The Synthesis of Spirobitetraline Phosphoramidite Ligands and their Application in Rhodium-Catalyzed Asymmetric Hydrogenation

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Abstract: A racemic 1,1′-spirobitetralin-8,8′-diol (SBITOL) was conveniently synthesized from 3-methoxybenzaldehyde in 26% yield over 9 steps and resolved *via* its bis-(*S*)-camphorsulfonates. The corresponding chiral spirobitetraline monophosphoramidite ligands have been prepared and their rhodium complexes were applied in the asymmetric hydrogenation of dehydroamino esters with good to excellent enantioselectivities (up to 99.3% *ee*).

Keywords: asymmetric catalysis; hydrogenation; monophosphoramidite; rhodium; spirobitetraline

Introduction

Asymmetric hydrogenation is one of the most powerful tools for the production of optically pure compounds and most of the highly efficient catalysts developed in recent decades for this transformation are transition metal complexes containing one or more chiral phosphorus ligands.[1] The first example of catalytic asymmetric hydrogenation was reported by Horner and Knowles who used P-chiral monodentate phosphane ligands which provided poor enantioselectivity.[2] By introducing a C_2-symmetric bidentate diphosphine ligand DIOP, which had a chirality on the backbone, Kagan significantly improved the enantioselectivity of asymmetric hydrogenation to a practically useful level.[3] Since then, the chiral bidentate phosphorus ligands, especially those with a C_2-symmetry, have predominated in asymmetric hydrogenation reactions. Enormous numbers of chiral bidentate phosphorus ligands such as BINAP,[4] BIPHEMP,[5] DuPhos,[6] PennPhos,[7] and P-Phos[8] have been developed and demonstrated to be highly enantioselective in asymmetric hydrogenation. On the contrary, due to synthetic difficulties and poor stability features, P-chiral monodentate phosphane ligands have received less attention. Recently, the potential of chiral monodentate phosphorus ligands was re-discovered, and several efficient chiral monophosphorus ligands, which have chirality on the backbone, instead of on a phosphorus atom, such as binaphthyl monophosphites[9] and monophosphoamidites,[10] have been developed and applied in the asymmetric hydrogenation

of functionalized olefins with good to excellent enantioselectivities. These results show that the enantioselectivities induced by chiral monophosphorus ligands are comparable or even superior to those obtained by chiral bidentate phosphorus ligands.

Besides binaphthyl monophosphorus compounds, the monophosphorus compounds containing a 1,1′-spirobiindane backbone were another type of efficient ligands in asymmetric hydrogenation. For instance, the monodentate spiro phosphoramidite SIPHOS (**1**) and phosphonites showed very high enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins such as α- and β-dehydroamino acid derivatives,[11] α-arylenamides,[12] and unprotected enamines.[13] The chiral spiro monophosphoramidite ligand **2** having a 9,9′-spirobixanthene backbone was reported by Zhang and co-workers and found to be efficient for the Rh-catalyzed asymmetric hydrogenations of functionalized olefins.[14] In order to search for new efficient ligands and to systematically study the effect of the spiro skeleton of ligands on the chiral induction and reactivity of catalysts, we "inserted" a CH_2 group into the five-membered rings of 1,1′-spirobiindane in ligand **1** to give new spiro monophosphoramidite ligands **3** (Figure 1). We reasoned that this structural change would increase the rigidity of the ligand and might thus influence the enantioselectivity of the catalysts in asymmetric hydrogenation. Herein, we described the synthesis of spiro phosphoramidite ligands **3** containing a 1,1′-spirobitetraline backbone and their application in Rh-catalyzed asym-
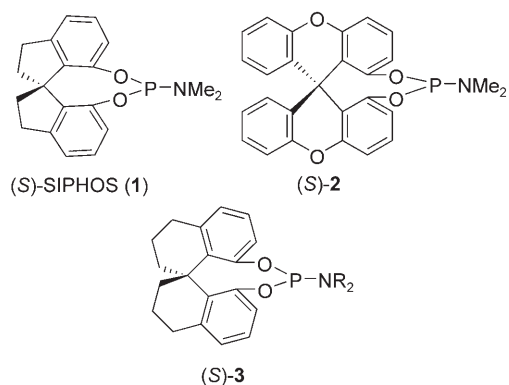
Figure 1. Chiral spiro monodentate phosphoramidite ligands.

metric hydrogenation of α-dehydroamino esters in excellent enantioselectivities.

Results and Discussion

Synthesis of Sirobitetraline Phosphoramidites

The 1,1′-spirobitetralin-8,8′-diol (**4**) was a key intermediate in the preparation of phosphoramidite ligands **3**. A literature survey revealed that the diol **4** was an unknown compound.[15] By following the double cyclization strategy for the synthesis of spiro diols such as 1,1′-spirobiindane-7,7′-diol and 9,9′-spirobifluorene-1,1′-diol,[16] the spiro diol **4** was prepared in high yield from 3-methoxyenzaldehyde. The synthetic route is outlined in Scheme 1. Under classical Knoevenagel reaction conditions, 3-methoxybenzaldehyde was condensed with malonic acid, followed by reduction with LiAlH$_4$ and bromination with PBr$_3$,

giving the bromide **5** in 62% yield.[17] The Grignard reagent generated from the bromide **5** reacted with methyl formate to provide the alcohol **6** in 85% yield. The alcohol **6** was then converted to the ketone **7** quantitatively using the Swern oxidation procedure. Selective bromination of the ketone **7** with NaBr in the presence of H$_2$O$_2$ yielded the dibromide **8** exclusively. In the ring-closing step, the dibromide **8** was smoothly cyclized in methanesulfonic acid by the same procedure which we used in the preparation of 9,9′-spirobifluorene-8,8′-diols,[16a] providing 1,1′-spirobitetraline **9** in 65% yield. After debromination of compound **9** with BuLi at −78°C followed by demethylation with NaSEt in DMF at 160–170°C, the racemic 1,1′-spirobitetralin-8,8′-diol (**4**) was obtained in 26% overall yield from 3-methoxybenzaldehyde.

The X-ray crystal structure of 1,1′-spirobitetralin-8,8′-diol (**4**) was measured and compared with that of 1,1′-spirobiindane-7,7′-diol (Figure 2). It was found that each of the six-membered rings in 1,1′-spirobitetralin-8,8′-diol adopt an envelope conformation and the "insertion" of CH$_2$ groups leads to a crowded and rigid spiro skeleton. The bond angle of C(9)−C(8)−C(17) in 1,1′-spirobitetralin-8,8′-diol (111.6°) was smaller than the corresponding bond angle of C(9)−C(8)−C(17) in 1,1′-spirobiindane-7,7′-diol (118.8°), which indicated that the two phenyl rings in the 1,1′-spirobitetralin-8,8′-diol (**4**) were squeezed closer to each other. The dihedral angle between the two phenyl rings in 1,1′-spirobitetralin-8,8′-diol (85.1°) is larger than that in 1,1′-spirobiindane-7,7′-diol (70.0°). The distance betweeen O(1) and O(2) in 1,1′-spirobitetralin-8,8′-diol (**4**) (3.96 Å) is also larger than that in 1,1′-spirobiindane-7,7′-diol (3.43 Å). These structural properties would make spirobitetraline phosphoramidite ligands more sensitive to the steric hindrance of
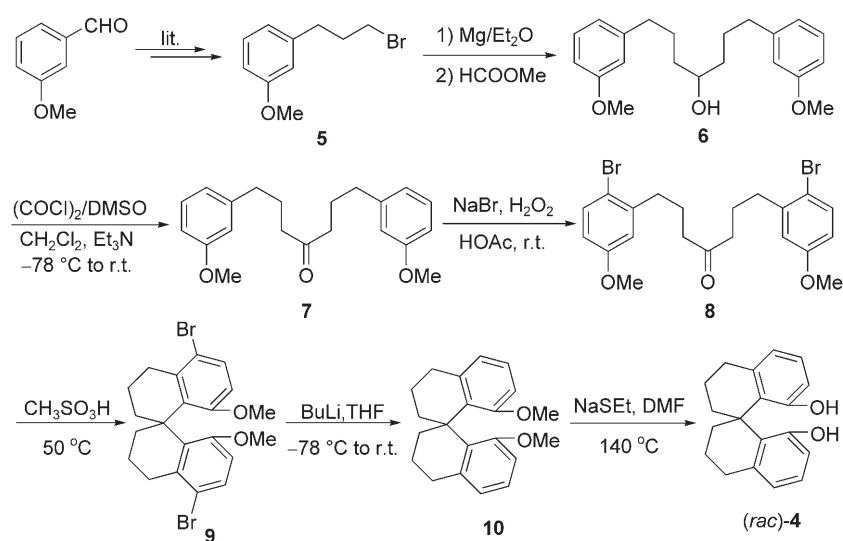
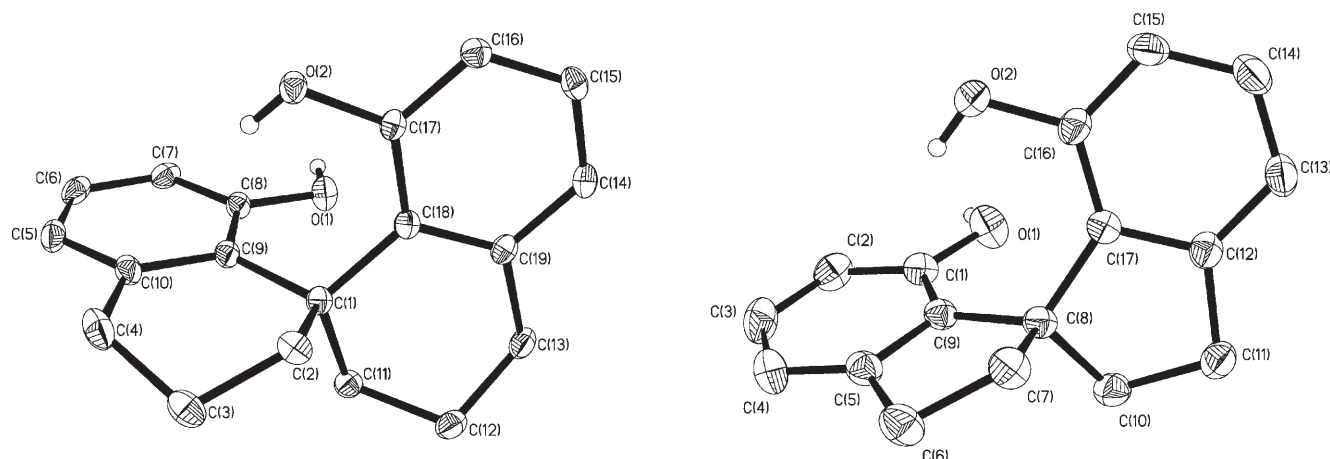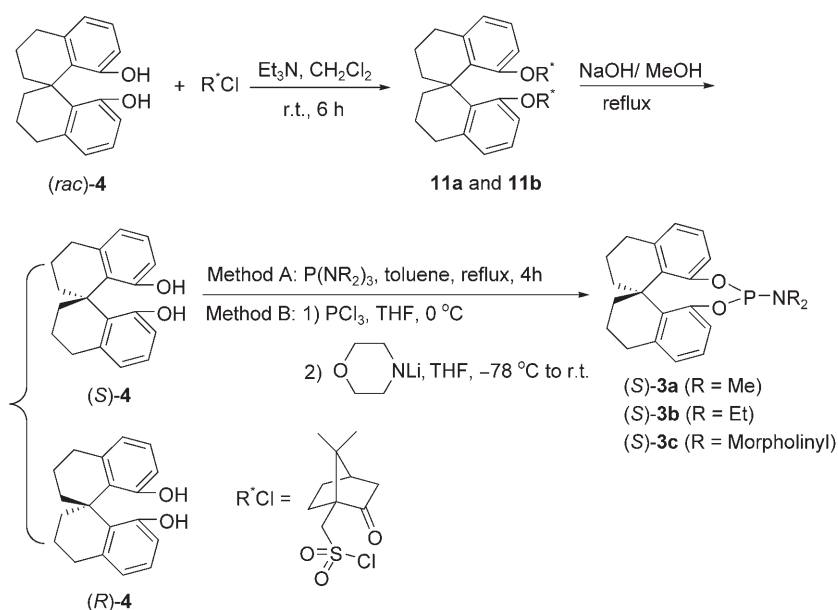**Scheme 1.** Synthesis of 1,1′-spirobitetralin-8,8′-diol (**4**).

Figure 2. Perspective views of 1,1′-spirobitetralin-8,8′-diol (*left*) and 1,1′-spirobiindane-7,7′-diol (*right*).

Scheme 2. Synthesis of the monophosphoramidate ligands (*S*)-**3**.

the substrate than spirobiindane phosphoramidite ligands in asymmetric reactions.

The racemic spiro diol **4** was resolved *via* the diastereomers of its bis-(*S*)-camphorsulfonates (Scheme 2). The racemic diol **4** was converted to the corresponding diastereomers **11a** and **11b** by reacting with (1*S*)-(+)-10-camphorsulfonyl chloride. The diastereomers **11a** and **11b** were separated in 95% and 96% yield, respectively, by chromatography on a silica gel column. The optically pure spiro diols (*S*)-(+)-**4** and (*R*)-(−)-**4** were obtained in good yield (80%) from the hydrolysis of **11a** and **11b** in refluxing aqueous NaOH/MeOH. The absolute configuration of the diol (*S*)-**4** was determined by X-ray diffraction analysis of a single crystal of its L-menthoxycarboxylate (Figure 3).

The spirobitetraline phosphoramidites (*S*)-**3** were prepared by using the procedure for the synthesis of the SIPHOS ligands.[11a] The diol (*S*)-**4** was heated with P(NMe₂)₃ or P(NEt₂)₃ in toluene at 100 °C for 4 h to produce the phosphoramidites (*S*)-**3a** and (*S*)-**3b** in 62% and 45% yield, respectively. The phosphoramidite (*S*)-**3c** was prepared in 67% yield by reacting (*S*)-**4** with PCl₃ in THF at room temperature, followed by treatment with lithium morpholide at −78 °C. The phosphoramidites (*R*)-**3a–c** were also synthesized from the diol (*R*)-**4**.

Asymmetric Hydrogenation of α-Dehydroamino Esters

In order to investigate the behavior of spirobitetraline monophosphoramidite ligands **3** in asymmetric catalysis, the rhodium-catalyzed hydrogenation of methyl α-acetamidocinnamate (**12a**) was performed. Solvent
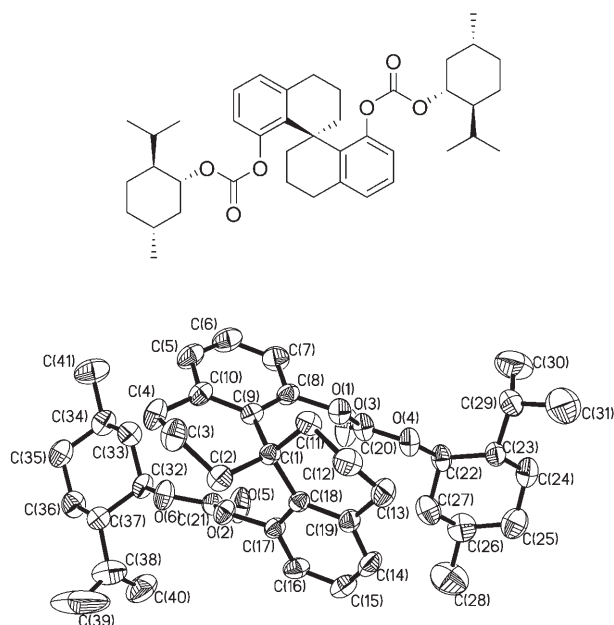
Figure 3. Perspective view of the ʟ-menthoxycarboxylate derivative of (S)-**4**.

experiments showed that the hydrogenation could be carried out in CH$_2$Cl$_2$ under the conditions of 1 mol % [Rh(COD)$_2$BF$_4$], 2.1 mol % (S)-**3a**, 1 atm H$_2$ at room temperature, providing the product (S)-**13a** with 97.5 % *ee* (Table 1, entry 1). Ethyl acetate and toluene also could serve as solvent for this hydrogenation, but due to the low solubility of **12a** in these solvents, the hydrogenation could not be completed and only moderate conversions were obtained (entries 2 and 3).

When using coordinating solvents such as MeOH, acetone and THF, no hydrogenation took place (entries 4 and 5). Considering both the enantioselectivity of reaction and conversion of substrate a mixture of CH$_2$Cl$_2$ and toluene (v/v = 1/4) was found to be the best choice of solvent. In this mixed solvent the hydrogenation reaction was completed within 36 h and the product (S)-**13a** was obtained in 99.6 % *ee* (entry 9). This result was better than those obtained by using the ligands SIPHOS (**1**) (98 % *ee*) and Mono-Phos (98 % *ee*) under the same reaction conditions. Increasing hydrogen pressure to 10 atm resulted in a faster reaction with no obviously diminished enantioselectivity (entry 10). Ligands (S)-**3b** and (S)-**3c** also can be used for this transformation albeit with lower reactivities and enantioselectivities (entries 11 and 12).

Under the optimized reaction conditions, various dehydroamido acid derivatives **12** can be hydrogenated with good to excellent enantioselectivities (Table 2). The superiority of spirotetraline phosphoramidite **3a** over the SIPHOS in terms of enantioselectivity was observed in the hydrogenation of the substrates having a *para*-substituent on the phenyl ring regardless of the electronic properties of the substituents (entries 2–5). However, in the hydrogenation of the substrates having a *meta*- or *ortho*-substituent the spirotetraline ligand **3a** gave lower enantioselectivities than those obtained by SIPHOS (entries 7 and 8). These results demonstrate that the crowded spirotetraline phosphoramidite ligands are more sensitive to the steric hindrance of the substrate than the spirobiindane phosphoramidite ligands.

Table 1. Asymmetric hydrogenation of methyl α-acetamidocinnamate (**12a**) catalyzed by the Rh complexes of ligands (S)-**3**.[a]
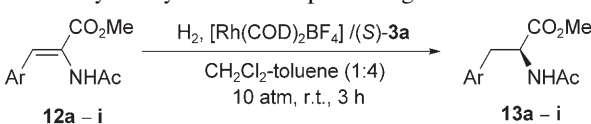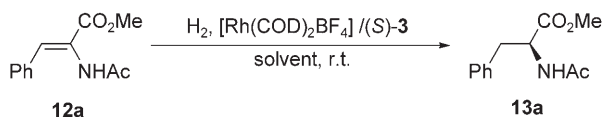

Entry	Solvent	Ligand	PH$_2$ [atm]	Time [h]	Yield [%]	% *ee*[b]
1	CH$_2$Cl$_2$	(S)-**3a**	1	24	100	97.5
2	EA	(S)-**3a**	1	36	48	98.3
3	Toluene	(S)-**3a**	1	36	52	99.6
4	MeOH	(S)-**3a**	1	36	NR[c]	ND[d]
5	Acetone	(S)-**3a**	1	36	NR	ND
6	THF	(S)-**3a**	1	36	NR	ND
7	CH$_2$Cl$_2$-Toluene (3/2)	(S)-**3a**	1	24	100	97.1
8	CH$_2$Cl$_2$-Toluene (2/3)	(S)-**3a**	1	36	100	99.2
9	CH$_2$Cl$_2$-Toluene (1/4)	(S)-**3a**	1	36	100	99.6
10	CH$_2$Cl$_2$-Toluene (1/4)	(S)-**3a**	10	2	100	99.2
11	CH$_2$Cl$_2$-Toluene (1/4)	(S)-**3b**	10	12	100	92.0
12	CH$_2$Cl$_2$-Toluene (1/4)	(S)-**3c**	10	15	100	87.3

[a] *Reaction conditions:* 0.1 mmol **12a**, 0.001 mmol [Rh(COD)$_2$]BF$_4$, 0.0021 mmol (S)-**3**, CH$_2$Cl$_2$/toluene (1/4, v/v).
[b] Determined by chiral GC (Chirasil-VAL III FSOT).
[c] No reaction.
[d] Not determined.

Table 2. Asymmetric hydrogenation of α-dehydroamino esters catalyzed by the Rh complex of ligand **3a**.[a]

Entry	Ar	Product	% ee[b]	Configuration
1	C_6H_5	**13a**	99.2 (98)	S
2	4-MeC$_6$H$_4$	**13b**	99 (98)	S
3	4-MeOC$_6$H$_4$	**13c**	99 (96)	S
4	4-ClC$_6$H$_4$	**13d**	99 (98)	S
5	4-NO$_2$C$_6$H$_4$	**13e**	99.3 (99)	S
6	3-MeOC$_6$H$_4$	**13f**	97 (97)	S
7	3-NO$_2$C$_6$H$_4$	**13g**	98 (99)	S
8	2-ClC$_6$H$_4$	**13h**	92 (97)	S
9	2-Naphthyl	**13i**	98	S

[a] *Reaction conditions:* 0.1 mmol **12**, 0.001 mmol [Rh-(COD)$_2$]BF$_4$, 0.0021 mmol (*S*)-**3a**, CH$_2$Cl$_2$/toluene (1/4, v/v), 10 atm of H$_2$, r.t., 2–3 h, 100% conversion.

[b] Determined by chiral GC (Chirasil-VAL III FSOT). The numbers in parentheses were obtained using (*S*)-SIPHOS.

Conclusions

A novel class of chiral spiro phosphoramidite ligands based on spirobitetraline backbone has been developed. The structure study revealed that the spirobitetraline backbone is crowded and rigid, which resulted in the enantioselectivity of the spirobitetraline phosphoramidite ligands being sensitive to the steric hindrance of the substrate in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives. The excellent enantioselective induction of the ligand **3a** in this study indicated a high potential for a wide application of the new spirobitetraline phosphoramidite ligands in transition metal-catalyzed asymmetric catalysis.

Experimental Section

General Remarks

All reactions and manipulations were performed using standard Schlenk techniques and in an argon-filled glovebox (VAC DRI-LAB HE 493). THF and toluene were distilled from sodium benzophenone ketyl. Ethyl acetate and DCM were distilled from calcium hydride. MeOH was distilled from Mg. Actone was distilled from P$_2$O$_5$. Hydrogen gas (99.999%) was purchased from Boc Gas Inc. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on Brucker-300 and Varian-400 spectrometers. Chemical shifts were reported in ppm downfield from internal Si(CH$_3$)$_4$ and external 85% H$_3$PO$_4$, respectively. Optical rotations were determined using a Perkin–Elmer 341 MC polarimeter. Elemental analyses were performed on Yanaca CDRDER MT-3 instrument.

Mass spectra were recorded on a LCQ advantage spectrometer with ESI resource. HR-MS were recorded on APEXII and ZAB-HS spectrometer. GC analyses were performed using Hewlett Packard Model HP 6890 Series. HPLC analyses were performed using a Hewlett Packard Model HP 1100 Series or Waters 2996 instruments.

Synthesis of Racemic 1,1′-Spirobitetralin-8,8′-diol (4)

1,7-Bis(3-methoxyphenyl)heptan-4-ol (6): A solution of methyl formate (2.4 g, 0.047 mol) in THF (20 mL) was added slowly to a stirred solution of 3-(3-methoxyphenyl)-propylmagnesium bromide in THF (160 mL), which was prepared from 1-(3-bromopropyl)-3-methoxybenzene (**5**)[17] (22.9 g, 0.10 mol) and magnesium (2.6 g, 0.11 mol), at 5 °C. After the addition, the ice-water bath was removed, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was re-cooled to 0 °C by an ice-water bath and aqueous HCl (4 M, 120 mL) was carefully added. The organic layer was extracted with ethyl acetate (3 × 100 mL), and washed with brine and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel column using ethyl acetate/petroleum ether (1:3) as eluent to afford *1,7-bis(3-methoxyphenyl) heptan-4-ol* (**6**) as a colorless oil; yield: 13.0 g (85%); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.17–7.21 (m, 2H), 6.77 (d, J = 7.2 Hz, 2H), 6.72 (s, 4H), 3.79 (s, 6H), 2.59 (t, J = 8.0 Hz, 4H), 1.75 (m, 2H), 1.63 (m, 2H), 1.48 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 159.8, 144.2, 129.5, 121.1, 114.4, 111.2, 71.9, 55.4, 37.2, 36.1, 27.5; MS (ESI): m/z = 327 (M$^+$); anal. calcd. for C$_{21}$H$_{28}$O$_3$: C 76.79, H 8.59; found: C 76.91, H 8.39.

1,7-Bis(3-methoxyphenyl)heptan-4-one (7): Dimethyl sulfoxide (3.5 mL, 45 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise to a stirred solution of oxalyl chloride (4.1 mL, 44 mmol) in CH$_2$Cl$_2$ (120 mL) at −50 °C. The mixture was stirred for 15 min, and a solution of 1,7-bis(3-methoxyphenyl)-heptan-4-ol (**6**) (13.0 g, 40 mmol) in CH$_2$Cl$_2$ (20 mL) was added dropwise during 15 min. The resulting mixture was stirred for an additional 30 min below −50 °C, triethylamine (21.0 mL, 150 mmol) was added dropwise. After stirring at −50 °C for 15 min and at room temperature for 2 h, 50 mL of water were added, the organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 50 mL). The combined organic layer was washed successively with dilute HCl solution, saturated Na$_2$CO$_3$ and brine, dried over anhydrous MgSO$_4$. After removal of the solvent, the residue was purified by chromatography on silica gel column using ethyl acetate/petroleum ether (1:6) as eluent to afford *1,7-bis(3-methoxyphenyl)heptan-4-one* (**7**) as a colorless oil; yield: 13.0 g (100%); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.19 (t, J = 8.0 Hz, 2H), 6.75–6.70 (m, 6H), 3.79 (s, 6H), 2.58 (t, J = 7.2 Hz, 4H), 2.38 (t, J = 7.2 Hz, 4H), 1.90 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 210.6, 159.7, 143.3, 129.3, 120.9, 114.2, 111.2, 55.1, 41.9, 35.1, 25.0; MS (EI): m/z = 326 (M$^+$); anal. calcd for C$_{21}$H$_{26}$O$_3$: C 77.27, H 8.03. Found: C 76.98, H 7.93.

1,7-Bis(2-bromo-5-methoxyphenyl)heptan-4-one (8): A solution of 20 mL 30% aqueous H$_2$O$_2$ in 60 mL acetic acid was added dropwise to a stirred solution of 1,7-bis(3-methoxyphenyl)heptan-4-one (**7**) (11.2 g, 34 mmol) and NaBr (7.03 g, 34 mmol) in acetic acid (200 mL). The mixture was

stirred at room temperature overnight. The solvent of the mixture was removed under reduced pressure, and the residue was re-dissolved with water (50 mL) and CH_2Cl_2 (200 mL). After separation of the organic layer, the aqueous layer was extracted with CH_2Cl_2 (2×70 mL). The combined organic layer was washed with dilute HCl, saturated Na_2CO_3 and brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel column using ethyl acetate/petroleum ether (1:7) as eluent to afford *1,7-bis(2-bromo-5-methoxyphenyl)heptan-4-one* (**8**) as a white solid; yield: 16.5 g (99%); mp 54–56°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 8.8$ Hz, 2H), 6.75 (d, $J = 2.8$ Hz, 2H), 6.64–6.61 (m, 2H), 3.77 (s, 6H), 2.68 (t, $J = 8.0$ Hz, 4H), 2.46 (t, $J = 7.2$ Hz, 4H), 1.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 210.3$, 158.9, 141.9, 133.3, 116.0, 114.9, 113.3, 55.4, 41.9, 35.4, 23.8; HR-MS (EI): $m/z = 482.0096$, calcd. for $C_{21}H_{24}Br_2O_3$: 482.0092.

5,5′-Dibromo-8,8′-dimethoxy-1,1′-spirobitetraline (9): The 1,7-bis(2-bromo-5-methoxyphenyl)-heptan-4-one (**8**) (4.0 g, 8.3 mmol) was added to MsOH (30.0 mL) while cooling by an ice bath. After stirring for 6 h, the solution was quenched by water. The resulting mixture was extracted with CH_2Cl_2 (3×100 mL), and the combined organic layer was washed with dilute HCl, saturated Na_2CO_3 and brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by recrystallization with ethyl acetate to afford *5,5′-dibromo-8,8′-dimethoxy-1,1′-spirobitetraline* (**9**) as a white solid; yield: 2.5 g (65%); mp 212–214°C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 8.4$ Hz, 2H), 6.46 (d, $J = 8.4$ Hz, 2H), 3.16 (s, 6H), 3.07 (m, 2H), 2.60 (m, 2H), 1.98 (m, 2H), 1.88 (m, 2H), 1.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.4$, 138.7, 138.4, 129.4, 116.7, 112.3, 55.7, 40.4, 33.9, 31.6, 20.0; MS (EI): $m/z = 466$ (M[+]); anal. calcd for $C_{21}H_{22}Br_2O_2$: C 54.10, H 4.76; mfound: C 53.79, H 5.20.

8,8′-Dimethoxy-1,1′-spirobitetraline (10): To a stirred solution of 5,5′-dibromo-8,8′-dimethoxy-1,1′-spirobitetraline (**9**) (5.36 g, 11.5 mmol) in dry THF (90 mL) was slowly added *n*-BuLi (25.2 mL, 53 mmol, 2.1 M in hexane) at −78°C within 1 h. The solution was stirred at −78°C for additional 1 h, and the reaction then quenched by slowly adding EtOH (4.3 mL) at −78°C. The solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by recrystallization with ethyl acetate to afford *8,8′-dimethoxy-1,1′-spirobitetraline* (**10**) as a white solid; yield: 3.50 g (99%); mp 143–145°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.98$ (t, $J = 4.8$ Hz, 2H), 6.71 (d, $J = 7.5$ Hz, 2H), 6.58 (d, $J = 8.1$ Hz, 2H), 3.20 (s, 6H), 2.80 (m, 4H), 2.02 (m, 4H), 1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.3$, 139.4, 136.5, 125.0, 121.4, 111.0, 55.5, 39.0, 35.0, 31.0, 20.3; HRMS (EI): $m/z = 308.1776$, calcd. for $C_{21}H_{24}O_2$: 308.1776.

1,1′-Spirobitetralin-8,8′-diol (4): To a suspension of NaH (5.0 g, 0.21 mol) in 150 mL DMF, EtSH (7.8 mL 0.12 mol) was added slowly while cooling by an ice bath. The 8,8′-dimethoxy-1,1′-spirobitetraline (**10**) (5.5 g, 18 mmol) was added in one portion, and the mixture was refluxed (160–170°C) for 12 h. The reaction was quenched by adding dilute HCl while cooling by an ice bath. Ethyl acetate

(200 mL) was added and the organic layer was separated. The aqueous layer was extracted with additional ethyl acetate (50 mL). The combined organic layer was washed with dilute HCl, saturated Na_2CO_3, brine, and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by chromatography on silica gel column using ethyl acetate/petroleum ether (1:6) as eluent to afford *1,1′-spirobitetralin-8,8′-diol* (**4**) as a white solid; yield: 3.8 g (76%); mp 132–133°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.09$ (t, $J = 7.5$ Hz, 2H), 6.78 (d, $J = 7.8$ Hz, 2H), 6.64 (d, $J = 7.5$ Hz, 2H), 4.84 (s, 2H), 2.90 (m, 4H), 2.16 (m, 2H), 2.04 (m, 2H), 1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 153.9$, 137.7, 127.5, 127.3, 121.7, 115.1, 37.9, 33.1, 29.7, 18.5; HR-MS (EI): $m/z = 280.1461$, calcd. for $C_{19}H_{20}O_2$: 280.1463.

A single crystal of 1,1′-spirobitetralin-8,8′-diol (**4**) was grown from hexane and analyzed by X-ray diffraction. Using the same procedure the single crystal of 1,1′-spirobiindane-7,7′-diol was also obtained and analyzed.

Resolution of 1,1′-Spirobitetralin-8,8′-diol (4)

(1*S*)-(+)-10-Camphorsulfonates of 1,1′-spirobitetralin-8,8′-diols (11a and 11b): (1*S*)-(+)-10-Camphorsulfonyl chloride (3.2 g, 12.8 mmol) was added to a stirred solution of *rac*-**4** (1.12 g, 4.0 mmol), NEt_3 (4.0 mL) in 40 mL of CH_2Cl_2 under nitrogen. After being stirred for 12 h at room temperature, the mixture was washed with water, dilute HCl and brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel column using ethyl acetate/toluene (1:10) as eluent to afford 8,8′-bis[(*S*)-camphorsulfonyl]-(*S*)-1,1′-spirobitetraline (**11a**) (yield: 1.35 g, 95%) and 8,8′-bis-[(*S*)-camphorsulfonyl]-(*R*)-1,1′-spirobitetraline (**11b**) (yield: 1.36 g, 96%), respectively.

8,8′-Bis-[(1*S*)-(+)-10-camphorsulfonyl]-(+)-1,1′-spirobitetraline (11a): White solid; mp 194–196°C; $[\alpha]_D^{20}$: +39.3 (*c* 1.4, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.51$ (d, $J = 8.4$ Hz, 2H), 7.11–7.01 (m, 4H), 3.19–3.04 (m, 4H), 2.90–2.85 (m, 2H), 2.39–2.31 (m, 4H), 2.22–2.17 (m, 2H), 2.10–2.03 (m, 6H), 1.90–1.84 (m, 6H), 1.57–1.35 (m, 6H), 1.02 (s, 6H), 0.83 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 148.6$, 140.3, 135.8, 127.0, 126.2, 116.5, 57.8, 47.7, 43.1, 42.4, 39.4, 34.7, 30.7, 26.8, 25.1, 19.8, 19.6, 19.2; HR-MS (EI): $m/z = 708.2795$, calcd. for $C_{39}H_{48}O_8S_2$: 708.2791.

8,8′-Bis-[(1*S*)-(+)-10-camphorsulfonyl]-(−)-1,1′-spirobitetraline (11b): White solid; mp 63–65°C; $[\alpha]_D^{20}$: +72.0 (*c* 2.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$ (d, $J = 7.2$ Hz, 2H), 7.06–7.00 (m, 4H), 3.17–3.06 (m, 2H), 2.97–2.87 (m, 4H), 2.68–2.55 (m, 2H), 2.25–2.036 (m, 6H), 1.91–1.76 (m, 4H), 1.55–1.38 (m, 6H), 1.12 (d, $J = 10.8$ Hz, 6H), 0.99 (s, 6H), 0.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.0$, 136.2, 129.2, 128.4, 127.5, 127.4, 126.2, 125.5, 117.4, 117.3, 58.0, 52.2, 48.1, 44.2, 43.7, 43.1, 42.6, 39.7, 34.8, 30.9, 27.7, 27.0, 26.9, 25.1, 21.8, 19.9, 19.7, 19.2; HR-MS (EI): $m/z = 708.2786$, calcd. for $C_{39}H_{48}O_8S_2$: 708.2791.

Hydrolysis of 11a and 11b: To a solution of NaOH (2.0 g, 50 mmol), H_2O (5 mL) and methanol (50 mL) was added **11a** or **11b** (680 mg, 1.0 mmol) under nitrogen atmosphere, and the mixture was refluxed for 6 h. The reaction mixture was cooled and the solvent was evaporated under reduced pressure. The residue was added 20 mL of water and extracted with CH_2Cl_2. The aqueous layer was acidified with 6

N HCl to produce a white precipitate, which was extracted with CH_2Cl_2. The combined organic layer was dried over anhydrous $MgSO_4$ and was concentrated under reduced pressure. The residue was purified by chromatography on silica gel column using ethyl acetate/petroleum ether (1:6) as eluent to yield the corresponding enantiomerically pure spiro diol.

(+)-1,1′-Spirobitetralin-8,8′-diol (4): White solid; mp 160–162 °C; $[\alpha]_D^{20}$: +214 (c 1.0, CH_2Cl_2).

(−)-1,1′-Spirobitetralin-8,8′-diol (4): White solid; mp 161–163 °C; $[\alpha]_D^{20}$: −209 (c 1.0, CH_2Cl_2).

Determination of the Absolute Configuration of Spiro Diol 4

The absolute configuration of spiro diol (+)-**4** was determined by X-ray diffraction analysis of the single crystal of L-menthoxycarboxylate of (+)-**4**. L-Menthyl chloroformate (3.5 g, 16 mmol) was added to a stirred solution of (+)-**4** (1.12 g, 4.0 mmol), NEt_3 (4.0 mL), and DMAP (48 mg, 0.4 mmol) in CH_2Cl_2 (40 mL) under nitrogen. After being stirred for 9 h at room temperature, the mixture was washed with water, dilute HCl and brine. The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was recrystallized with petroleum ether to yield a crystal of 8,8′-bis-(L-menthyloxycarbonyloxy)-(+)-1,1′-spirobitetraline suitable for X-ray analysis. White solid; mp 154–156 °C; $[\alpha]_D^{20}$: −43.8 (c 2.0, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.98–6.93$ (m, 2H), 6.83–6.75 (m, 4H), 4.29–4.21 (m, 2H), 2.98–2.86 (m, 2H), 2.76–2.70 (m, 2H), 1.99–1.49 (m, 18H), 1.27–1.19 (m, 4H), 0.84–0.73 (m, 16H), 0.69 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 151.2$, 147.9, 138.3, 135.7, 125.1, 124.7, 119.7, 77.4, 46.2, 39.7, 38.2, 34.6, 33.1, 30.3, 29.7, 25.0, 22.2, 21.0, 19.8, 19.0, 15.2; HRMS (EI): $m/z = 644.4062$, calcd. for $C_{41}H_{56}O_6$: 644.4077.

The configuration of the spirobitetraline diol moiety in the crystal of 8,8′-bis(L-menthyloxycarbonyloxy)-(+)-1,1′-spirobitetraline was determined to be *S* by X-ray diffraction analysis.

Synthesis of Chiral Spiro Phosphoramidite Ligand 3

(S)-(−)-O,O′-(1,1′-Spirobitetralin-8,8′-diyl)-N,N-dimethyl-phosphoramidate (S)-(−)-3a: To a stirred solution of (S)-(+)-**4** (224 mg, 0.8 mmol) in 2.0 mL dry toluene was added $P(NMe_2)_3$ (0.20 mL, 0.9 mmol). The solution was stirred at 100 °C for 4 h, and the toluene was removed under reduced pressure. Flash chromatography on silica gel with ethyl acetate/petroleum ether (1:10) afforded (S)-(−)-**3** as a colorless oil and solidified slowly on standing; yield: 184 mg (65 %); $[\alpha]_D^{20}$: −349 (c 0.8, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.08$ (t, $J = 8.0$ Hz, 1H), 7.00 (t, $J = 8.0$ Hz, 1H), 6.92–6.87 (m, 3H), 6.54 (d, $J = 8.0$ Hz, 1H), 2.94–2.90 (m, 4H), 2.19 (s, 6H), 1.99–1.88 (m, 4H), 1.83–1.79 (m, 2H), 1.73–1.72 (m, 2H); ^{31}P NMR (125 MHz, $CDCl_3$): $\delta = 119.5$; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 126.8$, 126.4, 126.3, 125.9, 122.3, 122.0, 41.6, 37.7, 37.6, 35.2, 29.7, 29.6, 22.9, 18.5, 15.5; HR-MS (EI): $m/z = 353.1546$, calcd. for $C_{21}H_{24}NO_2P$: 353.1545.

(S)-(−)-O,O′-(1,1′-Spirobitetralin-8,8′-diyl)-N,N-diethyl-phosphoramidate (S)-3b: The compound (S)-(−)-**3b** was prepared in 45 % yield from $P(NEt_2)_3$ by the same procedure as that for (S)-(−)-**3a**. $[\alpha]_D^{20}$: −497 (c 0.6, $CHCl_3$);

^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.08$ (t, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.92–6.86 (m, 3H), 6.64 (d, $J = 7.2$ Hz, 1H), 2.94–2.91 (m, 4H), 2.57–2.54 (m, 4H), 1.98–1.84 (m, 4H), 1.83–1.81 (m, 2H), 1.75–1.69 (m, 2H), 0.98 (t, $J = 6.8$ Hz, 3H); ^{31}P NMR (100 MHz, $CDCl_3$): $\delta = 124.2$; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.3$, 145.9, 141.6, 140.3, 138.1, 137.5, 126.5, 126.0, 125.9, 125.7, 122.7, 122.2, 41.6, 39.1, 37.8, 37.5, 30.0, 29.7, 18.5, 18.4, 15.2; HR-MS (ESI): $m/z = 382.1928$ (M + H), calcd. for $C_{23}H_{29}NO_2P$: 382.1936 (M + H).

(S)-(−)-O,O′-(1,1′-Spirobitetralin-8,8′-diyl)-P-(1-morpholinyl)-phosphoramidate (S)-(−)-3c: To a solution of (S)-(+)-**4** (336 mg, 1.2 mmol), Et_3N (0.26 mL, 2.52 mmol) and THF (20 mL) was added PCl_3 (0.12 mL, 1.4 mmol) under nitrogen atmosphere at 0 °C and the mixture was stirred for 20 h. After filtering off the solid under nitrogen, the filtrate was cooled to −78 °C and treated with lithium morpholide prepared from morpholine (104 mg, 1.2 mmol) and butyllithium (2.15 M solution in hexane, 0.6 mL, 1.3 mmol) in 15 mL THF at −30 °C. The resulting solution was warmed to room temperature and stirred overnight. The solvent was removed únder vacuum and the residue was passed through a silica gel plug with ethyl acetate/petroleum ether (1:20) as elute to afford (S)-(−)-**3c** as a colorless oil and solidified slowly on standing; yield: 317 mg (67 %); $[\alpha]_D^{20}$: −879 (c 0.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.92–6.31$ (m, 6H), 3.77–3.61 (m, 4H), 3.02–2.90 (m, 8H), 1.99–1.88 (m, 4H), 1.85–1.79 (m, 2H), 1.73–1.70 (m, 2H); ^{31}P NMR (125 MHz, $CDCl_3$): $\delta = 116.5$; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 148.9$, 126.8, 126.4, 126.3, 125.9, 122.3, 122.0, 68.7, 45.6, 41.6, 37.7, 37.6, 35.2, 29.7, 29.6, 22.9, 18.5; HR-MS (EI): $m/z = 395.1650$, calcd. for $C_{23}H_{26}NO_3P$: 395.1650.

General Procedure for Asymmetric Hydrogenation of α-Dehydroamino Esters

A solution of $[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and ligand (S)-(−)-**3a** (3.9 mg, 0.011 mmol) in CH_2Cl_2 (1.0 mL) was stirred in a glove-box for 30 min to generate the catalyst. This catalyst solution was added into the solution of substrate (0.50 mmol) in toluene (4.0 mL). Hydrogenation was performed in an autoclave with 10 atm of H_2 at room temperature for 3 h. After releasing H_2, the reaction mixture was passed through a short silica gel plug to remove the catalyst. The filtrate was subjected to measurement of the conversion and the enantiomeric excesses of products by GC.[11a]

X-Ray Crystallographic Study

Crystallographic datas (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-654423 for 1,1′-spirobitetraline-8,8′-diol, CCDC-654421 for 1,1′-spirobiindane-7,7′-diol and CCDC-654422 for 8,8′-bis-(L-menthyloxycarbonyloxy)-(+)-1,1′-spirobitetraline. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax.: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

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