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Optically active 1,1′-di-*tert*-butyl-2,2′-dibenzophosphetenyl: a highly strained P-stereogenic diphosphine ligand

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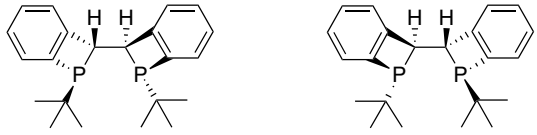
Abstract—Both enantiomers of 1,1′-di-*tert*-butyl-2,2′-dibenzophosphetenyl were prepared from 2-bromobenzyl chloride and *tert*-butyldichlorophosphine. These ligands exhibited excellent enantioselectivity in the rhodium catalyzed asymmetric hydrogenation of methyl α-acetylamidocinnamate.

1. Introduction

Optically active phosphine ligands have played a key role in transition metal catalyzed asymmetric reactions with numerous ligands of this class being designed and synthesized over the past three decades.[1] It has been well recognized that the conformational rigidity of a catalyst is one of the more important factors to realize excellent asymmetric induction. Outstanding chiral phosphine ligands such as DuPHOS,[2] PennPHOS,[3] BIPNOR,[4] MiniPHOS[5] and TangPhos[6] have been designed to have maximal conformational rigidity. These ligands have been successfully employed in asymmetric reactions, especially in the Rh-catalyzed asymmetric hydrogenations of α-dehydroamino acids and related substrates. These facts and our continuing studies on the synthesis and application of P-stereogenic phosphine ligands[7] led us to develop new ligands that are anticipated to form very rigid metal complexes. The newly designed ligands are (1*S*,1′*S*,2*R*,2′-*R*)-1,1′-di-*tert*-butyl-2,2′-dibenzophosphetenyl (*S*,*S*)-**1** and its enantiomer (1*R*,1′*R*,2*S*,2′*S*)-1,1′-di-*tert*-butyl-2,2′dibenzophosphetenyl (*R*,*R*)-**1** (Fig. 1).



(*S*,*S*)-**1** (*R*,*R*)-**1**

Figure 1.

These ligands are C_2-symmetric and consist of two directly bonded benzophosphetene units containing a pair of asymmetric phosphorus and carbon atoms. The conformational rigidity of the metal chelates together with an ideal asymmetric environment owing to the existence of two *tert*-butyl groups at the stereogenic phosphorus atoms might lead to very high enantioselection in catalytic asymmetric reactions.[8] Herein we report the preparation of the ligands and their stereodifferentiation ability in rhodium-catalyzed asymmetric hydrogenation.

2. Results and discussion

We planned to prepare the designed phosphine ligands by the oxidative coupling of 1-*tert*-butylbenzophosphetene oxide. At first, racemic 1-*tert*-butylbenzophosphetane oxide was prepared from 2-bromobenzyl chloride. Thus, the dihalide was converted to 1,2-dihydro-1-magnesacyclobutabenzene by treatment with a large excess of magnesium in tetrahydrofuran according to the procedure described.[9] The resulting organomagnesium reagent was reacted with *tert*-butyldichlorophosphine, followed by oxidation with hydrogen peroxide, to give the desired phosphine oxide *dl*-**2** in reasonable yield (Scheme 1).

Attempts to resolve the phosphine oxide by fractional crystallization using (+)-dibenzoyl-D-tartaric acid

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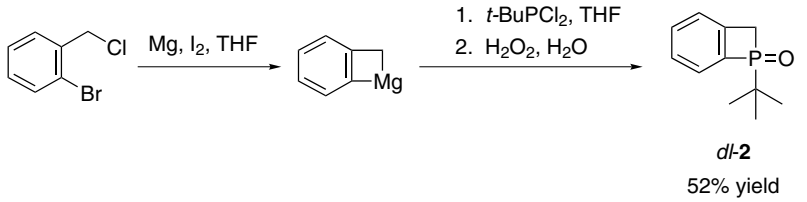
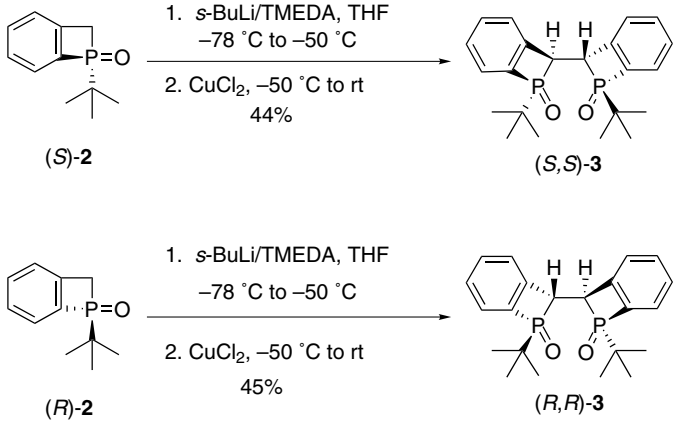


Scheme 1.

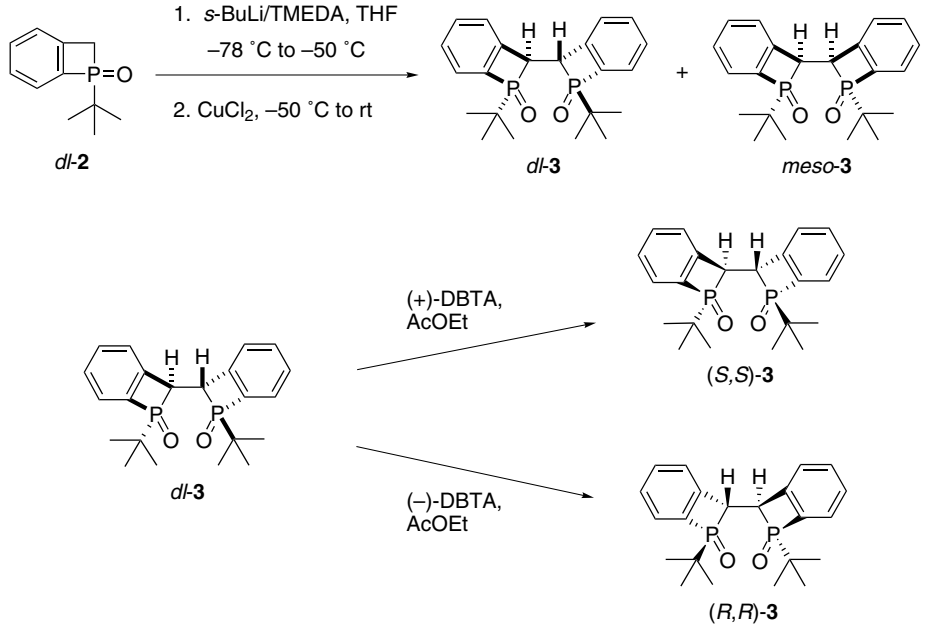
[(+)-DBTA] or (1*R*)-(−)-10-camphorsulfonic acid were unsuccessful. Alternatively, the direct separation of each enantiomer in gram scale was easily achieved by using a simulated moving bed (SMB) system. The respective optically active phosphine oxides (*R*)-**2** and (*S*)-**2** were reacted with *sec*-butyllithium and the resulting organolithium compounds oxidized with copper(II) chloride, to give the corresponding diphosphine oxides, (*R*,*R*)-**3** and (*S*,*S*)-**3**, in moderate yields (Scheme 2).

Similarly, racemic diphosphine oxide *dl*-**3** was prepared in moderate yield by oxidative dimerization of *dl*-**2**. This compound was resolved using (+)- and (−)-DBTA to give enantiomerically pure (*S*,*S*)-**3** and (*R*,*R*)-**3**, respectively (Scheme 3).

The absolute configurations of the compounds of interest above were established by single-crystal X-ray analysis of one of the chiral diphosphine oxides. Thus,



Scheme 2.



Scheme 3.

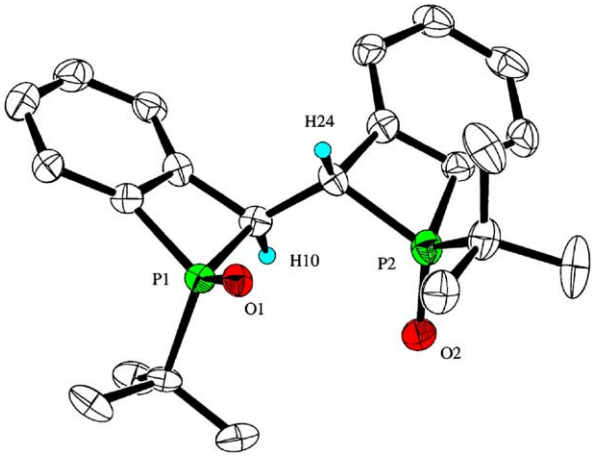


Figure 2.

one enantiomer $\{[\alpha]_D^{19} = -12.3$ (c 1.00, $CHCl_3$)$\}$ was subjected to X-ray analysis by the Flack parameter method. Figure 2 shows its molecular structure with a (1*S*,1′*S*,2*S*,2′*S*)-configuration.

Reduction of (*R*,*R*)-**3** and (*S*,*S*)-**3** to the corresponding optically active diphosphines was attempted using $PhSiH_3$, $HSiCl_3$/amine, $Cl_3SiSiCl_3$, $HSi(OEt)_3$ and MeOTf/$LiAlH_4$ as the reducing agents. However, the standard reaction conditions described in the literature were not effective in this case, even if reagents were used in large excess. Careful tuning of the reaction conditions using $Cl_3SiSiCl_3$ enabled the isolation of the desired diphosphines in moderate yields. The reduction of phosphine oxide with $Cl_3SiSiCl_3$ usually proceeds through inversion of configuration,[10] while in the reduction of four-membered phosphine oxides is known to occur with retention of configuration.[11] Therefore, we assume that these benzophosphetene oxides were reduced with retention of configuration.

The two enantiomer diphosphines (*S*,*S*)-**1** and (*R*,*R*)-**1** were highly air-sensitive, and hence were converted to the corresponding rhodium complexes by treatment with $[Rh(nbd)_2]BF_4$ (Scheme 4). The stereodifferentiation ability of the complexes was tested by typical Rh-catalyzed asymmetric hydrogenation of methyl α-acetamidocinnamate (MAC). A markedly high ee (96%) of the product was observed when complex **4** was used.[12]

This result was compared with those of hydrogenation obtained by the use of the rhodium complexes of structurally resembling chiral diphosphine ligands. Figure 3 illustrates representative C_2-symmetric ligands bearing *tert*-butyl groups and their enantioselectivity in Rh-catalyzed hydrogenation of MAC. It should be noted that ligand **5**, whose molecular structure closely resembles (*S*,*S*)-**1**, provided only 6.6% enantioselectivity.[13] This significantly low enantioselectivity is responsible for the conformational flexibility of the benzene ring. Ligands **6**–**8** afforded excellent to almost perfect enantioselectivity,[5,6,14] while in sharp contrast ligands **9**–**11** gave very low selectivity.[15,16] These dramatic differences are also ascribed to the rigidity/flexibility of the catalyst complexes. The use of ligand **12** resulted in 76% enantioselectivity.[17] The X-ray analysis of the Rh-complex of **12** shows that it is considerably rigid but not C_2-symmetric. The observed fairly good selectivity can be interpreted by considering these asymmetric environments around the rhodium metal centre.

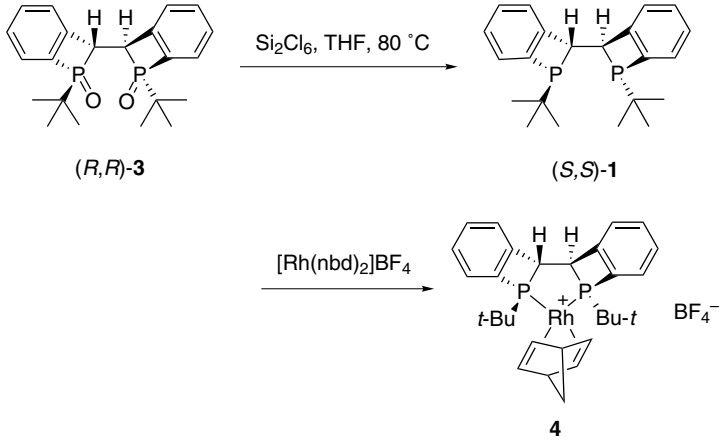
3. Conclusion

We have prepared both enantiomers of 1,1′-di-*tert*-butyl-2,2′-dibenzophosphetenyl and observed very high enantioselectivity in their application to Rh-catalyzed asymmetric hydrogenation of MAC. These results indicate the importance of the rigid conformation of the catalyst in highly enantioselective hydrogenation and suggest the potential utility of these highly strained ligands in other catalytic asymmetric reactions.

4. Experimental

4.1. General

All reactions except for the hydrogenation were carried out under an argon atmosphere. Dehydrated THF and



Scheme 4.

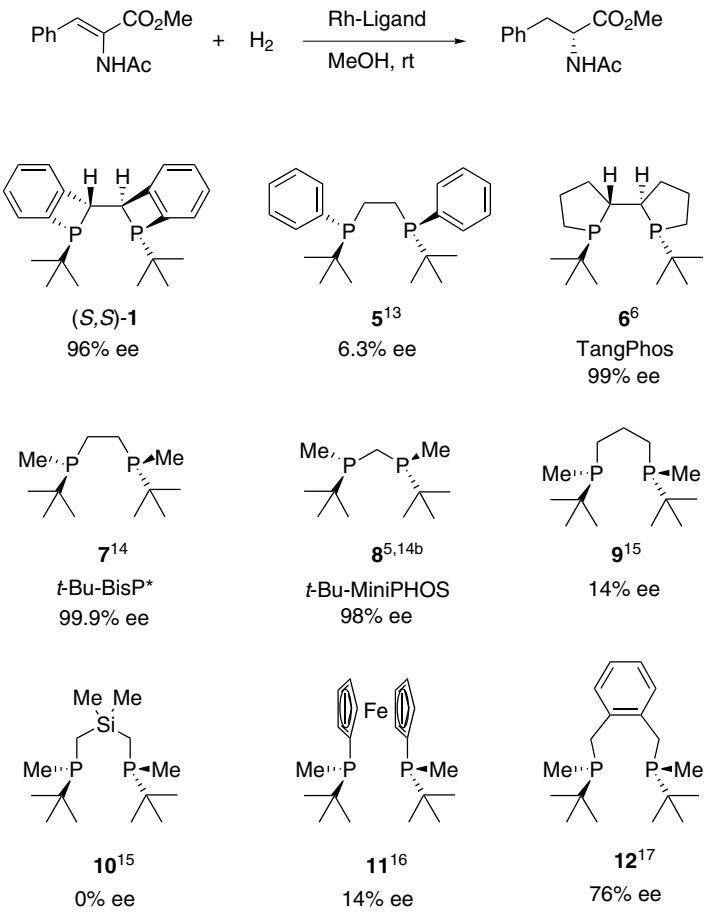


Figure 3.

diethyl ether were purchased from Kanto Chemical Co., Inc. and Wako Pure Chemical Industries, Ltd, respectively, and used as received. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded on JNM-LA400 or JNM-400s spectrometer. In both ^{1}H NMR and ^{13}C NMR, chemical shifts are reported in parts per million downfield from TMS. ^{31}P NMR chemical shifts are relative to 85% H_3PO_4. FT-IR spectra were performed with a Hitachi IR 215 spectrometer and recorded in the form of KBr disks or on NaCl plates. Mass spectra were obtained by EI at 70 eV or FAB. HPLC analysis was performed on a Shimadzu LC10AD liquid chromatograph system with chiral stationary columns. Optical rotations were measured using a JASCO P-1020 polarimeter with a 1 dm cell.

4.2. *tert*-Butylbenzophosphetane oxide *dl*-2

A solution of *o*-bromobenzyl chloride (3 g, 14.6 mmol) in dry THF (150 mL) was added dropwise to a suspension of dry magnesium turnings (3.5 g, 146 mmol) and a crystal of iodine in dry THF (30 mL) at room temperature under argon. The reaction mixture was initiated by the addition of 1,2-dibromoethane (0.1 mL). Once the reaction had started, the dihalide compound was added over 4 h. The mixture gradually turned into a light green milky aspect. The resulting organomagnesium reagent was stirred for an extra 2 h, decanted and transferred in small portions to a solution of *tert*-butyldichlorophosphine (2.32 g, 14.6 mmol) in dry THF (25 mL) at −50 °C. This mixture was gradually warmed to room temperature and stirred overnight. Water (30 mL) and H_2O_2 (30% aq, 2 mL) were successively added and the resulting mixture stirred for 1 h at room temperature. A saturated aqueous solution of $FeSO_4$ (40 mL) was added and the mixture extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel, eluting with ethyl acetate to give *dl*-**2** as an off-white solid. Yield: 52%.

4.3. (*S*)-*tert*-Butylbenzophosphetene oxide (*S*)-2 and (*R*)-*tert*-butylbenzophosphetene oxide (*R*)-2

Racemic *tert*-butylbenzophosphetene *dl*-**2** was subjected to HPLC analysis by using several kinds of chiral columns to find optimum resolution conditions. Use of Chiralcel OJ provided good separation of the two enantiomers: 0.7 mL/min, 25 °C, 5% 2-propanol/hexane, 17.1 min and 19.9 min. Based on the results, 3 g of *dl*-**2** were separated by preparative HPLC (SMB system) into 1.3 g of each enantiomer. The enantiomer with early retention time: mp 39–40 °C, >99.9% ee, $[\alpha]_D^{17} = -22.5$

(c 1.01, $CHCl_3$). This compound corresponds to (*S*)-**2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (d, $^3J_{HP}$ 16 Hz, 9H), 3.38–3.58 (m, 2H), 7.30–7.43 (m, 2H), 7.47–7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.16 (d, J_{CP} 1.7 Hz), 33.18 (d, J_{CP} 56.6 Hz), 36.12 (d, J_{CP} 56.6 Hz), 125.59 (d, J_{CP} 25.4 Hz), 127.20, 128.54 (d, J_{CP} 12.4 Hz), 133.91 (d, J_{CP} 3.3 Hz), 141.31 (d, J_{CP} 24.6 Hz), 141.73 (d, J_{CP} 42.6 Hz); IR (KBr): 3060, 2950, 2900, 2860, 1960, 1920, 1590, 1450 cm^{-1}; IR (KBr): 3060, 2950, 2900, 2860, 1960, 1920, 1590, 1450 cm^{-1}. Anal. Calcd for $C_{11}H_{15}PO$: C, 68.03, H, 7.78. Found: C, 68.13; H, 8.01. The compound with late retention time: mp 39–41 °C, 99.0% ee, $[\alpha]_D^{17} = +21.7$ (c 0.98, $CHCl_3$). This compound corresponds to (*R*)-**2**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.18 (d, ^{3} J_{HP} 16 Hz, 9H), 3.38–3.58 (m, 2H), 7.30–7.43 (m, 2H), 7.47–7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.09 (d, J_{CP} 1.6 Hz), 33.61 (d, J_{CP} 56.6 Hz), 36.05 (d, J_{CP} 56.6 Hz), 125.53 (d, J_{CP} 26.2 Hz), 127.13, 128.48 (d, J_{CP} 11.5 Hz), 133.86 (d, J_{CP} 3.3 Hz), 141.31 (d, J_{CP} 26.2 Hz), 141.65 (d, J_{CP} 40.2 Hz).

4.4. (1*S*,1′*S*,2*R*,2′*R*)-1,1′-di-*tert*-butyl-2,2′-dibenzophosphetenyl dioxide (*S*,*S*)-3 and (1*R*,1′*R*,2*S*,2′*S*)-1,1′-di-*tert*-butyl-2,2′-dibenzophosphetenyl dioxide (*R*,*R*)-3

s-Butyllithium (0.97 M in cyclohexane, 2.9 mL, 2.8 mmol) was added over 5 min to a solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (0.42 mL, 2.8 mmol) in dry THF (2 mL) at −78 °C under argon. After 30 min, a solution of (*S*)-**2** (500 mg, 2.57 mmol) in dry THF (3 mL) was added dropwise. The bright red mixture was stirred at this temperature for 2 h then −50 °C for 2 h. Dry copper(II) chloride (dried at 120–130 °C for 4 h in vacuo, 450 mg, 3.34 mmol) was added in one portion with vigorous stirring and the mixture then gradually warmed to room temperature overnight. Aqueous ammonia (25%, 5 mL) was added and the layers separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with 1 M HCl, water, and brine and dried over Na_2SO_4. The solvents were removed under reduced pressure and the residual (a yellow solid) was washed with a small amount of ethyl acetate (ca. 4 mL) to give (*S*,*S*)-**3** (220 mg, 44%). Mp 180 °C (decomp); R_f 0.11 (EtOAc); $[\alpha]_D^{19} = -12.3$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{HP}$ 16Hz, 18H), 4.46 (d, $^1J_{HP}$ 4 Hz, 2H), 7.31–7.39 (m, 2H), 7.41–7.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.11, 33.22–33.98 (m), 46.38–47.20 (m), 126.91–127.16 (m), 129.05–129.16 (m), 133.77, 140.79–141.61 (m, 2C), 144.72–144.76 (m); IR (KBr) 2950, 2860, 2360, 1590, 1480, 1450, 1190 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_2P_2$: C, 68.38; H, 7.30. Found: C, 68.10; H, 7.49.

In a similar manner, (*R*)-**2** was converted to (*R*,*R*)-**3** in 45% yield. Mp 180 °C (decomp); R_f 0.11 (EtOAc); $[\alpha]_D^{19} = +12.5$ (c 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{HP}$ 16 Hz, 18H), 4.45 (d, $^1J_{HP}$ 4 Hz, 2H), 7.32–7.40 (m, 2H), 7.41–7.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.11, 33.21–33.97 (m), 46.38–47.20 (m), 126.91–127.16 (m), 129.04–129.16 (m), 133.76, 140.79–141.70 (m, 2C), 144.71–144.76 (m); IR (KBr) 2950, 2860, 2360, 1590, 1480, 1450, 1190 cm^{-1}.

4.5. *dl*-1,1′-Di-*tert*-butyl-2,2′-dibenzophosphetanyl dioxide *dl*-3

Compound *dl*-**2** was treated subsequently with *s*-BuLi and copper(II) chloride to produce *dl*-**3** and *meso*-isomer in 83:17 ratio. Pure *dl*-**3** was obtained by chromatography on silica gel using EtOAc as the eluent. Mp 180 °C (decomp.). ^{1}H NMR (100 MHz, $CDCl_3$): δ 1.23 (d, $^3J_{HP}$ 15.9 Hz, 18H), 4.46 (d, $^1J_{HP}$ 4.1 Hz, 2H), 7.31–7.39 (m, 2H), 7.41–7.52 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.12, 33.22–33.98 (m), 46.38–47.20 (m), 126.91–127.16 (m), 129.05–129.16 (m), 133.77, 140.79–141.61 (m, 2C), 144.72–144.76 (m); ^{31} P NMR (202 MHz, $CDCl_3$): δ 60.95. IR (KBr): 2950, 2860, 2360, 1590, 1480, 1450, 1190 cm^{-1}.

4.6. Optical resolution of *dl*-3

A mixture of *dl*-**3** (38.6 mg, 0.1 mmol) and (2*S*,3*S*)-(+)-*O*,*O*′-dibenzoyltartaric acid [(+)-DBTA; 179 mg, 0.5 mmol] was dissolved in hot ethyl acetate (1 mL). The mixture was gradually cooled to room temperature. The precipitated crystalline solid was collected by filtration, washed with ethyl acetate, treated with 1 M NaOH (2 mL). The mixture was extracted with chloroform, dried over Na_2SO_4 and concentrated under reduced pressure to give (*S*,*S*)-**3** (8.1 mg) as a white powder. Enantiomeric excess of this product was determined to be 98.8% by HPLC analysis (Chiralcel OD-H, 0.5 mL, 25 °C, 2-propanol/hexane (1:19), (*S*,*S*) $t_1 = 16.9$ min, (*R*,*R*) $t_2 = 23.3$ min, (*meso*) $t_3 = 25.3$ min).

4.7. X-ray crystallographic analysis of (*S*,*S*)-3

A well shaped orthorhombic crystal of (*S*,*S*)-**3** was obtained by recrystallization from ethyl acetate. A colourless prism crystal of $C_{22}H_{28}O_2P_2$ having approximate dimensions of 0.40 × 0.30 × 0.20 mm was mounted in a glass capillary. All measurements were made on a Rigaku RAXIS-II Imaging Plate diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71070$ Å) at 173 K. Crystal data and refinement details: space group $P2_12_12_1$ (#19); $a = 9.722(7)$ Å, $b = 22.91(2)$ Å, $c = 9,65(1)$ Å; $V = 2149(3)$ Å^3; $Z = 4$, $D_{calcd} = 1.194$ g/cm^3; $F(000) = 824$; μ(Mo Kα) = 2.15 cm^{-1}; 1790 reflections measured, 1654 observed ($I > 2.00\sigma(I)$); 235 variables; $R = 0.072$, $R_w = 0.079$, GOF = 1.40. The absolute configuration was determined by the Flack parameter method. Cambridge Crystallographic Data Centre supplementary publication number CCDC 240727.

4.8. Reduction of bis(*tert*-butylbenzophosphetane)oxide and preparation of rhodium complex

Hexachlorodisilane (70 μL, 0.39 mmol) was added dropwise to a solution of (*R*,*R*)-**3** (50 mg, 0.13 mmol) in dry,

freshly degassed THF (3.5 mL) at room temperature under argon. The flask was immersed in a preheated oil bath (80 °C) and stirring continued for 90 min. The flask was removed from the oil bath, and hexachlorodisilane (70 μL, 0.39 mmol) again added. The reaction mixture was stirred at 80 °C for 70 min. The operation was repeated at 70 min interval until 12–15 equiv was used for disappearance of the starting diphosphine oxide and intermediate monophosphine oxide (TLC monitoring). The mixture was cooled to −10 °C. A well degassed aqueous solution of sodium hydroxide (10%, 3 mL) was added dropwise under argon and the mixture stirred for 5 min at this temperature and then 10 min at room temperature. Degassed benzene (2 mL) was added and the organic layer transferred onto Na_2SO_4 under argon. The extraction procedure was repeated three times. The solution was passed through a column of basic alumina under argon and the column washed using degassed benzene (15 mL). The eluent was removed under reduced pressure, releasing the pressure with argon, to give a white solid. This was dissolved in dry, degassed THF (3 mL) and then transferred to a stirred suspension of $[Rh(nbd)_2]BF_4$ (24.2 mg, 0.06 mmol) in THF (2 mL) under argon. The suspension turned immediately into an almost clear solution. After overnight stirring, the insoluble material was filtered off and the filtrate evaporated under reduced pressure. The residual solid was washed with hexane to give an orange powder, which was dried in vacuo. This product was used without further purification for the asymmetric hydrogenation of methyl α-acetamidocinnamate.

In a similar manner, (*S*,*S*)-**3** was reduced to (*R*,*R*)-**1** and converted to the corresponding rhodium complex.

4.9. Asymmetric hydrogenation of methyl α-acetamidocinnamate

The reaction was carried out according to the procedure described in the literature.[2,13] The ee of the product was determined by HPLC using a chiral column: Daicel Chiralcel OJ, 1.0 mL/min, hexane/2-propanol = 9:1, (*R*) $t_1 = 13.3$ min; (*S*) $t_2 = 19.3$ min.

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