2,2′-Dimethyl-6,6′-bis(diphenylphosphino)biphenyl (BIPHEMP) as a Chiral Ligand for Transition Metal Catalyzed Asymmetric Synthesis of Binaphthyls and for Asymmetric Hydrogenation. A Comparison with BINAP.[1]

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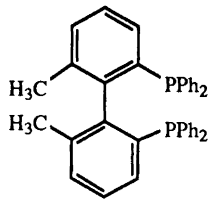
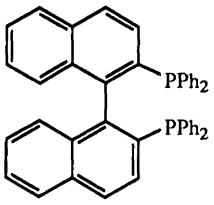
The chiral bisphosphine ligand **1** [2,2′-dimethyl-6,6′-bis(diphenylphosphino)biphenyl, BIPHEMP] has been prepared via optically active 2,2′-dilithio-6,6′-dimethylbiphenyl and used in the synthesis of optically active binaphthyls through palladium catalyzed cross-coupling of the corresponding aromatic halo and Grignard derivatives and in rhodium(I) catalyzed homogeneous hydrogenation of methyl (*Z*)-α-benzamidocinnamate. In comparison with **2** [2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, BINAP] it was found that **1** gave higher e.e.s in the former reaction but lower e.e.s in the latter.

Several years ago[1] we became interested in the possibility of using chiral ligands for the synthesis of optically active biaryls through transition metal cross-coupling of aromatic halides and Grignard reagents, since optically active biaryls were previously obtainable practically only via racemate resolution. During the last few years years other methods have been devised for the synthesis of chiral biaryls, which, however, are not based on catalysis where the chiral inducing agent is present in catalytic amounts only.[2–10] Transition metal catalyzed aromatic cross-coupling[11,12] using chiral ligands has recently been shown to give e.e.s as high as 95 % by the use of the ligand (*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyl methyl ether (**3**) together with $NiCl_2$.[13] Prior to this report the best e.e. (12 %) was reported by Kumada *et al.* in the synthesis of 2,2′-dimethyl-1,1′-binaphthyl with the use of ligand **4** and $NiCl_2$, while the combination of ligand **5** and $Pd(acac)_2$ gave only 4 % e.e.[14,15] In this paper we report our results using the chiral ligand BIPHEMP (**1**)[16–18] in the similar *palladium*-catalyzed cross-coupling of naphthylmagnesium halides and naphthyl halides, and in asymmetric homogeneous rhodium(I)-catalyzed hydrogenations of methyl (*Z*)-α-benzamidocinnamate. Some comparisons between (**1**) and the related ligand 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, **2**)[19,20] are made.

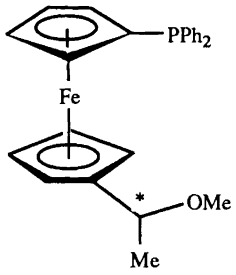
We recently reported that optically active 2,2′-dilithio-6,6′-dimethylbiphenyl was stable towards racemization in solution for several minutes at −10 °C.[21] An obvious extension of this work was to prepare the optically active



1 (BIPHEMP)



2 (BINAP)



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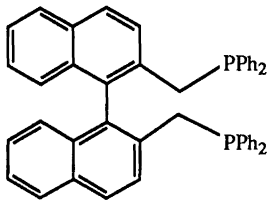

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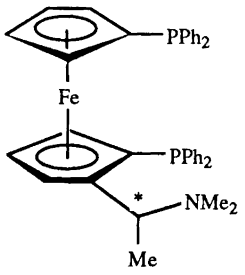

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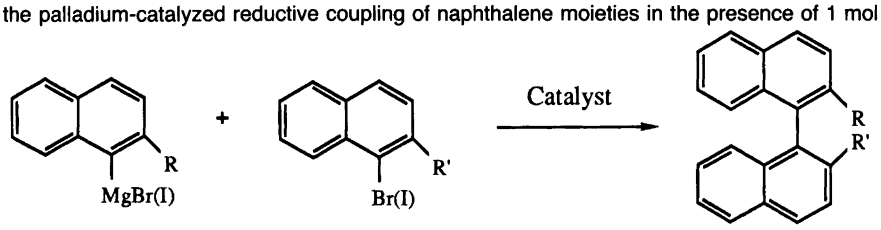
Table 1. Results of the palladium-catalyzed reductive coupling of naphthalene moieties in the presence of 1 mol % of the ligand **1** or **2**.



Entry	R	R'	Reaction conditions[a]		Yield/%	E.e./% (spec. rotation/°)
			Catalyst	Solvent/Temp/°C		
1	CH_3	CH_3	Pd/(+)-**1**	Ether/40	29–50	45(+8.6)[b]
2	CH_3	CH_3	Pd/(−)-**1**	Ether/40	29–50	36(−6.8)[b]
3	CH_3	CH_3	Pd/(−)-**1**	Toluene/40	23	26(−5.0)[b]
4	CH_3	CH_3	Pd/(−)-**1**	Toluene/80	30	13(−2.5)[b]
5	CH_3	H	Pd/(−)-**1**	Ether/40	43	5(−2.1)[c]
6	CH_3	H	Pd/(−)-**1**	Toluene/40	50	1(−0.48)[c]
7	CH_3	H	Pd/(−)-**1**	Toluene/80	34	3(−1.18)[c]
8	H	OCH_3	Pd/(−)-**1**	Ether/40	7	34(−11.4)[d]
9	H	OCH_3	Pd/(−)-**1**	Toluene/40	22	37(−12.4)[e]
10	H	OCH_3	Pd/(−)-**1**	Toluene/80	52	31(−10.4)[f]
11	CH_3	OCH_3	Pd/(−)-**1**	Ether or Toluene	Trace	–
12	OCH_3	OCH_3	Pd/(−)-**1**	Ether or Toluene	0	–
13	CH_3	CH_3	Pd/(+)-**2**	Ether/40	3	12(+2.3)[b]
14	CH_3	CH_3	Pd/(+)-**2**	Toluene/40	3	10(+1.9)[b]
15	CH_3	CH_3	Pd/(+)-**2**	Toluene/80	13	13(−2.5)[b]
16	CH_3	CH_3	Ni/(−)-**1**	Ether/40	7	6(−1.07)[b]

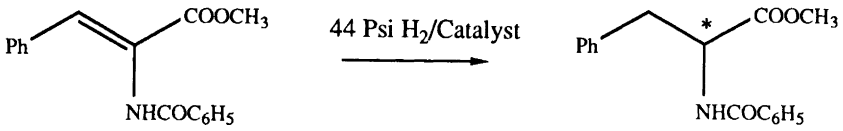
[a]The reaction temperature refers to the temperature of the oil bath. $Pd(acac)_2$ (1 mol%) was used as the metal salt in all cases except in Entry 16 where $NiCl_2$ was used; [b]$[\alpha]_D^{22}$ (*c* 1, EtOH); pure compound lit.[26] $[\alpha]_D^{22}$ 19° (*c* 1.3, EtOH); [c]$[\alpha]_D^{22}$ (*c* 1, $CHCl_3$); pure compound lit.[13] $[\alpha]_D^{20}$ 43.9° (*c* 1.0, $CHCl_3$); [d]$[\alpha]_{578}^{22}$(*c* 0.2, THF); pure compound lit.[4] $[\alpha]_{578}^{22}$ 33.24° (*c* 2.1, THF); [e]$[\alpha]_{578}^{22}$ (*c* 1.5, THF); [f]$[\alpha]_{578}^{22}$ (*c* 2.1, THF).

ligand **1** (BIPHEMP) from this bis-lithium derivative. Thus, a 57% yield of (−)-**1** was obtained from (−)-2,2′-diiodo-6,6′-dimethylbiphenyl[21,22] on successive treatment with butyllithium and chlorodiphenylphosphine. Compound (+)-**1** was prepared similarly. During the course of our work, the synthesis of (+)- and (−)-**1** and several other similar compounds was reported by Schmid *et al.* who also used these compounds as ligands in homogenous catalytic hydrogenation and isomerization of allylic amines to optically active enamines.[16,17]

Our results in the cross-coupling experiments with some different naphthyl systems are shown in Table 1. Although some of the highest e.e.s and best chemical yields were obtained when the reaction was started in diethyl ether solution (Entries 1,2) these results were difficult to reproduce. When the ether level was kept constant only traces of the coupling product was detected even after prolonged reaction time. We noticed, however, that the coupling product started to form after an induction period, during which most of the ether was swept away by the nitrogen gas stream. Also, when the ether was quickly removed at the start of the reaction the induction period was observed. The coupling was easier to reproduce in toluene but the e.e.s dropped to lower levels (Entries 3,4). As expected the temperature increase from 40 to 80 °C resulted in a lower e.e. Replacement of **1** with **2** gave lower chemical yields as well as e.e.s (Entries 13–15). Hayashi *et al.*[13] also noticed that **2** was an inefficient ligand.

In the coupling of 2-methyl-1-naphthylmagnesium bromide with 1-bromonaphthalene the e.e.s were very low but the chemical yields were in the same range as those of the 2-methylnaphthalene cases (Entries 5–7). Here the nickel complex with ligand **3** was reported to give up to 83% e.e. (92% yield).[13] Unfortunately, the coupling of two 2-methoxynaphthalene moieties did not occur at all under our conditions (Entry 12). However, when the *o*-methoxy group of the Grignard reagent was replaced with hydrogen the chemical yields were moderate and the e.e.s were better than 30% (Entries 8–10). The oxygen atom of the *o*-methoxy group in the former case is likely to give an intramolecular complex with the magnesium atom, which may reduce the reactivity of the reagent. The combination of 2-methyl-1-naphthylmagnesium bromide and 1-bromo-2-methoxynaphthalene gave only traces of binaphthyl products (Entry 11). In Entries 14 and 15 it is shown that with ligand **2** the direction of rotation of the product was reversed by increasing the temperature from 40 to 80 °C. Since both yield and e.e. were very low, this observation may not be relevant but no change of sign occurred in any of the cases where ligand **1** was involved. When $NiCl_2$ was used instead of $Pd(acac)_2$ only a 7% chemical yield and 6% e.e. of 2,2′-dimethyl-1-1′-binaphthyl was obtained

Table 2. Results of the catalytic hydrogenation of methyl (*Z*)-α-benzamidocinnamate. The conversion of the olefin was quantitative according to NMR spectroscopy.



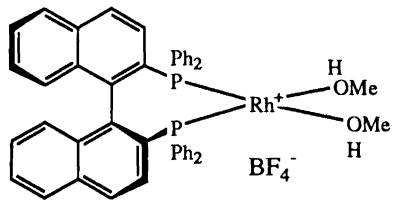
Entry	Catalyst	Solvent	E.e./%[a]
1	[Rh (nbd) **2**] ClO_4(**6**)	EtOH[19]	38
2	[Rh (nbd) (*R*)-(+)-**2**] ClO_4 [(+)-**6**]	Toluene	70
3	[Rh (nbd) (*S*)-(+)-**1**] ClO_4 [(+)-**7**]	EtOH	14
4	(+)-**7**	THF	28
5	(+)-**7**	Toluene	46
6	[Rh (nbd) (*R*)-(−)-**1**] BF_4	Toluene	46
7	[Rh $(MeOH)_2$ (*S*)-(+)-**1**] ClO_4 [(+)-**10**]	EtOH	12

[a]Determined by ^1H NMR spectroscopy ($CDCl_3$) using $Eu(hfc)_3$ as a chiral shift reagent.

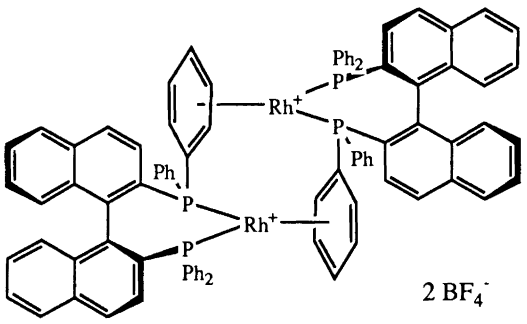
(Entry 16). This is in contrast with Ref. 13, in which it is stated that palladium–phosphine complexes were less active than the corresponding nickel–phosphine complexes.

Ligands **1** and **2** were also tested in hydrogenation reactions of methyl (*Z*)-α-benzamidocinnamate. The catalysts for these experiments, [(Ligand)Rh(I)nbd]ClO_4 (norbornadiene is abbreviated as nbd throughout), were prepared from the ligands **1** or **2** and Rh(nbd)acac in THF containing aqueous $HClO_4$. The catalysts could be recrystallized from methanol.[17] But this did not improve the enantiomeric excess of the resulting phenylalanine derivative, although the optical rotation of the catalyst itself was increased (see the Experimental). The results of the asymmetric hydrogenations of methyl (*Z*)-α-benzamidocinnamate are shown in Table 2.

When the hydrogenation was performed in ethanol with the BINAP-complex **6**, the resulting amino acid derivative had an e.e. of 38 % as reported by Noyori *et al.* [19] (Entry 1). We then tried the BIPHEMP-complex (+)-**7** under similar conditions, which gave only a 14 % e.e. (Entry 3), while changing the solvent to toluene increased the e.e. to 46 % for (+)-**7** (Entry 5) and to 70 % for (+)-**6** (Entry 2). THF gave a somewhat better e.e. than ethanol but was still worse than toluene (Entry 4). A change of counter-ion from perchlorate to tetrafluoroborate (Entry 6) did not effect the e.e. or the conversion of the starting material, which in all cases was essentially quantitative.



S-(−)-8



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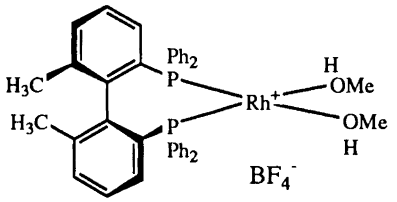

S-(+)-10

Both complexes give better e.e.s in toluene, although (+)-**6** was more effective than (+)-**7**. The lower e.e.s in ethanol may be explained by the formation of complexes with ethanol molecules as ligands, some of which may be less stereoselective catalysts than those formed in toluene. It has been shown that aromatic solvents coordinate more strongly than methanol to Rh(I)-complexes carrying chelating bis-phosphine ligands.[23] A related problem was discussed by Noyori *et al.*,[19] who obtained two complexes, in the ratio 9:1, on hydrogenation of (*S*)-(−)-**6** in methanol. In this process the norbornadiene ligand was replaced with methanol. The major complex, (*S*)-(−)-**8**, was an excellent hydrogenation catalyst when purified, while the other complex, the binuclear π-aromatic coordination complex **9**, was less efficient. In order to test the possibility of the involvement of two (or more) complexes also in our case, a ^{31}P NMR spectrum of a solution of hydrogenated (*S*)-(+)-**7** in methanol was recorded. Only one type of complex with a single phosphorus resonance (doublet) was found but there was no complex similar to **9**, which should give two ^{31}P signals. The resonance of the phosphorus atom in (*S*)-(+)-**7** appears as a doublet at 26.7 ppm while in the corresponding hydrogenated methanol complex it appears at 54.6 ppm. The ^{31}P shift for (*S*)-(−)-**8** appeared at 53.1 ppm.[19] This indicates that in the present case a complex was formed with a structure similar to (*S*)-(−)-**8** and is depicted as (*S*)-(+)-**10**. However, hydrogenation using this prehydrogenated complex did not improve the e.e. (Entry 7).

We noticed previously that in the crystalline state there were significant differences between the rhodium complexes of **1** and **2**.[18] The most obvious is that the plane of one of the phenyl rings in the $-PPh_2$ units of the complex [Rh(nbd)(*R*)-(+)-**2**]BF_4 is clearly tilted differently compared with [Rh(nbd)(*R*)-(−)-**1**]BF_4 (Fig. 1). Although this difference was shown in the crystalline state, it may still manifest itself in solution when used in transition metal catalyzed reactions. The effects of the orientation of the phenyl rings of the PPh_2-groupings in several bidentate bisphosphine ligands have been discussed by Knowles *et al.*[24] An alternating edge–face orientation was found to be a common desirable feature for giving high e.e.s. The orientation of the phenyl rings of the PPh_2-groups in the complex [Rh(nbd)(*R*)-(−)-**1**]BF_4 are not arranged in such an alternating edge–face fashion. This may cause the lower e.e.s obtained with [Rh(nbd)(*R*)-(−)-**1**]$^+$ compared with [Rh(nbd)(*R*)-(+)-**2**]$^+$ in which the edge–face orientation is much more pronounced.

Experimental

All reactions were carefully performed under oxygen-free conditions in solvents distilled from sodium wire or dried with 3Å molecular sieves. Sodium sulfate was used as a drying agent for organic extracts. NMR spectra were recorded with a Nicolet 360 or a Varian XL 300 NMR spectrometer. Optical rotations were measured on a Perkin Elmer 141 polarimeter. Melting points are given uncorrected. GLC analyses were performed with a Perkin Elmer 900 gas chromatograph (column: 3% OV 101 on 80–100 mesh Varaport 30, length 3.0, i.d. 2 mm, stainless steel). (*R*)-(+)-BINAP was purchased from Fluka AG.

(−)-2,2'-Diiodo-6,6'-dimethylbiphenyl.[21,22] Racemic 2,2-diiodo-6,6'-dimethylbiphenyl was resolved using a microcrystalline triacetylcellulose column (300×25 mm),[25] equipped with a UV-detector, and eluted with ethanol (99.5%). The (−)-form was eluted before the (+)-form (α value = 2.06).

*(R)-(−)-2,2'-Bis(diphenylphosphino)-6,6'-dimethylbiphenyl [(−)-**1**].*[16–18] Optically active (−)-2,2'-diiodo-6,6'-dimethylbiphenyl[21,22] (800 mg, 1.84 mmol) in ether (13 ml) was added to a cooled (−10 °C) solution of BuLi (2.6 ml, 3.77 mmol) in ether (7 ml). After the reaction mixture had been stirred for 40 min, chlorodiphenylphosphine (829 mg, 3.77 mmol) in ether (2.5 ml) was added. The mixture was allowed to reach room temperature, refluxed for 5 h and stirred at room temperature over night. The ether was evaporated *in vacuo* and the residue was partitioned between CH_2Cl_2 and water. The organic layer was washed once with water and dried. After evaporation of the solvent the crude product was chromatographed [SiO_2, CH_2Cl_2: petroleum ether (60–71 °C) 25:75] to give (−)-**1** (0.58 g, 57%); m.p. 212–214 °C; $[\alpha]_D^{23}$ −40.4° (*c* 1.0, $CHCl_3$). Lit[17] (m.p. 212–213 °C; $[\alpha]_D^{20}$ −43.1°). MS [CI, *m/z* (% rel. int.)]: 551 (*M*+1), 367, 289, 187. ^1H NMR and ^{31}P NMR data were identical with literature data.[17] ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.3 (s, CH_3), 127.8–128.2 (m), 128.4–128.6 (m), 129.2, 130.8, 132.2, 133.3 (t), 135.6 (t), 136.9 (t), 137.7 (t), 138.2 (t), 139.3 (t), 145.7 (t).

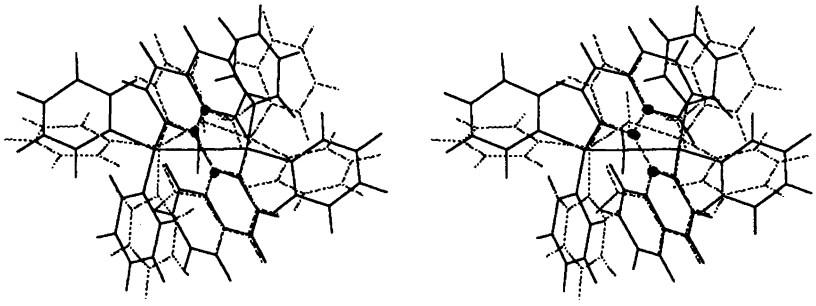

Fig. 1. Stereo view of part of the complexes [Rh(nbd)(*R*)-(−)-**1**]BF_4 (dotted lines) and [Rh(nbd)(*R*)-(+)-**2**]BF_4 (full lines) with coordinates obtained from X-ray data. The nbd and BF_4^- units are removed for clarity and the marked carbon atoms are positioned with best fit by the use of the MIMIC computer program.[28] The most differently tilted phenyl rings are shown to the left.

Compound (*S*)-(+)-**1**[16-18] was prepared similarly; m.p. 212–214 °C; $[\alpha]_D^{23}$ +40.2° (*c* 0.5, $CHCl_3$). Lit[17] m.p. 213–214 °C; $[\alpha]_D^{20}$ + 41.7°.

Typical procedure for asymmetric coupling in ether: 2,2'-dimethyl-1,1'-binaphthyl. A solution of 1-bromo-2-methylnaphthalene (0.221 g, 1.00 mmol) in ether (3.0 ml) was added to a mixture of $Pd(acac)_2$ (3.0 mg, 0.01 mmol) and (+)-**1** (5.5 mg, 0.01 mmol) under a nitrogen atmosphere, followed by a solution of 2-methyl-1-naphthylmagnesium bromide (4.6 ml, 0.26 M, 1.0 mmol). The mixture was heated with an oil bath at 40 °C for 65 h. During this time most of the ether evaporated but the residue was still a liquid. The residue was extracted with CH_2Cl_2 and the organic phase was washed with water and dried. The solvent was removed *in vacuo* and the residue was column chromatographed [SiO_2, petroleum ether (60–71 °C)] to give 2,2'-dimethyl-1,1'-binaphthyl,[26] 29–50 % yield (36–45 % e.e.). ^1H NMR spectral data were in agreement with literature data.[13]

This procedure was followed also for the other cases where ether was the solvent (for details see below and in Table 1).

Typical procedure for asymmetric coupling in toluene at 40 or 80 °C. The experiments were performed as described above except that the ether was allowed to evaporate over 30 min at room temperature by letting a stream of nitrogen gas pass through the reaction vessel. During this time no coupling had taken place as checked by GLC. Toluene (1 ml) was then added and the reaction mixture was kept at 40 °C (or 80 °C) for 65 h. Work-up was performed as described. The following compounds were obtained and the results are shown in Table 1.

2-Methyl-1,1'-binaphthyl[13] was synthesized and purified as above except that 1-iodonaphthalene was used as the halide component instead of the bromo derivative. ^1H NMR spectral data were in agreement with literature data.[13]

2-Methoxy-1,1'-binaphthyl[4,5] was synthesized as described, except that 1-iodonaphthalene was used as the precursor to the Grignard reagent, and purification was by flash chromatography [SiO_2, dichloromethane: petroleum ether (60–71 °C) (15:85)]. ^1H NMR spectral data were in agreement with literature data.[5]

(+)-[Rh (nbd) (+)-1] ClO_4 [(+)-7)]. A procedure adapted from Ref. 27 was used. Rh(nbd)(acac) (267 mg, 0.91 mmol) was suspended in THF (0.5 ml) and 70 % aq. $HClO_4$ (138 mg, 0.96 mmol) in THF (2.5 ml) was added. The complex dissolved and the mixture was kept at room temperature for 5 min. A solution of (*S*)-(+)-**1** (500 mg, 0.91 mg) in THF (2.0 ml) was then added dropwise using a syringe. The yellow solution turned dark red and within 2 min crystals were formed. Ether was added after 10 min in order to complete the precipitation. The crystals were collected by filtration, dissolved in CH_2Cl_2 and the resulting solution was dried (Na_2SO_4). After filtration the filtrate was reduced to half its original volume *in vacuo* and the complex was then precipitated by the addition of ether to give (+)-**7** (630 mg, 82 %); m.p. 233–235 °C; $[\alpha]_D^{22}$ +19.9° (*c* 1.1, $CHCl_3$). The ^1H NMR (300 MHz, $CDCl_3$) spectrum was identical with the reported one.[17] ^{31}P NMR (CD_3OD, external reference 85 % H_3PO_4): δ 26.7 (d, J_{Rh-P} 155.9 Hz).

(−)-[Rhodium(nbd) (−)-1] BF_4. Rh(nbd)acac (320 mg, 1.09 mmol) was dissolved in CH_2Cl_2 (3.0 ml) and the solution was cooled to 0 °C. Triphenylmethyl tetrafluoroborate (360 mg, 1.09 mmol) dissolved in CH_2Cl_2 (4.5 ml) was then added with stirring. The yellow solution was heated to +20 °C, stirred for 15 min and then cooled to 0 °C. A solution of (*R*)-(−)-**1** (600 mg, 1.09 mmol) in CH_2Cl_2 (2.5 ml) was added dropwise, whereafter the reaction mixture was stirred for 30 min at 0 °C then heated to +20 °C. The volume of the reaction mixture was then reduced to half its original volume under a stream of nitrogen gas and ether was added to precipitate the complex, which was collected and re-precipitated as above to give the title compound (726 mg, 80 %); m.p. 234–236 °C; $[\alpha]_D^{22}$ −21.8° (*c* 0.15, $CHCl_3$). Recrystallization from methanol raised the specific rotation to $[\alpha]_D^{22}$ −31° (*c* 1.1, $CHCl_3$); lit[17] ($[\alpha]_D^{20}$ −35.9°). ^1H NMR data were identical with those of (+)-**7**.

Note! The complexes should be stored at −20 °C protected from air since aging was observed even in the refrigerated samples (+5 °C). Their specific rotations gradually approached 0° and eventually changed sign. The perchlorate complex mutarotated even within minutes.[17] In order to be sure of the sign of the absolute rotation of the batch from which the X-ray sample of (−)-[Rh(nbd) (*R*)-(−)-**1**]BF_4 was obtained in Ref 18, it was checked some time after the X-ray investigation was finished. Unfortunately the sign had changed and this misled us to give the complex and the ligand the wrong signs. The correct notation should be as shown in the formula above. Its activity as a hydrogenation catalyst decreased along with the aging.

Hydrogenations of methyl (Z)-α-benzamidocinnamate. The cinnamate (66 mg, 0.235 mmol) and (+)-**7** (3.0 mg, 3.55×10^{-3} mmol) were placed in a hydrogenation vessel filled with nitrogen gas and equipped with a rubber septum. The dried, freshly distilled solvent (9.4 ml) was introduced with a syringe. The resulting solution was then thoroughly degassed by three freeze–thaw cycles. At the end of the last cycle hydrogen gas (44 psi) was introduced into the flask. The hydrogenation was interrupted after 48 h, the solvent was removed with a stream of nitrogen gas at room temperature and the crude product was analyzed by ^1H NMR spectroscopy using $Eu(hfc)_3$ as a chiral shift reagent for determination of the e.e. The experiments with the other complexes were performed similarly and the results are shown in Table 2.

*Hydrogenation of methyl (Z)-α-benzamidocinnamate using (+)-**10** in methanol.* Compound (+)-**7** (38.0 mg, 0.045 mmol) was dissolved in methanol (1.0 ml) under argon in a round-bottomed flask, equipped with a magnetic stirring bar, and hydrogenated at atmospheric pressure for 1 h. Then the red–orange solution was filtered through a glass frit into a 25 ml round-bottomed flask. This was done in order to ensure removal of an insoluble and inefficient complex, similar to **9**,[19] should it be present. However, no precipitate was noticed. The ^{31}P NMR (85 % H_3PO_4 was used as an external reference) spectrum on a sample of this solution showed only a doublet at δ 54.6 (J_{Rh-P} 206.8 Hz), which we ascribe to a single complex in which methanol had replaced norbornadiene i.e. [Rh(MeOH)$_2$(*S*)-(+)-**1**]ClO_4 [(+)-**10**]. Degassed ethanol (13.5 ml) was then added to the filtrate and after thorough mixing, 1.0 ml of the resulting solution was transferred with a syringe to a hydrogenation flask filled with argon and also containing methyl (*Z*)-α-benzamidocinnamate (84.3 mg, 0.30 mmol) in ethanol (10 ml). The reaction mixture was hydrogenated at 44 psi for 48 h and the crude product was analyzed as above. The result is shown in Table 2, Entry 7.

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