Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 612–617

Microwave-assisted, highly enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by chiral aminonaphthols

István Szatmári,[a] Reijo Sillanpää[b] and Ferenc Fülöp[a,*]

[a]*Institute of Pharmaceutical Chemistry and Research Group for Stereochemistry, Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary*
[b]*Department of Chemistry, University of Jyväskylä, FIN-40351 Jyväskylä, Finland*

Received 2 January 2008; accepted 18 January 2008
Available online 7 February 2008

Abstract—New optically active aminonaphthols were obtained by condensation of 2-naphthol, benzaldehyde and (*R*)-(+)-1-(1-naphthyl)ethylamine or (*R*)-(+)-1-(2-naphthyl)ethylamine. Their N-methylated derivatives were also synthesized. The new aminonaphthols **2**, **4**, **5** and **7** were found to catalyze the enantioselective ethylation of aryl aldehydes to 1-aryl-1-propanols (up to 92% ee). The reactions were accelerated greatly by microwave irradiation.

1. Introduction

The search for new chiral ligands, which can be efficiently applied in asymmetric catalysis is currently a field of great interest in organic chemistry. The asymmetric addition of Et_2Zn to aldehydes in the presence of catalytic amounts of chiral catalysts has attracted considerable attention.[1] Numerous efforts have been made to use chiral ligands, such as biaryl alcohols,[2] β-aminoalcohols,[3] amino thiols,[4] amines[5,6] and *o*-hydroxybenzylamines.[7]

Enantiopure 1-α-aminobenzyl-2-naphthol **1a** (Betti base derivatives[8,9]) and their non-racemic derivatives **1c**–**1e** and **2**[10–16] have been successfully applied as chiral ligands in the addition of Et_2Zn to benzaldehyde. The first aminonaphthol-based applied chiral ligand in the addition of Et_2Zn to benzaldehyde was the enantiomer of the Betti base **1a**, which exhibited relatively low enantioselectivity (Table 1, entry 1).[9] The ee value could be increased to 96% by using its *N*,*N*-dimethyl derivative **1b** (entry 2).[9] With this, the synthesis of aminonaphthols from the non-racemic α-methylbenzylamine **1c** or its *N*-methyl analogue **1d**, a new family of chiral ligands could be applied efficiently for the enantioselective alkylation of benzaldehyde (entries 3 and 4).[11] As an extension of the modified three-component Mannich reaction, different aldehydes and amines have been used, following the idea that a bulkier group at either the newly generated stereogenic centre **1e**[16] or on the N atom[12] should favour the enantioinduction. In contrast, when 1-[(*R*)-phenyl-1′(*R*)-(1-naphthyl)-ethylaminomethyl]-2-naphthol **2** was applied, only a moderate ee was achieved (Table 1, entry 5).[12] Our present aims were therefore to synthesize non-racemic aminonaphthol derivatives from commercially available (*R*)-(+)-1-(1-naphthyl)ethylamine and *R*-(+)-1-(2-naphthyl)ethylamine by the three-component modified Mannich reaction, to study the scope and limits of their application as chiral catalysts in the enantioselective alkylation of aryl aldehydes and to compare the enantioinduction of the two groups of catalysts differing in the connecting position of the naphthyl ring at the nitrogen (Fig. 1).

2. Results and discussion

Model compounds **2** and **5** were synthesized by solvent-free heating of a mixture of 2-naphthol, benzaldehyde and (*R*)-(+)-1-(1-naphthyl)ethylamine or (*R*)-(+)-1-(2-naphthyl)-ethylamine, respectively (Scheme 1). The diastereoselectivity of the asymmetric aminoalkylation of 2-naphthol can be explained by the presence of kinetic control at low temperature, and re-equilibration (by thermodynamic control) at high temperature.[10] The diastereomeric excess (de) was, therefore, followed by NMR spectroscopy during the reaction. The final 70% de for **5** was observed even after

* Corresponding author. Tel.: +36 62 545564; fax: +36 62 545705; e-mail: fulop@pharm.u-szeged.hu

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.01.025

Table 1. Enantioselective addition of Et_2Zn to aldehydes in toluene in the presence of **1**, **2**, **4**, **5** or **7**

Entry	X	Ligand	mol %	Conditions	Yield[a] (%)	ee[b] (%)
1	H	**1a**	13	20 °C, 24 h	85	35 [Ref. 9]
2	H	**1b**	13	20 °C, 12 h	93	96 [Ref. 9]
3	H	**1c**	15	20 °C, 24 h	97	72 [Ref. 11]
4	H	**1d**	15	20 °C, 24 h	95	99.4 [Ref. 11]
5	H	**2**	10	20 °C, 4 h	84	81 [Ref. 12]
6	H	**2**	10	−18 °C, 24 h	40	1.1[c]
7	H	**2**	10	4 °C, 24 h	97	75[c]
8	H	**2**	10	20 °C, 24 h	95	73[c]
9	H	**2**	10	40 °C, 40 min, M.W.	98	60[c]
10	H	**2**	10	60 °C, 40 min, M.W.	95	65[c]
11	H	**2**	10	80 °C, 40 min, M.W.	97	10[c]
12	H	**2**	10	60 °C, 60 min, M.W.	95	67[c]
13	OMe	**2**	10	60 °C, 60 min, M.W.	94	92[c]
14	Me	**2**	10	60 °C, 60 min, M.W.	96	67[c]
15	H	**5**	10	−18 °C, 24 h	78	71[d]
16	H	**5**	10	4 °C, 24 h	85	75[d]
17	H	**5**	10	20 °C, 24 h	88	79[d]
18	H	**5**	10	40 °C, 40 min, M.W.	92	75[d]
19	H	**5**	10	60 °C, 40 min, M.W.	94	71[d]
20	H	**5**	10	80 °C, 40 min, M.W.	90	70[d]
21	H	**5**	10	60 °C, 60 min, M.W.	95	68[d]
22	OMe	**5**	10	60 °C, 60 min, M.W.	95	71[c]
23	Me	**5**	10	60 °C, 60 min, M.W.	98	53[c]
24	H	**4**	10	−18 °C, 24 h	nd	nd
25	H	**4**	10	4 °C, 24 h	92	70[c]
26	H	**4**	10	20 °C, 24 h	97	84[c]
27	H	**4**	10	40 °C, 40 min, M.W.	87	72[c]
28	H	**4**	10	60 °C, 40 min, M.W.	90	74[c]
29	H	**4**	10	80 °C, 40 min, M.W.	nd	nd
30	H	**4**	10	50 °C, 60 min, M.W.	97	67[c]
31	OMe	**4**	10	50 °C, 60 min, M.W.	94	87[c]
32	Me	**4**	10	50 °C, 60 min, M.W.	96	72[c]
33	H	**7**	10	−18 °C, 24 h	42	40[c]
34	H	**7**	10	4 °C, 24 h	68	42[c]
35	H	**7**	10	20 °C, 24 h	75	82[c]
36	H	**7**	10	40 °C, 40 min, M.W.	85	58[c]
37	H	**7**	10	60 °C, 40 min, M.W.	88	73[c]
38	H	**7**	10	80 °C, 40 min, M.W.	90	70[c]
39	H	**7**	10	50 °C, 60 min, M.W.	95	72[c]
40	OMe	**7**	10	50 °C, 60 min, M.W.	97	86[c]
41	Me	**7**	10	50 °C, 60 min, M.W.	94	66[c]

[a] Determined by ^{1}H NMR analysis of the crude product.
[b] In all cases, the absolute configuration of the major enantiomer, as determined by comparison of the retention time with the reported values, was found to be (*S*).[17,18]
[c] Measured by chiral HPLC (Chiracel OD).
[d] Measured by chiral GC analysis (Chiracel-Dex CB).

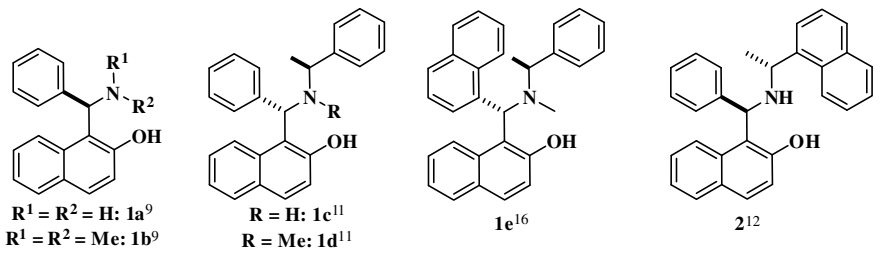
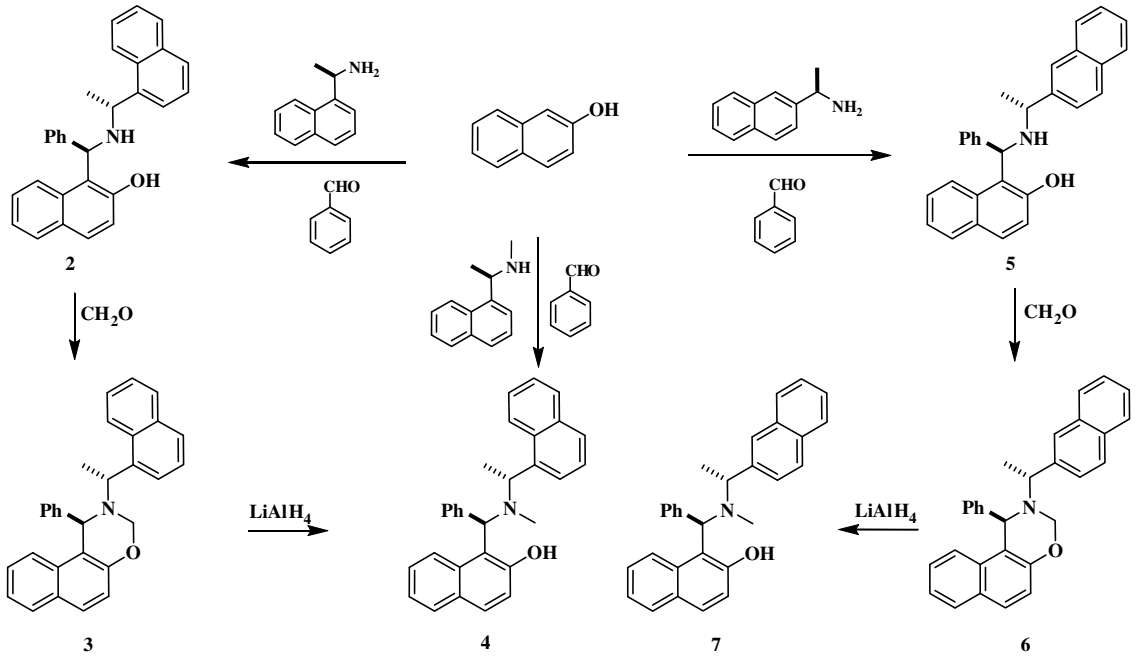


Figure 1.

a reaction time of only 4 h. For **2**, a stronger time-dependence of de was observed during the reaction time (72 h), leading to a final 96% de, which was reported by Palmieri and co-workers[12] to be 60% after a reaction time of 14 h. With regards to the structures of the starting amines, (*R*)-(+)-1-(2-naphthyl)ethylamine, which involves lower steric



Scheme 1.

hindrance, furnished higher diastereoselectivity. For both compounds **2** and **5**, the main diastereomers (1*R*,1′*R*)-**2** and (1*R*,1′*R*)-**5**, respectively, could be obtained from the crude reaction product, and were purified by recrystallization from *i*-Pr_2O.

To confirm the absolute configuration of the newly generated stereogenic centre at **2** and **5**, an X-ray study was carried out. The solid-state conformations of the two]compounds are stabilized by strong intramolecular hydrogen-bonding between the OH group and the N atom. The O···N distances are 2.562(2) Å for **2** and 2.580(3) Å for **5**. Figure 2 clearly shows that the configuration of the newly generated centre is (*R*) for both **2** and **5**.

Tertiary aminonaphthols generally give better enantioselectivities than secondary ones in the alkylation of aryl aldehydes,[9,11,13] and the N-methylation of (1*R*,1′*R*)-**2** and (1*R*,1′*R*)-**5** has been achieved. The *N*-methyl derivative of (1*R*,1′*R*)-**2** can be prepared by two different synthetic pathways: (a) direct solvent-free aminoalkylation of 2-naphthol with benzaldehyde and the commercially available *R*-(+)-*N*-methyl-1-(1-naphthyl)ethylamine, resulting in (1*R*,1′*R*)-**4** (Scheme 1); or (b) the ring closure of (1*R*,1′*R*)-**2** with formaldehyde, followed by reduction with $LiAlH_4$, leading to (1*R*,1′*R*)-**4**. As (*R*)-(+)-*N*-methyl-1-(2-naphthyl)ethylamine is not available commercially, the previously applied N-methylation procedure was applied to (1*R*,1′*R*)-**5** to obtain (1*R*,1′*R*)-**7** (Scheme 1).

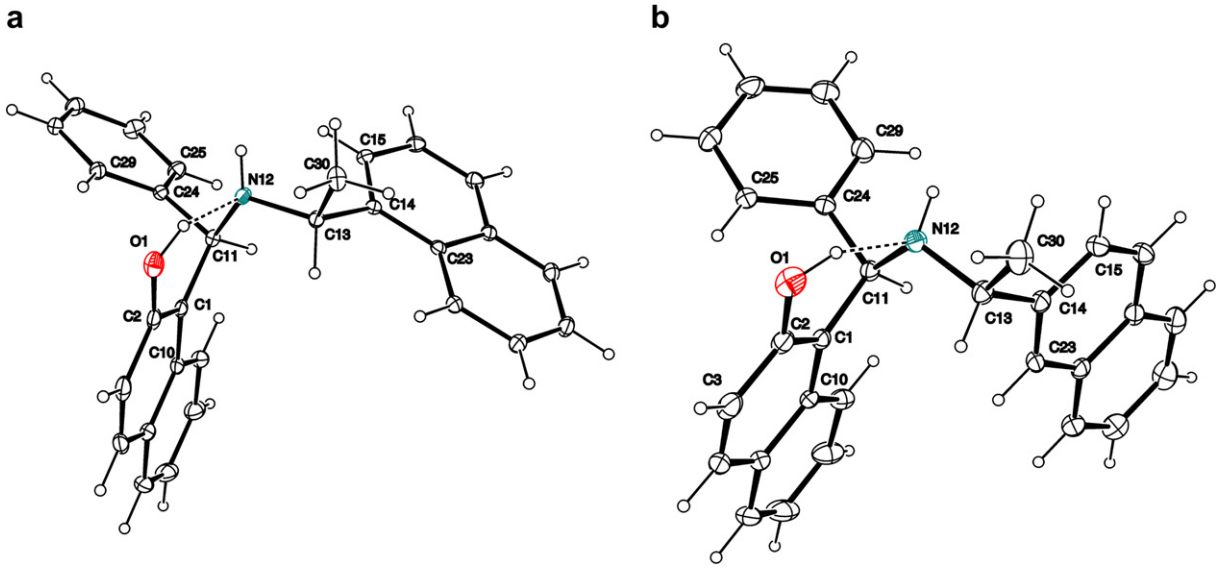
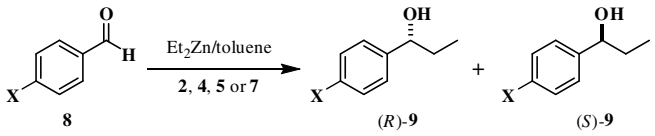


Figure 2. (a) Ortep plot of **2** with 30% thermal ellipsoids; (b) Ortep plot of **5** with 20% thermal ellipsoids.

Aminonaphthols **2**, **4**, **5** and **7** were then applied as chiral catalysts in the enantioselective addition of Et_2Zn to aryl aldehydes, resulting in chiral 1-aryl-1-propanols **9** (Scheme 2).



Scheme 2.

The results of the enantiomeric inductions of aminonaphthols **2**, **4**, **5** and **7** are listed in Table 1. The enantiomeric purities of the 1-aryl-1-propanols **9** produced were determined by chiral HPLC or by chiral GC analysis (see Section 4).

From a comparison of the enantioselectivities of the new catalysts **2**, **4**, **5** and **7** (Table 1, entries 8, 17, 26 and 35) with chiral ligands **1** (entries 1–5), known from the literature[9,11,12] used under the same reaction conditions, the moderate ee values obtained (73–84%) allow us to conclude that neither a 1-naphthylethyl nor a 2-naphthylethyl group on the N atom causes a significantly higher level of enantioinduction. To study the influence of the aryl substituent on the ee values in the asymmetric alkylation of aryl aldehydes, the experiments were extended to *p*-OMe-benzaldehyde and *p*-Me-benzaldehyde (entries 13, 14, 22, 23, 31, 32, 40 and 41). The best enantioselectivity (92%) was observed for **2** (entry 13). The same tendency was found for chiral ligands **4** and **7**, that is, the highest ee values were achieved when the aryl substituent on the substrate in the alkylation reaction was *p*-OMe (entries 31 and 40). For all four chiral ligands **2**, **4**, **5** and **7**, when a long reaction time (24 h) was applied (entries 6–8, 15–17, 24–26 and 33–35), the best enantioselectivity resulted when the reaction was performed at room temperature (entries 8, 17, 26 and 35). Tertiary aminonaphthols **5** and **7** gave somewhat higher enantioselectivities than the secondary ones **2** and **4** (entries 8, 17, 26 and 35).

Microwave irradiation (M.W.) is a process often applied to accelerate organic reactions.[19] Some of the enantioselective alkylations of the aryl aldehydes were, therefore, performed by microwave agitation. In all cases, the microwave conditions accelerated the reaction rate dramatically (instead of a reaction time of 24 h, 40 or 60 min was sufficient). Table 1 shows that, for all four non-racemic aminonaphthols **2**, **4**, **5** and **7**, there is an optimum temperature at which the chiral ligand in question functions with the highest enantioselectivity. This temperature is around room temperature for **5**, **4** and **7** (Table 1, entries 17, 26 and 35) and around 4 °C for **2** (Table 1, entry 7). It is interesting to note that increasing the temperature in combination with microwave agitation did not destroy the enantioselectivity until the reaction mixture exceeded a critical temperature, which seemed to depend on the structure of the chiral ligands, that is, on the relative stabilities of the transition states. For 1-[(*R*)-phenyl-1′(*R*)-(1-naphthyl)ethylaminomethyl]-2-naphthol **2** and its *N*-methyl derivative **4** at a reaction temperature >60 °C, the enantioselectivity decreased dramatically (Table 1, entries 10, 11 and 28, 29), while for 1-[(*R*)-phenyl-1′(*R*)-(2-naphthyl)ethylaminomethyl]-2-naphthol **5** and its *N*-methyl derivative **7**, even at a reaction temperature of 80 °C the enantioinduction was similar to that at a lower temperature (Table 1, entries 19, 20 and 37, 38). This can be explained by the different nature of the coupling of the naphthyl ring at position 1′. In **5** and **7**, the free rotation around the single bond is more restricted than for **2** and **4**.

3. Conclusions

In conclusion, with regards to the enantiomeric induction of the four synthesized chiral aminonaphthols **2**, **4**, **5** and **7** relative to the literature data, the bulkier naphthylethyl group on the N atom did not cause a significantly higher enantioselectivity in the alkylation of aryl aldehydes. Furthermore, the tertiary aminonaphthols did not improve the ee values significantly. Studies of the influence of aryl substituents in aryl aldehyde Et_2Zn addition demonstrated that higher ee values were achieved in all cases with *p*-OMe substituent rather than with *p*-Me or H. All reactions could be accelerated excellently by using microwave irradiation, while an increase in the temperature (depending on the structure of the chiral ligands) led to the same ee values or to the formation of the racemic 1-arylpropanol.

4. Experimental

Melting points were determined on a Kofler micro melting apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser. Merck Kieselgel $60F_{254}$ plates were used for TLC. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes, at room temperature, on a Bruker *Avance* DRX400 spectrometer at 400.13 (^1H) and 100.61 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard.

4.1. 1-[(*R*)-Phenyl-(1′*R*)-(1-naphthyl)ethylaminomethyl]-2-naphthol 2

Compound **2** was prepared according to the reported method with some modifications.[12] A mixture of 2-naphthol (1.44 g, 10.0 mmol), (*R*)-(+)-1-(1-naphthyl)ethylamine (Aldrich, cat. no. 237442), (1.78 g, 10.4 mmol) and benzaldehyde (1.27 g, 12.0 mmol) was stirred at 65 °C for 72 h. Then 20 mL of MeOH was added to the crude reaction mixture, and the white crystals which were separated out and filtered off, after which they were recrystallized from iPr_2O (40 mL). Yield: 3.30 g (82%). White crystals, mp: 165–167 °C, lit. mp[12] 159–162 °C; $[\alpha]_D^{20} = -351.5$ (*c* 0.5, $CHCl_3$), $[\alpha]_D^{20} = -339.4$ (*c* 1.0, $CHCl_3$), lit. $[\alpha]_D^{20} = -288.1$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ: 1.63 (d, 3H, $J = 6.7$ Hz), 2.56 (br s, 1H), 4.87 (m, 1H), 5.48 (s, 1H), 7.02–7.82 (m, 18H), 13.83 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 23.5, 51.8, 61.4, 113.8, 120.5, 121.7, 122.8, 122.9, 125.9, 126.1, 126.2, 126.5, 126.7, 126.8, 128.1, 128.4, 128.6, 128.9, 129.1, 129.3, 129.5,

129.5, 130.2, 132.3, 133.0, 142.0, 157.7. Anal. Calcd for $C_{29}H_{25}NO$ (403.5): C, 86.32; H, 6.24; N, 3.47. Found: C, 86.42; H, 6.27; N, 3.35.

4.2. (1*R*)-1-Phenyl-2-[(1′*R*)-1′-(1-naphthylethyl)]-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine 3

To a solution of **2** (1.21 g, 3.00 mmol) in toluene (30 mL), paraformaldehyde (0.18 g, 6 mmol) was added. The reaction mixture was stirred at room temperature for 10 h, after which TLC revealed no more starting material. The solution was dried with Na_2SO_4. The solvent was evaporated off under reduced pressure, and the residue was crystallized from a mixture of *n*-hexane–EtOAc (4:1). Yield: 1.18 g (95%). White crystals, mp: 87–88 °C; $[\alpha]_D^{20} = -218.3$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.71 (d, 3H, $J = 6.8$ Hz), 4.81 (q, 1H, $J = 6.4$ Hz), 5.07 (d, 1H, $J = 10.8$ Hz), 5.23 (d, 1H, $J = 12.2$ Hz), 5.25 (s, 1H), 6.81–7.93 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 21.4, 57.3, 58.5, 75.2, 113.0, 118.0, 119.2, 120.2, 123.4, 123.8, 124.4, 126.2, 126.3, 126.6, 127.1, 127.8, 128.7, 129.0, 129.5, 129.7, 130.0, 131.9, 132.2, 133.6, 134.9, 143.7, 152.9, 153.6. Anal. Calcd for $C_{30}H_{25}NO$ (415.2): C, 86.71; H, 6.06; N, 3.37. Found: C, 86.32; H, 6.10; N, 3.41.

4.3. *N*-Methyl-1-[(*R*)-phenyl-(1′*R*)-(1-naphthyl)ethylaminomethyl]-2-naphthol 4

(A) To a stirred solution of **3** (1.04 g, 2.5 mmol) in THF (50 mL), $LiAlH_4$ (1.40 g) was added. The resulting suspension was stirred at rt for 4 h. Water (2.8 mL) in THF (20 mL) was added dropwise to the stirred suspension and the stirring was continued for an additional 30 min. The mixture was filtered off and washed with EtOAc (2 × 20 mL). The filtrate was dried over Na_2SO_4 and the solvent was evaporated off. The crude product was crystallized from Et_2O (20 mL) and recrystallized from *i*Pr_2O (25 mL), Yield: 1.02 g (98%). White crystals, mp: 202–203 °C; $[\alpha]_D^{20} = -399.4$ (*c* 0.5, $CHCl_3$).

(B) A mixture of 2-naphthol (0.36 g, 2.5 mmol), (*R*)-(+)-*N*-methyl-1-(1-naphthyl)ethylamine (0.48 g, 2.6 mmol) and benzaldehyde (0.32 g, 3.0 mmol) was stirred at 65 °C for 72 h. Then, 20 mL of MeOH was added to the crude reaction mixture and the white crystals which separated out were filtered off and recrystallized from *i*Pr_2O (40 mL). Yield: 0.82 (78%). White crystals, mp: 201–203 °C; $[\alpha]_D^{20} = -397.4$ (*c* 0.5, $CHCl_3$).

In view of the very similar NMR spectroscopic and elemental analysis data on **4** obtained by methods A and B, analytical data are presented only for the compound prepared by using method B.

^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.66 (d, 3H, $J = 6.9$ Hz), 2.19 (s, 3H), 4.84 (m, 1H), 5.49 (s, 1H), 7.02–8.04 (m, 18H), 13.32 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 30.2, 34.2, 52.3, 69.5, 117.2, 120.6, 121.8, 123.1, 124.3, 125.3, 126.2, 126.3, 126.4, 126.5, 126.9, 127.0, 128.1, 129.1, 129.2, 129.5, 129.8, 130.1, 130.2, 132.6, 132.8, 134.8, 140.2, 156.4. Anal. Calcd for $C_{30}H_{27}NO$ (417.2): C, 86.30; H, 6.52; N, 3.35. Found: C, 86.51; H, 6.48; N, 3.31.

4.4. 1-[(*R*)-Phenyl-(1′*R*)-(2-naphthyl)ethylaminomethyl]-2-naphthol 5

A mixture of 2-naphthol (1.44 g, 10.0 mmol), *R*-(+)-1-(2-naphthyl)ethylamine (Fluka, cat. no. 70940), (1.78 g, 10.4 mmol) and benzaldehyde (1.27 g, 12.0 mmol) was stirred at 65 °C for 72 h. Then, 15 mL of MeOH was added to the crude reaction mixture and the white crystals, which separated out were filtered off and recrystallized from *i*Pr_2O (30 mL). Yield: 2.49 g (62%). White crystals, mp: 164–166 °C; $[\alpha]_D^{20} = -236.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.64 (d, 3H, $J = 6.8$ Hz), 2.43 (br s, 1H), 4.12 (q, 1H, $J = 6.7$ Hz), 5.56 (s, 1H), 7.15–8.05 (m, 18H), 13.68 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 23.6, 57.4, 61.0, 113.8, 120.8, 121.9, 123.1, 124.3, 126.8, 127.1, 127.2, 127.4, 128.4, 128.5, 128.5, 128.6, 129.3, 129.4, 129.7, 129.8, 130.5, 133.3, 133.8, 134.1, 140.8, 142.2, 158.0. Anal. Calcd for $C_{29}H_{25}NO$ (403.5): C, 86.32; H, 6.24; N, 3.47. Found: C, 86.27; H, 6.21; N, 3.51.

4.5. (1*R*)-1-Phenyl-2-[(1′*R*)-1′-(2-naphthylethyl)]-2,3-dihydro-1*H*-naphth[1,2-*e*][1,3]oxazine 6

To a solution of **5** (1.21 g, 3.00 mmol) in toluene (30 mL), paraformaldehyde (0.18 g, 6 mmol) was added. The mixture was stirred at room temperature for 12 h, after which TLC revealed no more starting material. The solution was dried with Na_2SO_4. The solvent was evaporated off at reduced pressure, and the residue was crystallized from a mixture of *n*-hexane–EtOAc (6:1). Yield: 1.14 g (92%). White crystals, mp: 173–175 °C; $[\alpha]_D^{20} = -143.0$ (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.61 (d, 3H, $J = 6.7$ Hz), 4.16 (q, 1H, $J = 6.7$ Hz), 4.99 (d, 1H, $J = 10.7$ Hz), 5.19 (d, 1H, $J = 11.1$ Hz), 5.26 (s, 1H), 6.94–7.97 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 22.0, 57.7, 59.7, 74.7, 112.6, 118.9, 123.1, 123.5, 126.1, 126.5, 126.9, 127.1, 127.6, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.3, 129.4, 129.6, 133.3, 133.6, 133.9, 143.3, 143.5, 153.2. Anal. Calcd for $C_{30}H_{25}NO$ (415.2): C, 86.71; H, 6.06; N, 3.37. Found: C, 86.81; H, 6.02; N, 3.35.

4.6. *N*-Methyl-1-[(*R*)-Phenyl-(1′*R*)-(2-naphthyl)ethylaminomethyl]-2-naphthol 7

To a stirred solution of **6** (1.04 g, 2.5 mmol) in THF (50 mL), $LiAlH_4$ (1.40 g) was added and the resulting suspension was stirred at rt for 6 h. Water (2.8 mL) in THF (20 mL) was then added dropwise to the stirred suspension and the stirring was continued for an additional 30 min. The mixture was next filtered off and washed with EtOAc (2 × 20 mL). The filtrate was dried over Na_2SO_4 and the solvent was evaporated off. The crude product was crystallized from Et_2O (20 mL) and recrystallized from *i*Pr_2O (20 mL). Yield: 1.00 g (96%). White crystals, mp: 195–196 °C; $[\alpha]_D^{20} = -255.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ: 1.64 (d, 3H, $J = 6.0$ Hz), 2.13 (s, 3H), 4.38 (m, 1H), 5.38 (s, 1H), 7.05–8.00 (m, 18H), 13.87 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ: 29.9,

33.7, 58.3, 68.8, 117.5, 120.7, 121.7, 123.1, 124.3, 125.3, 126.2, 126.4, 126.5, 126.9, 127.2, 128.4, 129.1, 129.4, 129.5, 129.8, 130.1, 130.2, 132.6, 132.8, 134.8, 140.2, 140.8, 156.4. Anal. Calcd for $C_{30}H_{27}NO$ (417.2): C, 86.30; H, 6.52; N, 3.35. Found: C, 86.51; H, 6.48; N, 3.31.

4.7. Reactions of diethylzinc with aryl aldehydes. General procedure

1 M Et_2Zn in toluene solution (0.5 mL, 0.5 mmol) was added under an argon atmosphere to the chiral ligand **2**, **4**, **5** or **7** (0.02 mmol). The reaction mixture was stirred for 30 min at room temperature, after which the aryl aldehyde (0.2 mmol) was added and the reaction mixture was treated as indicated in Table 1. The usual acidic work-up led to 1-aryl-1-propanol **9**. The enantiomeric excess (ee) and absolute configuration were determined by chiral HPLC (0.55 mL min^{-1}, *n*-hexane–*i*PrOH 97:3, 205 nm), using a chiral stationary phase (Chiracel OD column) or by chiral GC (derivatized with Ac_2O in the presence of 4-dimethylaminopyridine, 100 °C isotherm, 2 mL min^{-1}), using a chiral stationary phase (Chiracel-Dex CB column, 25 m).

4.8. X-ray crystallographic study

Crystallographic data were collected at 173 K with a Nonius-Kappa CCD area detector diffractometer, using graphite-monochromatized Mo-K_α radiation ($\lambda = 0.71073$ Å). The data were collected by φ and ω rotation scans and processed with the DENZO-SMN *v*0.93.0 software package.[20]

4.8.1. Crystal data for 2. $C_{29}H_{25}NO$, $M_r = 403.50$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.0953(3)$, $b = 13.9637(5)$, $c = 19.5793(6)$ Å, α, β, $\gamma = 90°$, $V = 2213.25(13)$ Å^3, $T = 173$ K, $Z = 4$, μ(Mo-K_α) = 0.073 mm^{-1}, 2342 unique reflections ($R_{int} = 0.0314$) which were used in calculations. The final $wR(F^2)$ was 0.0767 (all data).

4.8.2. Crystal data for 5. $C_{29}H_{25}NO$, $M_r = 403.50$, orthorhombic, space group $P2_12_12_1$ (no. 19), $a = 8.3649(2)$, $b = 11.2899(5)$, $c = 23.3274(12)$ Å, α, β, $\gamma = 90°$, $V = 2203.01(16)$ Å^3, $T = 173$ K, $Z = 4$, μ(Mo-K_α) = 0.073 mm^{-1}, 2440 unique reflections ($R_{int} = 0.037$) which were used in calculations. The final $wR(F^2)$ was 0.0948 (all data).

The structures were solved by direct methods by the use of the SHELXS-97 program,[21] and full-matrix, least-squares refinements on F^2 were performed with the SHELXL-97 program.[21] The CH hydrogen atoms were included at the fixed distances with the fixed displacement parameters from their host atoms. The OH hydrogen atoms were refined isotropically with the thermal displacement 1.2 times that of the host atom. The figures were drawn with ORTEP-3 for Windows.[22] The deposition numbers CCDC 664280 and 664281 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgement

The authors' thanks are due to the Hungarian Research Foundation (OTKA No. D48669 and No. T049407) for financial support.

References

1. Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.
2. Bringmann, G.; Breuning, M. *Tetrahedron: Asymmetry* **1998**, *9*, 667–679.
3. Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry* **1998**, *9*, 1489–1492.
4. Anderson, J. C.; Harding, M. *Chem. Commun.* **1998**, 393–394.
5. Chelucci, G.; Conti, S.; Falorni, M.; Giacomelli, G. *Tetrahedron* **1991**, *47*, 8251–8258.
6. Conti, S.; Falorni, M.; Giacomelli, G.; Soccolini, F. *Tetrahedron* **1992**, *48*, 8993–9000.
7. Palmieri, G. *Tetrahedron: Asymmetry* **2000**, *11*, 3361–3373.
8. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Schingaro, E.; Scordari, F. *Tetrahedron: Asymmetry* **1998**, *9*, 3667–3675.
9. Cardellicchio, C.; Ciccarella, G.; Naso, F.; Perna, F.; Tortorella, P. *Tetrahedron* **1999**, *55*, 14685–14692.
10. Cimarelli, C.; Mazzanti, A.; Palmieri, G.; Volpini, E. *J. Org. Chem.* **2001**, *66*, 4759–4765.
11. Liu, D.-X.; Zhang, L.-C.; Wang, Q.; Da, C.-S.; Xin, Z.-Q.; Wang, R.; Choi, M. C. K.; Chan, A. S. C. *Org. Lett.* **2001**, *3*, 2733–2735.
12. Cimarelli, C.; Palmieri, G.; Volpini, E. *Tetrahedron: Asymmetry* **2002**, *13*, 2417–2426.
13. Ji, J.-X.; Qiu, L.-Q.; Yip, C. W.; Chan, A. S. C. *J. Org. Chem.* **2003**, *68*, 1589–1590.
14. Szatmári, I.; Fülöp, F. *Curr. Org. Synth.* **2004**, *1*, 155–165.
15. Cappanini, L.; Cimarelli, C.; Giuli, S.; Palmieri, G.; Petrini, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1022–1029.
16. Ji, J.-X.; Wu, J.; Au-Yeung, T. T. L.; Yip, C. W.; Haynes, R. K.; Chan, A. S. C. *J. Org. Chem.* **2005**, *70*, 1093–1095.
17. Paleo, R. M.; Cabeza, I.; Sardina, J. F. *J. Org. Chem.* **2000**, *65*, 2108–2113.
18. Solá, L.; Reddy, K. S.; Vidal-Ferran, A.; Moyano, A.; Pericás, M. A.; Riera, A.; Alvarez-Larena, A.; Piniella, J.-F. *J. Org. Chem.* **1998**, *63*, 7078–7082.
19. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
20. Otwinowski, Z.; Minor, W. Methods in Enzymology. In *Macromolecular Crystallography, Part A*; Carter, C. W., Jr., Sweet, R. M., Eds.; Academic Press: New York, 1997; Vol. 2/6, pp 307–326.
21. Sheldrick, G. M. SHELX-*97*; University of Göttingen: Germany, 1997.
22. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565–567.