

New indane derived aminoalcohols as chiral ligands for the catalytic enantioselective addition of diethylzinc to aldehydes

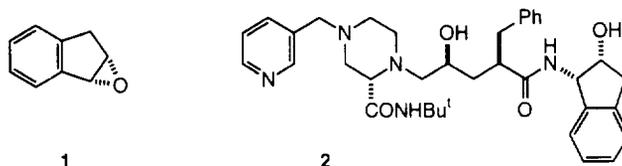
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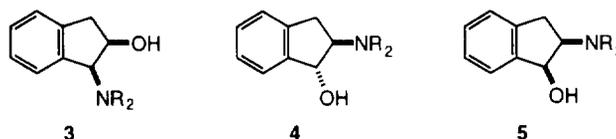
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Abstract: Secondary amines react with (1*R*,2*S*)-indene oxide **1** in a completely regioselective manner leading to *trans*-2-dialkylamino-1-indanols **4a–d** in high yield. A Mitsunobu inversion *via* the corresponding *p*-nitrobenzoates, followed by reduction with DIBALH leads to the *cis*-2-dialkylamino-1-indanols **5a–d** also in high yield. These two new classes of aminoindanols have been tested as chiral ligands for the enantioselective addition of diethylzinc to both aliphatic and aromatic aldehydes, leading to 1-substituted 1-propanols with up to 80% e.e. A very simple procedure for the enantiomeric enrichment of **1** from 88% to ≥99% e.e. is also reported. © 1997 Elsevier Science Ltd

Indene oxide **1**, nowadays readily available in enantioenriched form through a manganese–salen catalysed Jacobsen epoxidation,¹ has gained considerable importance as a chiral starting material. Being a potential precursor to the *cis*-aminoindanol moiety present in Merck's HIV protease inhibitor Indinavir **2**,² it has also been studied by chemists at Merck and by others as a source of *cis*-aminoalcohols and related species with activity as chiral ligands for enantioselective catalysis.³



Up to now, the functionalization of **1** has relied on regioselective Ritter reactions leading exclusively to 1-amino-2-indanol derivatives **3**.⁴ We report in the present paper efficient methodology allowing the preparation of both the *cis* and *trans* stereoisomers of the regioisomeric 2-amino-1-indanols **4** (*trans*) and **5** (*cis*). Initial results on the catalytic activity of these substances in the enantioselective addition of diethylzinc to aldehydes are also reported.



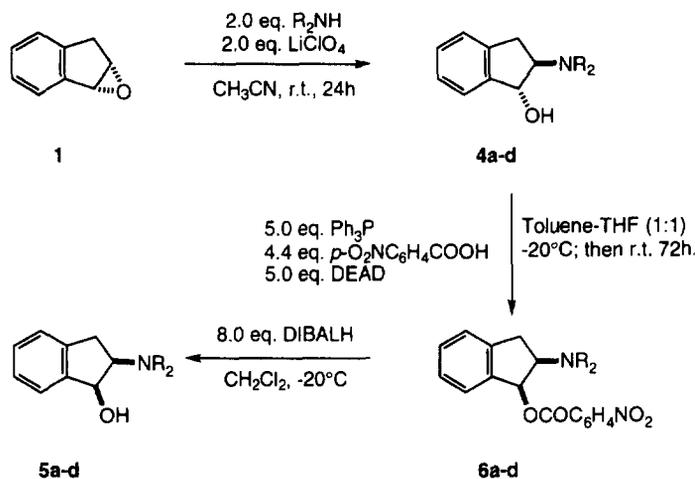
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The starting material for the present study has been readily available 88% e.e. (1*R*,2*S*)-indene oxide **1**, prepared by sodium hypochlorite oxidation of indene in dichloromethane at 0°C mediated by the (*R,R*) enantiomer of the standard Jacobsen catalyst.⁵

In order to test the operation of non-linear effects in the reactions catalysed by our target ligands, we have investigated ways for the improvement of the enantiomeric purity of **1**. As a result of these efforts, we have now developed a very simple procedure for the enantiomeric enrichment of this compound up to 99.0% e.e. Our method is based on the fact that **1**, a liquid at room temperature, solidifies near 0°C. Moreover, being appreciably soluble in hexane at room temperature, it crystallises with enantiomeric enrichment at -20°C affording samples of **1** with an e.e. higher than 99%.

When **1** was treated at room temperature with 2 eq. of a secondary amine and 2 eq. of lithium perchlorate in acetonitrile solution, under the conditions developed by Crotti,⁶ a completely regioselective and stereospecific ring opening took place leading in high yield to *trans*-2-amino-1-indanols **4a-d** (Scheme 1 and Table 1).



Scheme 1.

Table 1. Yields^a in the synthesis of ligands **4a-d** and **5a-d**

| Entry | R ₂ NH | 4[%] | 6[%] | 5[%] |
|-------|---|-----------------|------|------|
| a | ⁱ Pr ₂ NH | 75 | 75 | 100 |
| b | | 70 | 86 | 70 |
| c | (<i>n</i> -C ₄ H ₉) ₂ NH | 72 | 93 | 85 |
| d | | 85 ^b | 87 | 80 |

^aReaction conditions as indicated in scheme 1. ^bRing-opening was performed at 65°C for 48h.

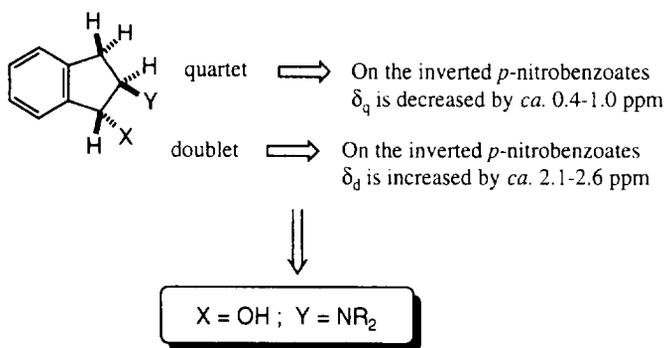


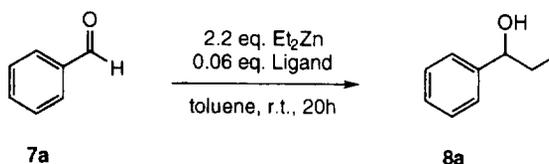
Figure 1. Confirmation of the regiochemistry of **4**, **5**, and **6** from NMR data.

The observed regioselectivity of this ring opening is highly remarkable. Thus, when performing the same reaction on styrene oxide, Crotti observed that only very bulky amines such as diisopropylamine or dicyclohexylamine are able to induce a completely regioselective attack to the β -carbon.^{6a} Piperidine, in turn, reacts with styrene oxide with complete lack of regioselectivity while in the present case (entry b in Table 1) the ring-opening is totally regioselective.

With **4a-d** in hand, we planned to gain access to the more interesting *cis* stereoisomers **5a-d**. According to previous experience in our laboratories, a Mitsunobu inversion⁷ at C-1 followed by reduction appeared as the safest alternative in terms of stereocontrol. Bearing in mind the rather congested nature of **4a-d**, the Mitsunobu inversion was performed with *p*-nitrobenzoic acid, a more efficient nucleophile for the inversion of congested secondary alcohols.^{7c} In this way, the *cis p*-nitrobenzoates **6a-d** were obtained in 75–93% yield. Reduction of **6a-d** with DIBALH in dichloromethane led in high yield (70–100%) to the desired *cis* aminoalcohols **5a-d** in diastereomerically pure form.

The regiochemistry of the final compounds was established by comparison with its unambiguously prepared regioisomer *cis*-1-di-*n*-butylamino-2-indanol.⁸ Moreover, the NMR data of **4a-d** fully supports the 2-amino-1-indanol regiochemistry as summarised in Figure 1.

In order to determine the optimal ligand structure, all eight species (**4a-d**, **5a-d**), obtained from 88% e.e. **1**, were initially tested in the enantioselective addition of diethylzinc⁹ to benzaldehyde (**7a**) leading to 1-phenyl-1-propanol (**8a**) under the experimental conditions shown in Scheme 2. The results of these reactions are summarised in Table 2.



Scheme 2.

Not unexpectedly, the *cis* ligands **5a-d** are superior to the corresponding *trans* ones **4a-d** both in terms of turnover (conversion) and enantioselectivity. This can be clearly related to the greater ease of the *cis* ligands for the fulfilment of the geometrical restrictions associated to the formation of a zinc chelate, as it is assumed to occur when aminoalcohols interact with Et_2Zn .

On the other hand, in agreement with previous studies by our group,¹⁰ it is seen that the branched and acyclic diisopropyl group is rather inefficient as a building block for these ligands. Conversely, the

Table 2. Enantioselective addition of diethylzinc to benzaldehyde mediated by ligands **4** or **5**

| Ligand ^a | Conversion ^b [%] | Selectivity ^c [%] | Absolute config. of 8a ^d | Enantiomeric excess ^e of 8a [%] |
|---------------------|--------------------------------|---------------------------------|---|--|
| 4a | 51 | 89 | <i>R</i> | 1 |
| 4b | 100 | 98 | <i>R</i> | 29 |
| 4c | 88 | 90 | <i>R</i> | 31 |
| 4d | 91 | 88 | <i>R</i> | 56 |
| 5a | 79 | 90 | <i>S</i> | 35 |
| 5b | 99 | 97 | <i>S</i> | 40 |
| 5c | 95 | 92 | <i>S</i> | 44 |
| 5d | 99 | 95 | <i>S</i> | 73 |

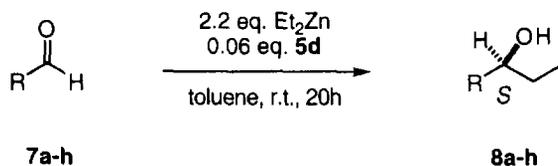
^aAll ligands reported in this table are derived from 88% e.e. **1**, and are thus assumed to be of 88% e.e. ^bDetermined by integration of residual **7a** in front of all new products in the gas chromatogram of the reaction crude. ^cDetermined by integration of **8a** (both enantiomers in front of other reaction products in the gas chromatogram of the reaction crude. ^dEstablished by comparison of retention times in GC (β -DEXTM 120 column; isothermal at 112°C; $t_R(R)$: 48.5 min, $t_R(S)$: 51.1 min) with those of authentic samples. ^eBy GC as in c (see above).

presence of a piperidino substituent is optimal in terms of turnover, and the *cis*-2,6-dimethylpiperidino fragment¹¹ induces the highest enantioselectivities both in the *cis* and in the *trans* series.

The influence of the enantiomeric purity of the ligands on the enantioselectivity of the addition reaction was tested with ligands **4d** and **5d**. Thus, working with 99.0% e.e. ligands (derived from 99.0% e.e. **1**) under the conditions shown in Scheme 2, the enantiomeric excess of (*R*)-**8a** obtained with **4d** did not show any appreciable variation with respect to the value reported in Table 2. On the other hand, in the case of **5d** the enantiomeric excess of (*S*)-**8a** increased from 73 to 78%.

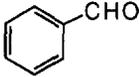
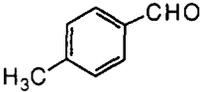
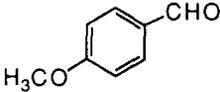
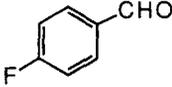
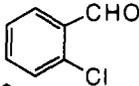
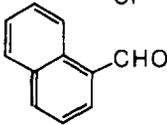
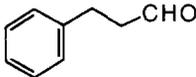
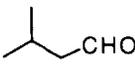
For **5d**, the influence of the reaction temperature on enantioselectivity was also studied. Rather unexpectedly, lowering the reaction temperature to 0°C provoked a significant decrease (from 78 to 73%) in the e.e. of the resulting (*S*)-**8**.

In view of these results, **5d** of 99.0% e.e. was used as a catalytic ligand in the addition at room temperature of Et₂Zn to a family of aldehydes comprising both aromatic and aliphatic specimens as shown in Scheme 3 and Table 3.

**Scheme 3.**

In all cases, the *S* enantiomer of the resulting alcohol was preferentially obtained, as it could be established in every case by comparison of the retention times of the enantiomers on α - or β -DEXTM

Table 3. Enantioselective addition of diethylzinc to aldehydes^a **7a–h** mediated by ligand **5d**^b

| Starting Aldehyde | Resulting Alcohol | Conversion ^c [%] | Selectivity ^d [%] | Enantiomeric Excess ^e [%] |
|---|-------------------|-----------------------------|------------------------------|--------------------------------------|
|  (7a) | 8a | 99 | 94 | 78 |
|  (7b) | 8b | 97 | 92 | 69 |
|  (7c) | 8c | 88 | 96 | 71 |
|  (7d) | 8d | 98 | 95 | 80 |
|  (7e) | 8e | 92 | 72 | 66 |
|  (7f) | 8f | 81 | 83 | 65 |
|  (7g)^f | 8g | 74 | 92 | 69 |
|  (7h)^f | 8h | 93 | 94 | 56 |

^aUnless otherwise stated, the reactions were performed at room temperature. ^b99.0% e.e. **5d** was used throughout the study. ^cDetermined by integration of residual **7** in front of all new products in the gas chromatogram of the reaction crude. ^dDetermined by integration of **8** (both enantiomers) in front of other reaction products. ^eBy GC using either a β -DEXTM 120 column (for **8a–8f**) or a α -DEXTM 120 column (for **8g** and **8h**). ^fReaction performed at 0°C

columns (see Table 3) with those of samples of known configuration. This is in agreement with the empirical predictive model developed by Noyori.^{9b}

Among the aromatic aldehydes, the best results are obtained with the parent benzaldehyde **7a** and with the *p*-substituted ones **7b–d**, specially in terms of chemical selectivity. Thus, reduction becomes a serious problem with *o*-substituted substrates **7e–f**. Finally, for the normally more problematic non-conjugated substrates **7g–h**, the reaction temperature was lowered to 0°C. In this way, the enantiomeric excess of the resulting alcohols **8g–h** was kept in a level similar to that of the benzyl alcohols **8b–f**.

Conclusions

In summary, we have developed a very simple method for the enantiomeric enrichment of the very important intermediate indene oxide **1** up to 99.0% e.e. We have subsequently developed short and efficient routes for the preparation of the hitherto unknown homochiral *trans*- and *cis*-2-dialkylamino-1-indanols **4** and **5**, regioisomers of the much employed as chiral ligands and auxiliaries 1-dialkylamino-2-indanols **3**. The aminoalcohols **4** and **5** have been tested as ligands in the enantioselective addition of diethylzinc to aldehydes. Although the enantioselectivities achieved in these reactions are only modest, in the only example where a direct comparison with the regioisomeric aminoindanol **3** is possible **5c**, the presently developed ligand has similar or even slightly better characteristics. According to that, it can be anticipated that other ligands and auxiliaries based on the *cis* 2-amino-1-indanol structure will probably depict interesting properties. Work in this area is being actively pursued in our laboratories and will be reported in due course.

Experimental section

General

Optical rotations were measured at room temperature on a Perkin–Elmer MC 241 polarimeter (concentration in g/100 mL). ¹H-NMR spectra were recorded on Varian Gemini 200, Varian-Unity-300 and Varian-Unity-Plus-300 spectrometers in CDCl₃ operating at 200 or 300 MHz respectively. ¹³C-NMR spectra were obtained on the same instruments operating at 50 or 75 MHz respectively. Chemical shifts are quoted relative to TMS for ¹H-NMR and relative to the solvent for ¹³C-NMR (77.0 ppm for ¹³C of CDCl₃). Coupling constants (*J*) are given in Hz. Signal multiplicities in ¹³C-NMR were established by DEPT experiments. IR spectra were recorded on a Nicolet 510 FT-IR instrument in Fourier transform mode. Mass spectra were recorded on a Hewlett Packard HP-5988A instrument at 70 eV ionizing voltage and ammonia was used for chemical ionization (CI). THF was distilled under N₂ from sodium benzophenone ketyl; CH₂Cl₂ was distilled under N₂ from CaH₂; the required secondary amines were distilled from CaH₂ prior to use, the aldehydes were distilled just before being used and all the other commercial chemicals were used as received. All reactions were performed in oven-dried glassware under a N₂ atmosphere. Reaction progress was followed by TLC (Merck DC-Alufolien KIESELGEL 60 F254). Chromatographic separations were carried out using Et₃N pre-treated (2.5% v/v) SiO₂ (70–230 mesh). (1*R*, 2*S*)-indene oxide **1** was prepared following the procedure described by Jacobsen *et al.*^{5a}

Indene oxide **1** enantiomeric enrichment

Indene oxide **1** (17.8 g, 88% e.e.) was dissolved in dry hexane at room temperature and the resulting solution was cooled to –18°C overnight. 4.7 g of yellow crystals (99% e.e., by HPLC using a Chiralcel[®] OB column) were separated at –20°C. [α]_D²³ = –40.3 (*c* = 1.7 in CHCl₃).

(1*R*, 2*R*)-2-Diisopropylamino-1-indanol **4a**

Diisopropylamine (1.45 mL, 10 mmol) was added *via* syringe into a mixture of 88% e.e. indene oxide **1** (0.66 g, 5 mmol) and LiClO₄ (1.06 g, 10 mmol) in acetonitrile (2 mL) at room temperature under N₂. After stirring for 24 h at room temperature, H₂O (40 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3×40 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was purified by chromatography using hexane:EtOAc (100:0–70:30) as eluent to give 0.87 g (75%) of **4a** as an oil: [α]_D²³ = +18.3 (*c* = 1.41 in CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 7.25–7.15 (m, 4H), 4.34 (q, 1H, *J* = 7.8 Hz), 4.22 (d, 1H, *J* = 7.2 Hz), 3.25–3.0 (m, 3H), 2.74 (d×d, 1H, *J* = 15.9 Hz, *J* = 8.1 Hz), 1.12 (d, 12H, *J* = 6.6 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ 143.6 (C), 139.3 (C), 127.0 (CH), 126.5 (CH), 125.6 (CH), 77.0 (CH), 67.8 (CH), 44.7 (CH), 37.6 (CH₂), 24.2 (CH₃), 23.3 (CH₃); IR (KBr) 3396, 2962, 1460, 1393, 1362, 1231, 1198, 1071, 741; MS (CI, NH₃) *m/z* 234 (C₁₅H₂₃NO.H⁺, 100%).

(1R,2R)-2-Piperidino-1-indanol 4b

Piperidine (2 mL, 20 mmol), 88% e.e. indene oxide **1** (1.32 g, 10 mmol) LiClO₄ (2.13 g, 20 mmol) in acetonitrile (4 mL) were treated as described for **4a**. The work-up was identical to the one described for **4a** to give 1.52 g (70%) of **4b** as an oil: $[\alpha]_D^{23}=+3.0$ (c=1.00 in CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 7.3–7.1 (m, 4H), 4.7–4.6 (m, 1H), 4.05 (d, 1H, *J*=5.2 Hz), 3.45 (bs, 1H), 3.25 (d×d, 1H, *J*=16.2 Hz, *J*=7 Hz), 2.80 (d×d, 1H, *J*=16 Hz, *J*=5.6 Hz), 2.65–2.55 (m, 4H), 1.60–1.40 (m, 6H); ¹³C-NMR (75 MHz, CDCl₃); δ 140.9 (C), 140.0 (C), 127.7 (CH), 126.3 (CH), 125.9 (CH), 124.9 (CH), 78.5 (CH), 73.6 (CH), 50.7 (CH₂), 40.1 (CH₂), 26.3 (CH₂), 24.5 (CH₂); IR (KBr) 3265, 2937, 2860, 2800, 1455, 1341, 1162, 1106, 1038, 999 i 745 cm⁻¹; MS (CI, NH₃) *m/z* 218 (C₁₄H₁₉NO.H⁺, 100%).

(1R,2R)-2-Di-n-butylamino-1-indanol 4c

Di-*n*-butylamine (6.8 mL, 40 mmol), 88% e.e. indene oxide **1** (2.64 g, 20 mmol) LiClO₄ (4.26 g, 40 mmol) in acetonitrile (8 mL) were treated as described for **4a**. The work-up was identical to the one described for **4a** to give 3.7 g (71%) of **4c** as an oil: $[\alpha]_D^{23}=+20.4$ (c=1.05 in CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 7.25–7.15 (m, 4H), 4.44 (q, 1H, *J*=7.4 Hz), 4.22 (d, 1H, *J*=6.6 Hz), 3.2 (d×d, 1H, *J*=15.6 Hz, *J*=7.4 Hz), 2.78 (d×d, 1H, *J*=15.6 Hz, *J*=7.4 Hz), 2.59 (t, 4H, *J*=7.2 Hz), 2.4 (br s, 1H), 1.6–1.2 (m, 8H), 0.88 (t, 6H); ¹³C-NMR (50 MHz, CDCl₃) δ 141.6 (C), 139.7 (C), 127.3 (CH), 126.4 (CH), 124.9 (CH), 75.0 (CH), 73.8 (CH), 52.4 (CH₂), 38.6 (CH₂), 31.7 (CH₂), 20.4 (CH₂), 14.1 (CH₃); IR (KBr) 3355, 2958, 1607, 1461, 1378, 1181, 1077, 868, 745 cm⁻¹; MS (CI, NH₃) *m/z*: 262 (C₁₇H₂₇NO.H+100%).

(1R,2R)-2-(cis-2,6-Dimethylpiperidino)-1-indanol 4d

cis-2,6-Dimethylpiperidine (2.1 mL, 15.1 mmol) was added *via* syringe into a mixture of 99% e.e. indene oxide **1** (1.0 g, 7.6 mmol) and LiClO₄ (1.6 g, 15.1 mmol) in acetonitrile (6 mL) at room temperature under N₂. After stirring for 48 h at 65°C, H₂O (50 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3×50 mL). The work-up was identical to the one described for **4a** to give 1.57 g (85%) of **4d** as an oil: $[\alpha]_D^{23}=+1.0$ (c=2.18 in CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 7.35 (m, 1H), 7.15 (m, 3H), 4.84 (q, 1H, *J*=7.6 Hz), 4.7 (d, 1H, *J*=7.0 Hz), 3.31 (d×d, 1H, *J*=16 Hz, *J*=8.0 Hz), 3.1–2.9 (m, 2H), 2.8 (d×d, 1H, *J*=16 Hz, *J*=7.5 Hz), 1.8–1.5 (m, 4H), 1.4–1.3 (m, 4H), 1.05 (d, 3H, *J*=4.2 Hz), 1.0 (d, 3H, *J*=4.0 Hz); ¹³C-NMR (50 MHz, CDCl₃) δ 143 (C), 138.5 (C), 126.6 (CH), 126.0 (CH), 124.7 (CH), 124.4 (CH), 76.7 (CH), 71.4 (CH), 55.6 (CH), 54.5 (CH), 38.5 (CH₂), 35.9 (CH₂), 35.4 (CH₂), 23.6 (CH₂), 23.5 (CH₃), 23.1 (CH₃); MS (CI, NH₃) *m/z*: 246 (C₁₆H₂₃NO.H⁺ 100%).

4-Nitrobenzoic acid (1S,2R)-2-diisopropylamino-1-indanyl ester 6a

A solution of 88% e.e. **4a** (364 mg, 1.63 mmol), PPh₃ (2.09 g, 8 mmol) and 4-nitrobenzoic acid (1.2 g, 7.2 mmol) in toluene (16 mL) and THF (16 mL) under N₂ was cooled at –20°C. Diethyl azodicarboxylate (DEAD) (1.26 mL, 8.0 mmol) was added *via* syringe into the solution. The mixture was stirred at –20°C for 3 h, allowed to reach room temperature and stirred for another 72 h. The solvents were removed *in vacuo* and the residual oil was purified by chromatography using hexane:EtOAc (95:5) as eluent to give 490 mg (75%) of **6a** as a yellow oil: $[\alpha]_D^{23}=-122.4$ (c=1.1 in CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 8.30 (m, 4H), 7.30–7.15 (m, 4H), 6.52 (d, 1H, *J*=8.2 Hz), 3.9 (q, 1H, *J*=8.4 Hz), 3.3–3.1 (m, 2H), 3.05–2.95 (m, 2H), 1.08 (d, 6H, *J*=6.2 Hz), 0.99 (d, 6H, *J*=6.6 Hz); ¹³C-NMR (50 MHz, CDCl₃) δ 166 (C), 151 (C), 141.5 (C), 139.5 (C), 136.5 (C), 130.8 (CH), 128.5 (CH), 126.8 (CH), 125.0 (CH), 124.1 (CH), 123.5 (CH), 79.7 (CH), 63.6 (CH), 45.0 (CH), 34.2 (CH₂), 23.4 (CH₃) 22.0 (CH₃); IR (KBr) 3110, 3070, 3050, 2966, 1761, 1528, 1341, 1273, 1123, 749, 720 cm⁻¹; MS (CI, NH₃) *m/z*: 383 (C₂₂H₂₆N₂O₄.H+100%).

4-Nitrobenzoic acid (1S,2R)-2-piperidino-1-indanyl ester 6b

Compound **4b** of 88% e.e. (500 mg, 2.03 mmol), PPh₃ (2.62 g, 10 mmol), 4-nitrobenzoic acid (1.49 g, 8.9 mmol) in toluene (22 mL), THF (22 mL) and DEAD (1.58 mL, 10 mmol) were treated

as described for **6a** to give 0.49 g (69%) of **6b** as a yellow oil: $[\alpha]_D^{23} = -149$ ($c = 1.125$ in CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.4–8.3 (m, 4H), 7.4–7.2 (m, 4H), 6.71 (d, 1H, $J = 5.6$ Hz), 3.65–3.55 (m, 1H), 3.30 (d×d, 1H, $J = 16$ Hz, $J = 8$ Hz), 3.0 (d×d, 1H, $J = 16$ Hz, $J = 7.5$ Hz), 2.7–2.5 (m, 4H), 1.8–1.4 (m, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 165 (C), 151 (C), 141.8 (C), 140.0 (C), 136.1 (C), 131.4 (CH), 129.7 (CH), 127.6 (CH), 125.5 (CH), 125.2 (CH), 124.0 (CH), 81.0 (CH), 72.5 (CH), 52.4 (CH_2), 34.9 (CH_2), 26.5 (CH_2), 24.8 (CH_2); IR (KBr) 2937, 2860, 2795, 1723, 1528, 1343, 1271, 1117, 1015, 751, 720 cm^{-1} ; MS (CI, NH_3) m/z : 267 ($\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_4 \cdot \text{H}^+$ 100%).

4-Nitrobenzoic acid (1S,2R)-2-di-n-butylamino-1-indanyl ester **6c**

Compound **4c** of 88% e.e. (600 mg, 2.3 mmol), PPh_3 (2.96 g, 11.3 mmol), 4-nitrobenzoic acid (1.67 g, 10.1 mmol) in toluene (22 mL) and THF (22 mL) and DEAD (1.96 mL, 11.3 mmol) were treated as described for **6a** to give 0.87 g (93%) of **6c** as a yellow oil: $[\alpha]_D^{23} = -109.5$ ($c = 0.97$ in CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.30–8.25 (m, 4H), 7.35–7.25 (m, 4H), 6.65 (d, 1H, $J = 6.2$ Hz), 4.1–3.9 (m, 1H), 3.22 (d×d, 1H, $J = 16$ Hz, $J = 6.9$ Hz), 2.95 (d×d, 1H, $J = 16$ Hz, $J = 8$ Hz), 2.7–2.5 (m, 4H), 1.6–1.5 (m, 4H), 1.4–1.25 (m, 4H), 0.88 (t, 6H, $J = 7.3$ Hz); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 164.6 (C), 150.5 (C), 141.3 (C), 139.5 (C), 135.6 (C), 130.7 (CH), 128.9 (CH), 127.0 (CH), 124.9 (CH), 123.5 (CH), 80.4 (CH), 67.9 (CH), 50.9 (CH_2), 32.2 (CH_2), 30.2 (CH_2), 20.4 (CH_2), 14.0 (CH_3); IR (KBr) 2958, 2880, 1725, 1609, 1530, 1463, 1272, 1104, 1015, 874, 720 cm^{-1} ; MS (CI, NH_3) m/z : 411 ($\text{C}_{24}\text{H}_{30}\text{N}_2\text{O}_4 \cdot \text{H}^+$ 100%).

4-Nitrobenzoic acid (1S,2R)-2-(cis-2,6-dimethylpiperidino)-1-indanyl ester **6d**

Compound **4d** of 99% e.e. (500 mg, 2.03 mmol), PPh_3 (2.62 g, 10 mmol), 4-nitrobenzoic acid (1.49 g, 8.9 mmol) in toluene (22 mL) and THF (22 mL) and DEAD (1.58 mL, 10 mmol) were treated as described for **6a** to give 0.49 g (69%) of **6d** as a yellow oil: $[\alpha]_D^{23} = -105.3$ ($c = 1.05$ in CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 8.30–8.25 (m, 4H), 7.30–7.20 (m, 4H), 6.82 (d, 1H, $J = 7.2$ Hz), 4.35 (q, 1H, $J = 7.5$ Hz), 3.25–3.0 (m, 2H), 2.9–2.75 (m, 2H), 1.7–1.6 (m, 4H), 1.45–1.35 (m, 2H), 1.14 (d, 3H, $J = 6.3$ Hz), 1.13 (d, 3H, $J = 6.3$ Hz); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 164.6 (C), 140.6 (C), 139.2 (C), 135.6 (C), 130.7 (CH), 128.8 (CH), 127.0 (CH), 125.0 (CH), 124.9 (CH), 123.5 (CH), 82.2 (CH), 65.1 (CH), 53.8 (CH), 53.5 (CH), 34.2 (CH_2), 33.4 (CH_2), 20.7 (CH_2), 20.8 (CH_3), 20.5 (CH_3); IR (KBr) 2939, 1717, 1530, 1273, 1123, 874, 745, 720 cm^{-1} ; MS (CI, NH_3) m/z : 395 ($\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4 \cdot \text{H}^+$ 100%).

(1S,2R)-2-Diisopropylamino-1-indanol **5a**

To a solution 4-nitrobenzoic acid (1S,2R)-2-diisopropylamino-1-indanyl ester **6a** of 88% e.e. (380 mg, 0.95 mmol) in CH_2Cl_2 (8 mL) at -20°C under N_2 . DIBALH (1 M in hexanes, 7.8 mL, 7.6 mmol) was added dropwise. The mixture was stirred at -20°C for 19 h. Brine (60 mL) and CH_2Cl_2 (90 mL) were added carefully and the mixture stirred vigorously. The organic phase was separated and the aqueous layer extracted with CH_2Cl_2 (2×30 mL). The combined organic extracts were dried and concentrated *in vacuo*. The residual oil was purified by chromatography using hexane:EtOAc (95:5) as eluent to give 215 mg (100%) of **5a** as an oil: $[\alpha]_D^{23} = -79.9$ ($c = 1.2$ in CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.4–7.2 (m, 4H), 4.92 (d, 1H, $J = 7$ Hz), 3.30–3.20 (m, 3H), 2.9–2.8 (m, 2H), 1.11 (d, 6H, $J = 5.2$ Hz), 1.06 (d, 6H, $J = 4.8$ Hz); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 142.0 (C), 139.6 (C), 127.4 (CH), 126.5 (CH), 124.5 (CH), 123.6 (CH), 75.9 (CH), 67.2 (CH), 45.0 (CH), 34.5 (CH_2), 24.9 i 21.6 (CH_3); IR (KBr) 3400 (t, OH), 2975, 1475, 1400, 1360, 1225, 1050, 750 cm^{-1} ; MS (CI, NH_3) m/z : 334 ($\text{C}_{15}\text{H}_{23}\text{NO} \cdot \text{H}^+$ 100%).

(1S,2R)-2-Piperidino-1-indanol **5b**

Compound **6b** of 88% e.e. (445 mg, 1.24 mmol) in CH_2Cl_2 (11 mL) and DIBALH 1 M in hexanes (9.9 mL, 9.9 mmol) were treated as described for **5a** to give 185 mg (70%) of **5b** as an oil: $[\alpha]_D^{23} = -27.1$ ($c = 0.9$ in CHCl_3); $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 7.6–7.0 (m, 4H), 5.18 (d, 1H, $J = 6.2$ Hz), 3.0–2.8 (m, 3H), 2.7–2.5 (m, 4H), 1.8–1.4 (m, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ 143.4 (C), 139.3 (C), 127.9 (CH), 126.7 (CH), 124.4 (CH), 124.0 (CH), 77.3 (CH), 76.4 (CH), 52.3 (CH_2), 32.3

(CH₂), 25.6 (CH₂), 24.2 (CH₂); IR (KBr) 3395, 2941, 1459, 1212, 1127, 1063, 890, 754. 652 cm⁻¹; MS (CI, NH₃) *m/z*: 218 (C₁₄H₁₉NO.H⁺ 100%).

(1R,2R)-2-Di-n-butylamino-1-indanol 5c

Compound **6c** of 88% e.e. (650 mg, 1.46 mmol) in CH₂Cl₂ (13 mL) and DIBALH (1 M in hexanes, 11.7 mL, 11.7 mmol) were treated as described for **5a** to give 323 mg (85%) of **5c** as an oil; [α]_D²³ = -46.2 (c=0.385 in CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 7.45–7.25 (m, 4H), 5.18 (d, 1H, *J*=7.4 Hz), 3.50 (q, 1H, *J*=7.6 Hz), 3.0 (d×d, 1H, *J*=15.6 Hz, *J*=7.6 Hz), 2.85 (d×d, 1H, *J*=15.6 Hz, *J*=6.6 Hz), 2.8–2.4 (m, 4H), 1.65–1.45 (m, 4H), 1.5–1.3 (m, 4H), 0.95 (t, 6H, *J*=7.3 Hz); ¹³C-NMR (75 MHz, CDCl₃) δ 143.7 (C), 139.7 (C), 127.9 (CH), 126.8 (CH), 124.8 (CH), 124.0 (CH), 77.3 (CH), 72.8 (CH), 51.3 (CH₂), 30.7 (CH₂), 30.0 (CH₂), 20.7 (CH₂), 14.1 (CH₃); IR (KBr) 3375, 2958, 2871, 1617, 1462, 1378, 1169, 1057, 747 cm⁻¹; MS (CI, NH₃) *m/z*: 262 (C₁₇H₂₇NO.H⁺ 100%).

(1S,2R)-2-(cis-2,6-Dimethyl-1-piperidino)-1-indanol 5d

Compound **6d** of 99% e.e. (313 mg, 0.79 mmol) in CH₂Cl₂ (5 mL) and DIBALH (1 M in hexanes, 6.4 mL, 6.4 mmol) were treated as described for **5a** to give 185 mg (70%) of **5b** as an oil; [α]_D²³ = -15.6 (c=1.70 in CHCl₃); ¹H-NMR (200 MHz, CDCl₃) δ 7.35–7.2 (m, 4H), 5.30 (d, 1H, *J*=7.6 Hz), 3.85 (q, 1H, *J*=9.2 Hz), 3.0–2.8 (m, 3H), 2.7 (br s, 1H), 1.8–1.2 (m, 6H), 1.20 (d, 3H, *J*=6.3 Hz), 1.12 (d, 3H, *J*=6.3 Hz); ¹³C-NMR (50 MHz, CDCl₃) δ 143.0 (C), 139.7 (C), 127.8 (CH), 126.7 (CH), 124.8 (CH), 124.5 (CH), 78.9 (CH), 69.7 (CH), 54.8 (CH), 54.5 (CH), 34.5 (CH₂), 34.4 (CH₂), 29.9 (CH₂), 21.7 (CH₂), 21.6 (CH₃), 21.1 (CH₃); IR (KBr) 3400, 2931, 1611, 1463, 1378, 1318, 1216, 1154, 1055, 942, 747 cm⁻¹; MS (CI, NH₃) *m/z*: 246 (C₁₆H₂₃NO.H⁺ 100%).

General procedure for the enantioselective aminoalcohol-catalyzed addition of diethylzinc to aldehydes

The aldehyde (1 mmol) was added at room temperature to a solution of the chiral ligand (0.06 mmol, 6 mol%) in toluene (2 mL), the mixture was stirred for 20 min and then cooled (if necessary) to the desired temperature and diethylzinc (2.2 mL of a 1 M hexanes solution, 2.2 mmol) was added dropwise. The reaction mixture was stirred for the corresponding reaction time under N₂, quenched by the addition of a saturated NH₄Cl solution (10 mL), and the mixture was then extracted with CH₂Cl₂ (3×10 mL). The combined organic extracts were dried and concentrated *in vacuo* and the enantiomeric excesses were determined from the crude mixture by GC analyses. Conditions of GC analyses: β-DEX[®] or α-DEX[®] 120 column, 30 m length, 0.25 mm intern diameter, isotherm temperature program, He as carrier gas (2.4 mL/min). For 1-phenylpropanol: β-DEX 120[®] column, 112°C, *t_R* *R* isomer 49.3 min, *t_R* *S* isomer 52.0 min. For 1-(*p*-tolyl)propanol: β-DEX 120[®] column, 120°C, *t_R* *R* isomer 48.1 min, *t_R* *S* isomer 51.9 min. For 1-(4-methoxyphenyl)propanol: β-DEX 120[®] column, 135°C, *t_R* *R* isomer 65.3 min, *t_R* *S* isomer 68.1 min. For 1-(4-fluorophenyl)propanol: β-DEX 120[®] column, 112°C, *t_R* *R* isomer 53.1 min, *t_R* *S* isomer 58.8 min. For 1-(2-chlorophenyl)propanol: β-DEX 120[®] column, 135°C, *t_R* *R* isomer 45.8 min, *t_R* *S* isomer 50.2 min. For 1-(1-naphthyl)propanol: β-DEX 120[®] column, 160°C, *t_R* *S* isomer 96.5 min, *t_R* *R* isomer 101.1 min. For 1-phenyl-3-pentanol: α-DEX 120[®] column, 115°C, *t_R* *R* isomer 74.4 min, *t_R* *S* isomer 75.6 min. For 5-methyl-3-hexanol: α-DEX 120[®] column, 65°C, *t_R* *R* isomer 14.7 min, *t_R* *S* isomer 15.2 min.

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11. Theoretical and experimental results on the rational design of *cis*-2,6-dimethylpiperidino containing ligands will be reported separately.

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