PREPARATION OF NEW BINAPHTHOL-BASED TRIDENTATE LIGANDS FOR ENANTIOSELECTIVE SYNTHESIS

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Dedicated to Professor Otakar Červinka on the occasion of his 75th birthday.

A versatile method for resolution of 2,2′-dihydroxy-[1,1′-binaphthalene]-3-carboxylic acid has been developed. Four enantiomerically pure tridentate ligands, namely 3-(hydroxymethyl)[1,1′-binaphthalene]-2,2′-diol (**3**), 3-[(2-hydroxyethoxy)[1,1′-binaphthalene]-2,2′-diol (**4**), 3-(2-hydroxy-5-methylbenzyl)[1,1′-binaphthalene]-2,2′-diol (**5**), and 3-(2-hydroxy-4,6-di-*tert*-butylbenzyl)[1,1′-binaphthalene]-2,2′-diol (**6**), were synthesised in excellent yields and used as chiral modifiers of $LiAlH_4$. A modest enantioselectivity was found for the reduction of acetophenone with $LiAlH_4$ modified with ligand **4**.

Key words: Enantioselective reductions; Biaryls; Binaphthyls; Axial chirality; Resolution; BINAL-H.

Enantioselective syntheses are extremely important in synthesis of natural products, drugs and many other classes of compounds[1]. Despite the fact that many very elegant and efficient procedures have been established even in industry[2], the intensity of research in this field is still increasing.

The reduction of prochiral ketones with an optically active reducing agent is a conceptually simple approach to enantiomerically enriched secondary alcohols. This traditional approach is far from being new[3]. Historically, lithium aluminium hydride-based reagents were the first effective reducing agents[4]. The general topic of asymmetric reducing agents has been reviewed[5,6] summarising many applications including those of Červinka group[7]. One of the most effective agents for asymmetric reduction of ketones (BINAL-H) is derived from one equivalent of ethanol, optically active [1,1′-binaphthalene]-2,2′-diol and lithium aluminium hydride[8–10]. The reagent is especially effective for the reductions of aromatic ketones, α,β-unsaturated ketones, and acetylenic ketones. Formation of the major enantiomer of the product in the reduction of an aryl methyl ketone can be

rationalised by assuming a chairlike six-membered-ring transition state in which the small methyl group assumes axial position and the π-electron-containing group assumes equatorial position thus minimising the unfavourable n/π interaction between the axial oxygen of [1,1′-binaphthalene]-2,2′-diol and an unsaturated system if it is in axial position (Fig. 1).

Although other axially chiral diols as modifiers of $LiAlH_4$ have been re-

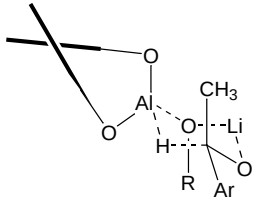


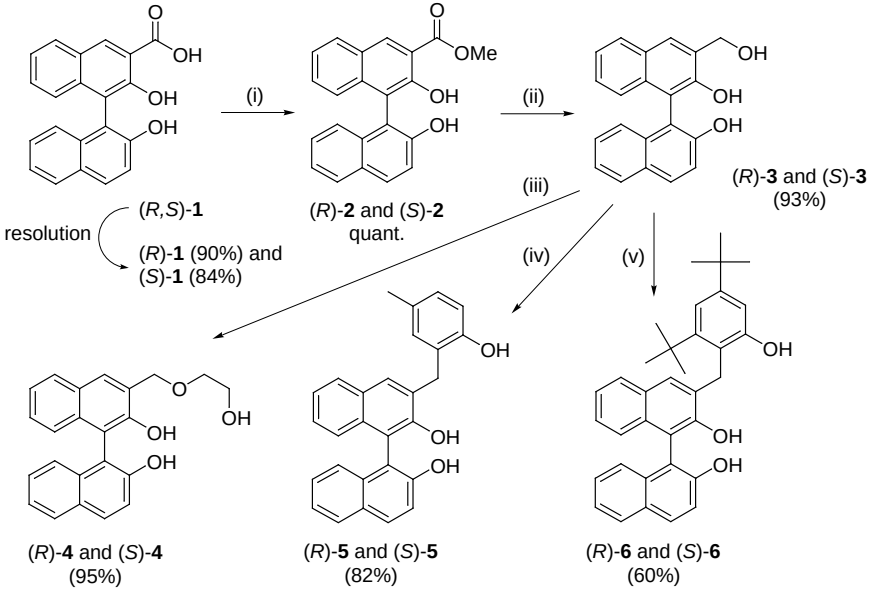
FIG. 1
BINAL-H reduction – transition state

ported in the literature[11–13], the scope of their application has been found similar. More recently[14] it was found that crowned [1,1′-binaphthalene]-2,2′-diol is an excellent chiral modifier in asymmetric $LiAlH_4$ reduction of a variety prochiral ketones including aliphatic ketones. The only drawback of this procedure is the complicated synthesis and poor overall yield of the macrocyclic modifier[15].

Recently, we have reported[16] on a versatile building block – non-symmetrically substituted [1,1′-binaphthalene]-2,2′-diols (binaphthol) which are easily accessible in multigram quantity in racemic form using cross-coupling reaction[17–19]. Enantioselective version of Cu-chiral amine catalysed cross-coupling has also been reported and its mechanism thoroughly studied[20]. We have considered this type of compounds as promising from different points of view. First, they are versatile axially chiral building blocks for chiral dendrimer synthesis[21–23]. Second, they have been used for the synthesis of chiral calix[4]arenes[24] as well as 2,2′-bipyridine-based ligands for cation complexation[25,26]. Moreover, we have found a versatile synthesis of two types of racemic tridentate ligands based on the same synthon namely **4** (ref.[26]) and **5**, **6** (ref.[16]). Both are in principle suitable for an *in situ* preparation of "covalent" BINAL-H shown schematically in Fig. 2.

Here we report on a robust and facile resolution of 2,2′-dihydroxy-[1,1′-binaphthalene]-3-carboxylic acid, furnishing both enantiomers in amounts of tens of grams, synthesis of optically active tridentate ligands **4**, **5**, and **6** (Scheme 1) and finally on a preliminary screening of their applica-

tion as modifiers in lithium aluminium hydride for the enantioselective reduction of acetophenone.



SCHEME 1

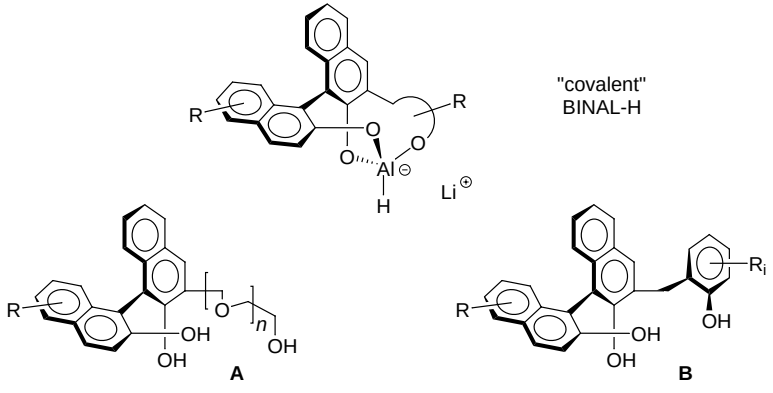


FIG. 2
Covalent template – design of compounds **A** and **B**

Carboxylic acid **1** is readily accessible in large amounts by direct oxidative coupling of methyl 3-hydroxy-2-naphthoate and 2-naphthol followed by hydrolysis of the resulting ester[18–20]. The next step is the resolution of acid **1** performed by sequential crystallisation with cinchonidine and cinchonine. The optimised procedure routinely gives 90% (isolated yield) of pure (+)-*R*-**1** and 84% of (–)-*S*-**1** both in ee better than 99%, cinchonidine and cinchonine being recovered in 92 and 72% yields, respectively. This preparatively very suitable method renders the acid **1** a valuable compound as it can be transformed to wide range of [1,1′-binaphthalene]-2,2′-diol derivatives. Both acids were quantitatively transformed to methyl esters (*R*)-**2** and (*S*)-**2** with diazomethane and reduced to (*R*)-**3** and (*S*)-**3**, respectively, in high yields (93%). These non-symmetrically substituted triols served as building blocks in the synthesis of two types of tridentate ligands, **A** and **B** (Fig. 2) already published in a preliminary form[16,27]. The synthesis of the type-**A** ligand is based on acid-mediated ionisation of benzyl alcohol **3** in the corresponding α,ω-alkanediol as a solvent. Several acids proved to be very efficient in this reaction giving excellent preparative yields of a wide range of ligands **A** (ref.[27]). The same reaction, however, when carried out with enantiomerically pure **3** was accompanied by racemisation of **4**. The necessary prerequisite was the development of a rapid and reliable analytical method for determination of optical purity of (*R*)-**4** and (*S*)-**4**. Fortunately, we have found that a commercially available HPLC chiral column is efficient enough to attain the base-line separation of both enantiomers. Therefore, we have undertaken a detailed study of this reaction and finally we have found the conditions where the racemisation is almost completely suppressed. Some of the results are summarised in Table I.

It is clear that $TiCl_4$ was found to be the best Lewis acid for the reaction accepting also higher concentration of reaction components. The temperature, however, should be around ambient in order to keep racemisation in acceptable limits.

We have further developed a synthetic protocol for preparation of tridentate ligands of general structure **B**. This methodology is based on Friedel–Crafts alkylation of substituted phenols with benzyl-type alcohol **3** in the presence of $BF_3 \cdot OEt_2$. Enantiomeric purity of the resulting ligands **5** and **6** was checked either directly using an appropriate chiral HPLC column or by converting **6** into the tri-*O*-methyl derivative and subsequent ^1H NMR analysis in the presence of a ten-fold excess of the commercially available enantiomerically pure 1-(9-anthryl)-2,2,2-trifluoroethan-1-ol as a chiral solvating agent (CSA).

TABLE I
Racemisation observed in transformation of **3** to **4** in 5 ml of ethylene glycol using various catalysts

Entry	Catalyst : **3** ratio, mg/mg	Temperature, °C	Reaction time	ee, %
		SiO_2·Cl		
1	250 : 100	100	24 h	76
2	250 : 50	100	3.5 h	96.4
3	500 : 50	100	45 min	90.4
4	500 : 50	100	20 min	91.8
5	500 : 50	80	70 min	97
6	500 : 50	80	130 min	95.8
7	500 : 50	60	6 h	98.3
8	125 : 62	60	96 h	91
9	125 : 125	60	120 h	90
10	1 000 : 250	60	7 h	90
11	500 : 250	60	28 h	97.5
		$AlCl_3$		
12	8.5 : 20	100	1 h	92.4
13	25 : 42.5	80	2.5 h	94.6
14	10 : 50	75	26 h	96.2
		BF_3·Et_2O		
15	45 : 50	100	30 min	89
16	45 : 50	120	10 min	70
		$SnCl_4$		
17	40 : 50	100	160 min	92
18	40 : 50	80	26 h	92
		$TiCl_4$		
19	30 : 50	100	135 min	96.2
20	30 : 50	80	3 h	96.6
21	30 : 50	60	24 h	95.2
22	30 : 50	40	14 d	99
23	1 500 : 2 500	40	10 d	98.8

Ligands **4**, **5**, and **6** were treated with one equivalent of $LiAlH_4$ in tetrahydrofuran at room temperature and the resulting solutions were studied by ^{27}Al NMR spectroscopy. The original and well documented[28,29] quintet observed in the ^{27}Al NMR spectrum of $LiAlH_4$ in THF quickly disappeared after the addition of one equivalent of ligand **4**, **5**, or **6** and new signals developed almost immediately, centred at 73 ppm with a shoulder at 45 ppm for ligand **4**, at 67 ppm (diffuse) and 33 ppm (sharp) for ligand **5**, and at 68 ppm (diffuse) and 35 ppm (sharp) for ligand **6**. It is very likely, that the structure of the complex hydride formed *in situ* from ligand **4** is very close to the pure trialkoxyaluminium form[28,29] but the complex hydride formed from both ligands **5** and **6** is composed of at least two species. Additional NMR experiments would be needed[29] to gain better information about the composition and structures in these solutions. As the reduction abilities of the complex hydrides thus obtained were disappointing (see below), we did not study this phenomenon further.

The efficiency of modified $LiAlH_4$ was tested on reduction of acetophenone. This reaction proceeds with low to modest ee. Our results are summarised in Table II. The highest ee of product have been obtained when conversion was kept bellow 50% (entries 3, 4). Higher temperature

TABLE II
Reductions of acetophenone with **4**·$LiAlH_4$

Entry	Conc. of **4** in THF mol/l	Temperature °C	Reaction time	Conversion %	ee of product %
1	0.33	0	6 h	>99	0.3
2	0.17	0	6 h	98	5.2
3	0.11	0	6 h	69	47.4
4	$8.33 \cdot 10^{-2}$	–20	6 d	45.5	58.3
5	$8.33 \cdot 10^{-2}$	–20	19 d	50	51.5
6	$8.33 \cdot 10^{-2}$	25	18 d	53.5	47.1
7	$8.33 \cdot 10^{-2}$	67	3 h	54	39.1
8	$8.33 \cdot 10^{-2}$	67	12 h	56	26.9
9	$8.33 \cdot 10^{-2}$	67	24 h	56	32.9
10	$6.67 \cdot 10^{-2}$	25	40 h	73	35.0
11	$3.33 \cdot 10^{-2}$	25	40 h	59	26.8

(boiling THF) keeps the reaction time in hours instead of days (ambient temperature) but ee obtained is lower (entries 6–9).

Even worse situation has been found with ligands **5** and **6** used for modification of $LiAlH_4$ as the resulting solutions have not been able to reduce acetophenone to a detectable extent at ambient temperature in THF even in large excess and in refluxing THF. The idea that compound **4** should serve as efficient chiral modifier of $LiAlH_4$ failed probably due to at least two possible conformations of the ligand **4** in the coordination sphere of aluminium. This assumption was in agreement with preliminary results of calculation[30]. The compounds **4** and **5**, however, have the third ligating arm one carbon atom shorter. This can be the reason for low reducing power of modified reagents formed *in situ* with $LiAlH_4$.

Despite the unsatisfactory enantioselectivities in reductions presented here, we still believe that ligands **4**, **5**, and **6** possess many potentials for further utilisation. They could serve as ligands for the preparation of chiral Lewis acids as catalysts for enantioselective Diels–Alder reaction[31], allylation of aldehydes[32], or chiral titanium nucleophiles formed from trialkoxytitanium chlorides, or arylmagnesium halogenides that could be applied in the synthesis of diarylmethanols[33].

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. NMR spectra were measured on a Varian Gemini 300HC spectrometer (^1H at 300.07 Hz and ^{13}C at 75.46 Hz) with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants *J* in Hz. Mass spectra were recorded on a ZAB-EQ (VG Analytical) instrument using the EI (70 eV) or FAB (Xe, 8 kV) techniques. IR spectra were obtained on a Nicolet 750 FT IR spectrometer. Optical rotations were determined on a JASCO DIP370 digital polarimeter. Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 ml. Thin-layer chromatography (TLC) was carried out on Polygram SIL-G/UV254 (Macherey–Nagel) plates. HPLC analyses were performed on a ECOM chromatograph with a UV detector operating at 254 nm. Enantiomeric purity was tested on a column with chiral stationary phase Chiralpak OP+ (Daicel) using methanol as a mobile phase.

Resolution of 2,2′-Dihydroxy-[1,1′-binaphthalene]-3-carboxylic Acid (**1**)

Racemic acid **1** (45.3 g, 0.137 mol) was dissolved in 3020 ml of ethyl acetate–toluene 3 : 2 at 50 °C. Pure cinchonidine (40.37 g, 0.137 mol) was added to the warm solution, refluxed for 5 min and allowed to cool to ambient temperature (overnight). Fine crystals of (+)-(*R*) salt (41.0 g) were filtered with suction, washed with a small amount of a cold mixture of solvents, and dried in air. The filtrate was evaporated in vacuum giving 44.0 g of crude (–)-(*S*) salt. Both salts were suspended in water (50 ml/g), heated to 70 °C, acidified with 10% HCl to pH 1 and each hot suspension was filtered with suction leaving pure (+)-(*R*)-**1** (20.4 g,

90%, ee > 99%, $[\alpha]_D^{28}$ +117.1 (*c* 1, CH_3OH)) and impure (–)-(*S*)-**1** (24.8 g) after washing with a small amount of hot water and drying at 50 °C. Cinchonidine was recovered by addition of excess of solid NaOH to the filtrate from (+)-(*R*)-**1** (37.3 g, 92%).

Impure (–)-(*S*)-**1** (24.8 g) was dissolved in 2 500 ml of ethyl acetate–toluene 3 : 2 at 50 °C and cinchonine (22.1 g, 0.075 mol) was gradually added. The resulting solution was refluxed for 5 min and allowed to cool to ambient temperature (overnight). The resulting salt (in form of voluminous solid foam) was filtered off (sometimes a very tedious operation), washed with small amount of the solvent mixture, and dried in air. Solids (11.4 g) can be recovered by evaporation of the filtrate and used in next run after acidification. The dry salt was suspended in water (50 ml/g), heated to 70 °C, and acidified with 10% HCl to pH 1. Pure acid was collected by filtration with suction of a hot suspension giving after drying at 50 °C, 19.0 g, 84% of (–)-(*S*)-**1**, ee > 99%, $[\alpha]_D^{28}$ –116.8 (*c* 1, CH_3OH), cinchonine can be again recovered by basification of the filtrate with solid NaOH giving 16.0 g (72%). Following analytical data were reported[34] for (+)-(*R*)-**1**: ee min. 98%, $[\alpha]_D^{20}$ +118.2 (*c* 1, CH_3OH). ^{1}H NMR ($CDCl_3$): 7.09 d, *J* = 8.3, 1 H; 7.18–7.45 m, 6 H; 7.86–8.02 m, 3 H; 8.83 s, 1 H; 10.48 bs, 1 H.

(*R*)- and (*S*)-Methyl 2,2′-Dihydroxy-[1,1′-binaphthalene]-3-carboxylate (**2**)

Pure (*R*)-**1**, (*S*)-**1**, or racemic **1** (1.0 g, 3.05 mmol) was suspended in 50 ml of ether and slightly more than one equivalent of diazomethane solution in ether was gradually added with stirring. The reaction was monitored by TLC and when the spot of starting acid is no more visible, the excess of diazomethane was decomposed by addition of acetic acid and the reaction mixture was evaporated to yield methyl ester **2** in quantitative yield. HPLC retention times of optically pure methyl esters (Chiralpak OP+, Daicel; 0.5 ml/min of MeOH as mobile phase and UV (254 nm) detector), were 18.70 min for (+)-(*R*)-**2** and 28.0 min for (–)-(*S*)-**2**. Analytical data were in agreement with those published before[18,19].

(*R*)- and (*S*)-3-(2-Hydroxymethyl)[1,1′-binaphthalene]-2,2′-diol (**3**)

Ester **2** (16.0 g, 46.48 mmol) was dissolved in anhydrous ether (250 ml) and gradually added to a stirred suspension of $LiAlH_4$ (8.8 g, 232 mmol) in anhydrous ether. The reaction mixture was stirred for another 4 h (monitored by TLC) at ambient temperature and quenched by dropwise addition of 100 ml of ethyl acetate, 100 ml of ethanol and finally 50 ml of 10% (v/v) HCl. The resulting mixture was filtered with suction through the bed of Celite, the organic phase was separated, washed with saturated solution of $NaHCO_3$ and water (250 + 250 ml), dried with anhydrous $MgSO_4$, and evaporated. The yield was 13.67 g (93.3%) of pure (ee >99%) alcohol (*R*)-**3**, $[\alpha]_D^{28}$ +20.10 (*c* 1.0, CH_3OH) or (*S*)-**3**, $[\alpha]_D^{28}$ –19.90 (*c* 1.0, CH_3OH). HPLC retention times (Chiralpak OP+, Daicel; 0.5 ml/min of MeOH as mobile phase and UV (254 nm) detector) were 10.40 min for (+)-(*R*)-**3** and 16.08 min for (–)-(*S*)-**3**. Spectral data are in agreement with those published in literature for racemic **3** (refs[35,36]) and (+)-(*R*)-**3** (ref.[37]).

(*R*)- and (*S*)-3-[(2-Hydroxyethoxy)methyl][1,1′-binaphthalene]-2,2′-diol (**4**).
General Procedure

Alcohol **3** and a Lewis acid were stirred in dry ethylene glycol. The reaction was quenched by partitioning between water (300 ml of water per 100 ml of the reaction mixture) and diethyl ether (200 ml per each 100 ml of the reaction mixture). The ether layer was dried with anhydrous magnesium sulfate, filtered and evaporated. The product was isolated by column

chromatography on Kiesegel 60 using elution with toluene–acetone 4 : 1. Determination of ee was done by HPLC (Chiralpak OP+, Daicel; 0.5 ml/min of MeOH as mobile phase, UV (254 nm) detector), retention times were 11.12 min for (+)-(*R*)-**4**, m.p. 73–75 °C, $[\alpha]_D^{28}$ +36.50 (*c* 1.0, CH_3OH) and 18.94 min for (–)-(*S*)-**4**, m.p. 75–77 °C, $[\alpha]_D^{28}$ –35.90 (*c* 1.0, CH_3OH). The results are summarised in Table I. For $C_{23}H_{20}O_4$ (360.4) calculated: 76.65% C, 5.59% H; found: 76.80% C, 5.50% H. ^{1}H NMR ($CDCl_3$): 2.21 t, *J* = 5.2, 1 H; 3.71–3.78 m, 4 H; 4.83 d, *J* = 12.3, 1 H; 4.91 d, *J* = 12.3, 1 H; 5.16 s, 1 H; 6.19 s, 1 H; 7.07–7.16 m, 2 H; 7.25–7.39 m, 5 H; 7.80–7.89 m, 4 H.

(*R*)- and (*S*)-3-(2-Hydroxy-5-methylbenzyl)[1,1′-binaphthalene]-2,2′-diol (**5**)

To a mixture of **3** (2.0 g, 6.38 mmol) and 4-methylphenol (3.42 g, 31.6 mmol) in 170 ml of CH_2Cl_2, $BF_3{\cdot}Et_2O$ (0.897 g, 6.32 mmol) was added at 5 °C with stirring. The reaction mixture was quenched with water (150 ml) after 2 h at the same temperature. The organic layer was separated, the aqueous layer was extracted with dichloromethane (2 × 50 ml), the organic phases were combined, dried with anhydrous $MgSO_4$ and evaporated. Excess of 4-methylphenol was distilled off by short-path distillation *in vacuo* and the residual product was chromatographed on column of silica gel using gradient elution (10% petroleum ether in toluene to 7% ethyl acetate in toluene for *R* enantiomer and 10% petroleum ether in toluene to 5% acetone in toluene for *S* enantiomer). Yield 2.089 g (81.6%) of (*R*)-**5**, m.p. 95–97 °C, $[\alpha]_D^{28}$ +42.7 (*c* 1.0, CH_3OH) and 2.095 g (82 %) for (*S*)-**5**, m.p. 90–93°C, $[\alpha]_D^{28}$ –43.4 (*c* 1.0, CH_3OH). HPLC retention times (Chiralpak OP+, Daicel; 0.5 ml/min of MeOH as mobile phase, UV (254 nm) detector) were 22.5 min for (+)-(*R*)-**5** and 58.3 min for (–)-(*S*)-**5**. For $C_{28}H_{22}O_3$ (406.2) calculated: 82.74% C, 5.46% H; found: 82.58% C, 5.40% H. ^{1}H NMR ($CDCl_3$): 2.31 s, 3 H; 4.16 dd, *J* = 21.5, 6.5, 2 H; 5.03 bs, 1 H; 5.79 bs, 1 H; 6.17 bs, 1 H; 6.73 d, *J* = 8.2, 1 H; 6.95 d, *J* = 7.9, 1 H; 7.10–7.39 m, 8 H (Ar); 7.84–7.98 m, 4 H (Ar). ^{13}C NMR ($CDCl_3$): 20.50, 31.19, 111.25, 111.77, 116.36, 117.82, 124.00, 124.23, 124.24, 124.31, 125.95, 126.90, 127.47, 127.97, 128.40, 128.60, 129.03, 129.10, 129.51, 129.79, 130.23, 130.85, 131.35, 131.39, 132.45, 133.41, 150.37, 151.41, 152.71.

(*R*)- and (*S*)-3-(2-Hydroxy-4,6-di-*tert*-butylbenzyl)[1,1′-binaphthalene]-2,2′-diol (**6**)

To a mixture of **3** (0.5 g, 1.58 mmol) and 3,5-di-*tert*-butylphenol (1.63 g, 7.9 mmol) in 60 ml of CH_2Cl_2, $BF_3{\cdot}Et_2O$ (0.224 g, 1.58 mmol) was added at 5 °C with stirring. The reaction mixture was quenched with water (100 ml) after 2 h at the same temperature. The organic layer was separated, the aqueous layer was extracted with dichloromethane (2 × 50 ml), the organic phases were combined, dried with anhzdrous $MgSO_4$ and evaporated. Excess of 3,5-di-*tert*-butylphenol was distilled off by short-path distillation *in vacuo* and the residual product was chromatographed on a column of silica gel using gradient elution (10% petroleum ether in toluene to 10% acetone in toluene for *R* enantiomer and 10% petroleum ether in toluene to 5% acetone in toluene for *S* enantiomer). Yield 0.464 g (59%) of (*R*)-**6**, 141–143 °C, $[\alpha]_D^{28}$ –11.1 (*c* 1.0, CH_3OH) and 0.474 g (60%) for (*S*)-**6**, m.p. 138–141 °C, $[\alpha]_D^{28}$ +12.1 (*c* 1.0, CH_3OH). HPLC retention times (Chiracel OD-H, Daicel; 0.5 ml/min of hexane–isopropyl alcohol 9 : 1 as mobile phase and UV (254 nm) detector) were 27.9 min for (–)-(*R*)-**6** and 32.6 min for (+)-(*S*)-**6**. For $C_{35}H_{36}O_3$ (504.3) calculated: 83.30% C, 7.19% H; found: 83.10% C, 7.31% H. ^{1}H NMR ($CDCl_3$): 1.36 bs, 9 H (*t*-Bu); 1.41 bs, 9 H (*t*-Bu); 4.21 s, 2 H (-CH_2-); 5.05 bs, 1 H (-OH); 5.66 bs, 1 H (Ar-OH); 6.60 bs, 1 H (Ar-OH); 7.13 d, *J* = 8.2,

1 H (Ar); 7.25–7.41 m, 7 H (Ar); 7.81–8.01 m, 6H (Ar). ^{13}C NMR ($CDCl_3$): 28.14, 31.45, 31.99, 34.82, 36.36, 110.53, 111.18, 111.34, 116.38, 117.85, 120.19, 123.84, 123.92, 124.05, 124.29, 126.62, 127.54, 128.21, 128.44, 129.01, 129.12, 129.49, 129.57, 131.43, 132.14, 133.53, 149.84, 150.43, 151.44, 152.93, 155.02.

Enantioselective Reductions of Acetophenone. General Procedure

A solution of 1 M $LiAlH_4$ in THF (0.5 ml, 0.5 mmol) was treated with 0.5 mmol of ligand (180 mg of **4**, 203 mg of **5**, or 252 mg of **6**) and stirred for 30 min (ligand **4**) up to 18 h (ligands **5**, **6**) at ambient temperature. Acetophenone (0.33 equivalents, 20 mg, 0.0195 ml) was added. The reaction conditions for ligand **4** are summarised in Table II. The reaction mixture was stirred both at ambient temperature and under reflux for 2 h for ligands **5** and **6**. The reaction was quenched by addition of ether saturated with water, and then of water and the organic layer was directly analysed on a chiral HPLC column (Chiralcel OD-H, Daicel; 0.5 ml/min of 10% isopropyl alcohol in hexane phase, UV (254 nm) detector), retention times were 13.07 min for *R*- and 14.61 min for *S*-enantiomer of 1-phenylethan-1-ol.

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