 0.92, 0.91, 0.87, 0.83 (5s, 9H). ^{13}C NMR ($CDCl_3$): δ 163.1, 162.6, 148.3, 148.3, 137.3, 137.2, 123.1, 123.0, 121.1, 121.0, 80.3, 74.5, 52.8, 52.6, 51.0, 49.9, 49.4, 47.1, 47.0, 42.6, 39.6, 35.6, 33.8, 30.0, 25.6, 22.3, 21.9, 20.5, 20.0, 18.6, 14.4, 12.0. HRMS calcd for M^++H ($C_{16}H_{24}NO$) 246.1852; found 246.1852.

trans-**4** (2-*exo*,3-*endo*): $R_f=0.10$ (silica, hex./AcOEt 2:1). $[\alpha]_D^{20}$ +9.2 (*c* 0.79, MeOH). Mp 77–78°C. ^1H NMR ($CDCl_3$): δ 8.46 (m, 1H), 7.60 (ddd, $J=7.6$ Hz, $J=7.6$ Hz, $J=1.6$ Hz, 1H), 7.20 (d, $J=7.6$ Hz, 1H), 7.12–7.09 (m, 1H), 4.90–4.60 (bs, 1H), 3.33 (d, $J=4.0$ Hz, 1H), 3.00–2.87 (m, 2H), 2.62–2.56 (m, 1H), 1.66–1.62 (m, 3H), 1.45–1.39 (m, 1H), 1.16 (s, 3H), 1.05–1.00 (m, 1H), 0.94 (s, 3H), 0.88 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 161.9, 148.6, 136.3, 123.6, 121.0, 86.1, 49.8, 49.5, 47.8, 47.6, 39.4, 35.2, 20.7, 20.6, 19.8, 11.5. HRMS calcd for M^++H ($C_{16}H_{24}NO$) 246.1852; found 246.1852.

4.6. Reduction of 3 with ethylmagnesium bromide

In a 25 mL two-necked round-bottomed flask under argon was dissolved 1,7,7-trimethyl-*endo*-3-(pyrid-2-ylmethyl)-bicyclo[2.2.1]heptan-2-one **3**, (700 mg, 2.9 mmol, 7.5:1 *endo*/*exo* mixture) in dry THF (7 mL) and the contents of the flask were cooled to 0°C. EtMgBr (1 M in THF, 3 mL, 3.0 mmol) was added dropwise, the resulting mixture was stirred overnight at rt and quenched with sat. NH_4Cl solution (10 mL). The layers were separated and the aqueous one extracted with Et_2O (3×5 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (silica, hex./AcOEt 4:1) rendering *cis*-**4** as an oil (330 mg, 1.3 mmol, 46%) and a mixture 6:1 2-*endo*,3-*endo*/2-*exo*,3-*exo* and recovered starting material (300 mg, mmol, 43%). $[\alpha]_D^{20}$ +34.1 (*c* 1.59, MeOH).

4.7. 1,7,7-Trimethyl-2-phenyl-3-(pyrid-2-ylmethyl)-bicyclo[2.2.1]heptan-2-ol 5

In a 25 mL two-necked round-bottomed flask under argon was placed freshly distilled bromobenzene (1.05 mL, 10.0 mmol) in dry THF (4 mL). The solution was cooled to −78°C, BuLi (1.6M in hexanes, 7.0 mL, 11.2 mmol) was added dropwise and stirring was continued for 1 h. 1,7,7-Trimethyl-3-(pyrid-2-ylmethyl)-bicyclo-[2.2.1]heptan-2-one **3** (7:3 *exo*:*endo*) (500 mg, 2.06 mmol) in dry THF (1 mL) followed dropwise and the resulting solution was allowed to warm from −78°C to rt overnight. The reaction mixture was treated with sat. NH_4Cl solution (10 mL), the layers were separated and the aqueous phase was extracted with ether (3×5 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (silica, hex./AcOEt 10:1 and 5:1). The fraction containing the product was dissolved in Et_2O (15 mL) and extracted with 3% HCl (3×10 mL). The acidic phase was washed with Et_2O (5 mL), basified with 5% Na_2CO_3 to pH = 8 and extracted with AcOEt (3×10 mL), which was washed with H_2O (10 mL), dried ($MgSO_4$), filtered and the solvent evaporated in vacuum. 1,7,7-Trimethyl-2-phenyl-3-(pyrid-2-ylmethylidene)-bicyclo[2.2.1]heptan-2-ol was obtained as a white solid (120 mg, 0.37 mmol, 18%). $R_f=0.46$ (silica, hex./AcOEt 4:1). $[\alpha]_D^{20}$ +88.9 (*c* 0.27, $CHCl_3$). Mp = 101–102°C. ^1H NMR ($CDCl_3$): δ 7.84 (m, 1H), 7.46 (ddd, $J=7.6$ Hz, $J=7.6$ Hz, $J=2.0$ Hz, 1H), 7.37 (d, $J=7.6$ Hz, 2H), 7.09 (t, $J=7.6$ Hz, 2H), 7.02 (m, 1H), 6.80 (m, 1H), 7.76–6.66 (bs, 1H), 3.64 (t, $J=13.2$ Hz, 1H), 2.86 (dd, $J=13.2$ Hz, $J=3.2$ Hz, 1H), 2.57 (dd, $J=12.8$ Hz, $J=3.2$ Hz, 1H), 1.87–1.78 (m, 1H), 1.76 (d, $J=4.4$ Hz, 1H), 1.57 (s, 3H), 1.29–1.00 (m, 4H), 0.90 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 161.4, 147.6, 147.4, 136.9, 127.0, 126.6, 125.5, 122.8, 120.8, 84.5, 55.5, 53.9, 52.1, 51.3, 40.6, 30.5, 29.9, 23.7, 23.3, 10.3. HRMS calcd for M^++H ($C_{22}H_{28}NO$) 322.2156; found 322.2165.

4.8. 1,7,7-Trimethyl-2-methyl-3-(pyrid-2-ylmethyl)-bicyclo[2.2.1]heptan-2-ol 6

In a 100 mL 3-necked round-bottomed flask under argon was placed MeLi (1.6 M in Et_2O, 32.0 mL, 51.2 mmol) and 1,7,7-trimethyl-3-(pyrid-2-ylmethyl)-bicyclo-[2.2.1]heptan-2-one **3** (7:3 *exo*:*endo*) (500 mg, 2.06 mmol) in dry THF (2 mL) was added dropwise and the resulting solution was heated under reflux for 2 h and stirred for an additional 16 h at rt. The reaction mixture was cooled to 0°C, treated with sat. NH_4Cl solution (20 mL), the layers were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The com-

bined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (silica, hex./AcOEt 5:1) rendering the target as a clear oil that crystallizes slowly with time (110 mg, 0.42 mmol, 21%). $R_f = 0.17$ (silica, hex./AcOEt 4:1). $[\alpha]_D^{20}$ +15.7 (*c* 0.43, $CHCl_3$). Mp = 85–86°C. ^{1}H NMR ($CDCl_3$): δ 8.44 (m, 1H), 7.63 (ddd, $J = 7.6$ Hz, $J = 7.6$ Hz, $J = 2.0$ Hz, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 7.14–7.09 (m, 1H), 5.90–4.50 (bs, 1H), 3.49 (t, $J = 13.0$ Hz, 1H), 2.78 (dd, $J = 13.0$ Hz, $J = 3.0$ Hz, 1H), 1.76 (m, 1H), 1.66 (dd, $J = 13.0$ Hz, $J = 3.0$ Hz, 1H), 1.59–1.53 (m, 2H), 1.46–1.30 (m, 2H), 1.40 (s, 3H), 1.05–1.00 (m, 1H), 0.99 (s, 3H), 0.92 (s, 3H), 0.85 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 162.6, 148.0, 137.2, 123.3, 121.2, 80.6, 59.4, 52.9, 52.5, 49.4, 40.9, 30.8, 30.1, 28.4, 23.0, 10.2. HRMS calcd for M^++H ($C_{17}H_{26}NO$) 260.2018; found 260.2009.

4.9. 1,7,7-Trimethyl-2-butyl-3-(pyrid-2-ylmethyl)bicyclo-[2.2.1]heptan-2-ol 7

In a 25 mL two-necked round-bottomed flask under argon was placed BuLi (1.6 M in hexanes, 7.0 mL, 11.2 mmol) and was cooled to −78°C. 1,7,7-Trimethyl-3-(pyrid-2-ylmethyl)-bicyclo[2.2.1]heptan-2-one **3** (7:3 *exo*:*endo*) (500 mg, 2.06 mmol) in dry hexane (1 mL) was added dropwise and the resulting solution was allowed to warm to rt and stirred for an additional 2 h. The reaction mixture was treated with sat. NH_4Cl solution (10 mL), the layers were separated and the aqueous phase was extracted with ether (3×5 mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (silica, hex./AcOEt 5:1) rendering the target as a clear oil (170 mg, 0.56 mmol, 27%) (2:1:1 mixture of diastereoisomers). $R_f = 0.39$ (silica, hex./AcOEt 4:1). $[\alpha]_D^{20}$ +20.4 (*c* 0.63, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 8.59, 8.57 and 8.45 (m, 1H), 7.63–7.55 (m, 1H), 7.17–7.01 (m, 2H), 4.80–4.40 (bs, 1H), 3.44 and 2.90 (dd and ddd, $J = 13.6$ Hz, $J = 11.2$ Hz and $J = 10.8$ Hz, $J = 10.8$ Hz, $J = 3.6$ Hz, 1H), 2.84–2.74 (m, 1H), 2.66–2.58 and 2.54–2.45 (m, 1H), 2.84–2.74 and 2.41 (m and d, $J = 10.8$ Hz, 1H), 2.90–1.00 (m, 10H), 1.00–0.76 (m, 12H). ^{13}C NMR ($CDCl_3$): δ 163.8, 163.2, 162.8, 149.7, 149.3, 148.3, 136.9, 135.9, 135.8, 123.6, 123.6, 123.4, 121.2, 121.1, 121.0, 82.7, 59.6, 59.0, 58.5, 58.4, 53.2, 53.1, 51.5, 51.0, 50.3, 47.4, 47.0, 46.7, 46.1, 45.1, 42.7, 40.9, 34.6, 34.4, 31.0, 30.3, 30.2, 29.6, 29.6, 29.5, 29.3, 26.5, 23.6, 22.9, 22.9, 22.6, 21.9, 20.8, 20.3, 19.6, 19.0, 14.0, 13.9, 11.5, 9.8, 9.5. HRMS calcd for M^++H ($C_{20}H_{32}NO$) 302.2481; found 302.2478.

4.10. General procedure for the enantioselective addition of diethylzinc to aldehydes

In a 25 mL two-necked round-bottomed flask under argon was placed the chiral ligand (25.0 μmol) in dry solvent (1 mL) and the solution was cooled to 0°C. Diethylzinc (1.1 M solution in toluene, 1.0 mL, 1.1 mmol) was added dropwise, the mixture was allowed to warm to rt, stirred for 30 min and brought to the reaction temperature. The aldehyde (0.50 mmol) was added dropwise, the reaction mixture was stirred for *t* h and treated with 3% HCl (5 mL). The layers were separated and the aqueous one extracted with Et_2O (3×5 mL). The combined organic extracts were washed with H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was analyzed by HPLC (Chiralcel OD, hex./IPA 95:5, 1.0 mL/min, 254 nm; 1-phenylpropanol: $t_{R\ (R)} = 11.3$ min, $t_{R\ (S)} = 12.2$ min; 1-(*p*-MeO-phenyl)propanol: $t_{R\ (R)} = 13.7$ min, $t_{R\ (S)} = 14.9$ min; 1-(*p*-Cl-phenyl)propanol: $t_{R\ (R)} = 11.5$ min, $t_{R\ (S)} = 10.7$ min) and ^{1}H NMR.

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