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Preparation of a rigid bicyclic diphosphine by radical cyclisation

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Abstract—Bromodiphosphine oxide **3** was obtained from the selectively protected chiral diol **2** by the double [2,3]-sigmatropic shift of an intermediate phosphinite. The bromophosphine oxide derivative **3** was converted by radical cyclisation into rigid bicyclic diphosphine **1**. The diphosphine **1** was characterised and tested as a ligand in several metal catalytic reactions. © 2001 Published by Elsevier Science Ltd.

1. Introduction

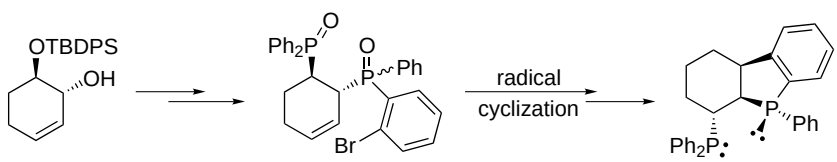
Methods for the stereoselective preparation of 1,*n*-diphosphines (where $n=3$–5) with a rigid backbone are important since these homochiral molecules are potentially useful ligands in asymmetric metal catalytic systems.[1,2]

Radical cyclisations have proven to be an excellent method for forming five-membered carbocycles and heterocycles.[3] Herein, we report an enantioselective synthesis of the rigid diphosphine **1** starting from the selectively protected diol **2** via the key intermediate **3**. The use of the diphosphine **1** in standard asymmetric metal-catalysed reactions was also examined (Scheme 1).

2. Results

The readily available (*R*,*R*)-diol derivative **2** (98% e.e.)[4,5] was first converted to the corresponding phosphinite **4** by treatment with chlorodiphenylphosphine in the presence of DMAP in ether (20°C, 0.5 h). Heating **4** in mesitylene for 2 h led to a smooth [2,3]-sigmatropic shift[5,6] affording the corresponding phosphine oxide with complete transfer of stereochemistry. After removal of the silyl protecting group by treatment with conc. HF in CH_3CN (20°C, 24 h) the allylic alcohol **5** was obtained with 99% e.e. The reaction sequence was performed on 150 mmol scale in 77% overall yield from **2**. Alcohol **5** was again converted to a phosphinite by reaction with 2-bromophenyl(phenyl)phosphine chloride **6**.

After heating in refluxing mesitylene for 2 h, the desired phosphine oxide **3** was obtained as a 1:1 mixture of two diastereoisomers at phosphorus. The mixed chlorophosphine **6** was prepared in 55% yield from 2-bromophenylmagnesium chloride by iodine–magnesium exchange[7] in THF using *i*-PrMgCl, at −30°C over 2 h and subsequent reaction with dichlorophenylphosphine at −30 to 0°C over 1 h (Scheme 2). The phosphindoline oxide[8] **7** was obtained by a radical cyclisation using Bu_3SnH (1.2 equiv.) and AIBN (0.1 equiv.) in toluene at 80°C over 2 h. Interestingly, only one diastereoiso-



2 **3** **1**

Scheme 1.

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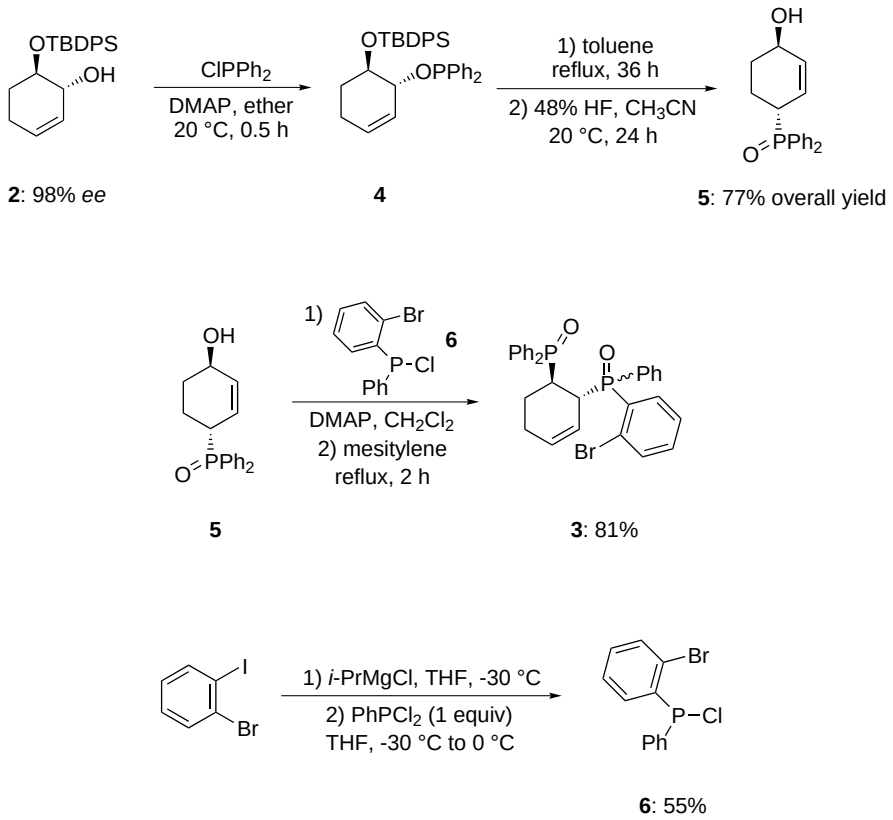


Scheme 2.

mer formed, as confirmed by X-ray analysis (Fig. 1).[9] Reduction of the phosphine oxide with $HSiCl_3$ (excess, toluene, 120°C, 14 h) in an autoclave afforded the diphosphine with retention of configuration at phosphorus.[10] The selective formation of one diastereoisomer during the cyclisation of **3** may be explained by assuming a [1,5] H-shift[11] of the radical. The radical chain reaction leads to the two diastereoisomeric radicals **8a** and **8b**. Whereas **8b** can readily undergo cyclisation leading to **7**, the diastereoisomeric radical **8a** has to undergo a [1,5] H-shift affording **8b**, which then cyclises (Scheme 3).

The diphosphine ligand **1** was tested in several typical metal-catalysed reactions (Scheme 4).

The asymmetric hydrogenations of (*Z*)-α-methyl acetamidocinnamate[13] **9**, (*E*)-ethyl 4-methyl-3-acetamido-2-pentenoate[14] **10** and dimethyl itaconate[15] **11** were chosen as preliminary test reactions. The hydrogenation

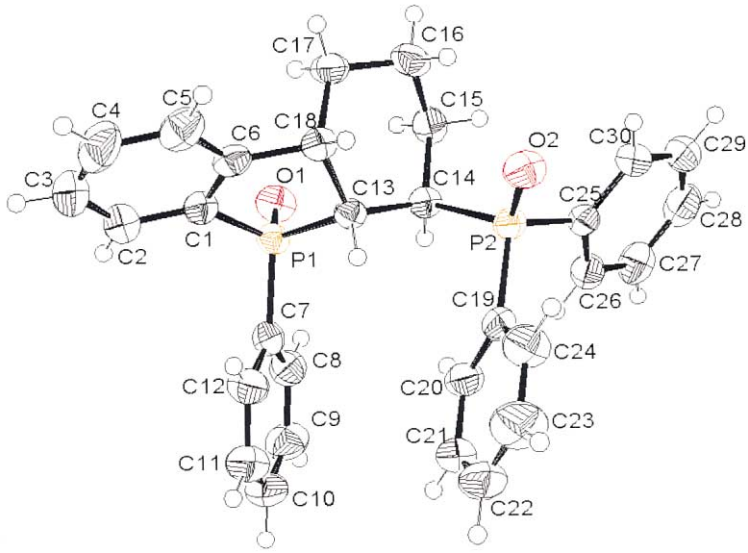
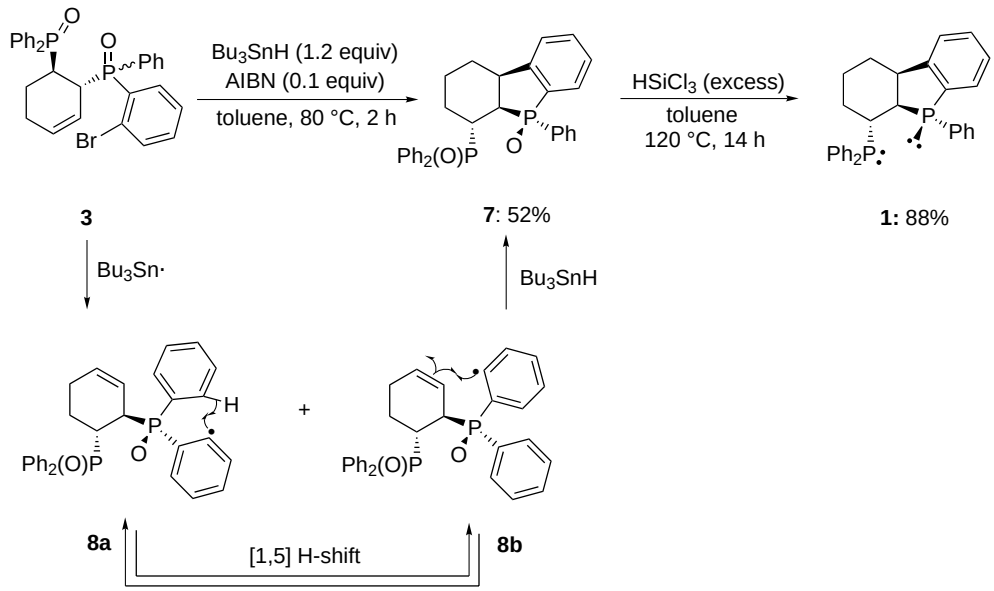
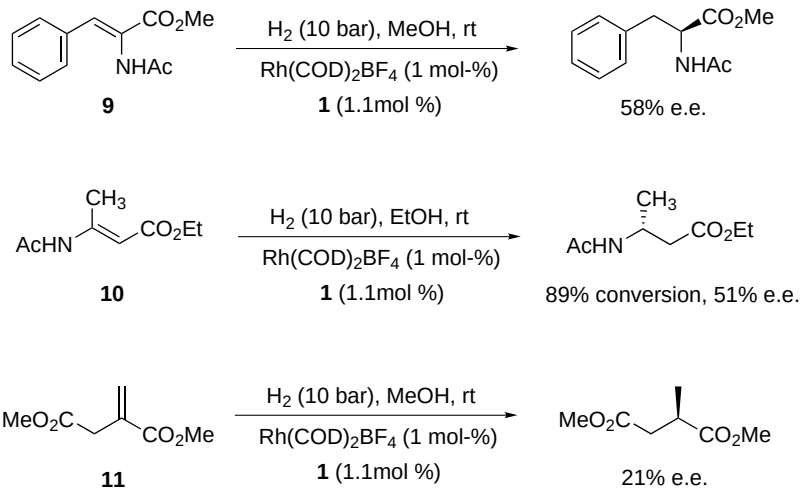


Figure 1. X-Ray structure of the diphosphine oxide **7**.



Scheme 3.



Scheme 4.

reactions were performed at room temperature under 10 bar H_2 using $Rh(COD)_2BF_4$ (1 mol%) and ligand **1** (1.1 mol%) in MeOH or EtOH. For the reduction of **9** and **10**, modest e.e.s of 58 and 51% were obtained, respectively, whereas the reaction of dimethyl itaconate **11** provided the hydrogenated product only with e.e. of 21%.

Furthermore, **1** was tested in the Rh-catalysed asymmetric hydroboration of styrene.[16] The reaction was carried out in THF at 0°C using $Rh(COD)_2BF_4$ (1 mol%), ligand **1** (1.1 mol%) and catecholborane (1.1 equiv.). After oxidative work-up, the two isomeric alcohols were isolated in a good regioselectivity (branched to linear: 94:6); the (*R*)-configured secondary alcohol was obtained with 16% e.e.

Since the ^{31}P NMR spectrum of the complex formed by **1** with $Rh(COD)_2BF_4$ shows that **1** acts as a bidentate ligand (^{31}P NMR (81 MHz, $CDCl_3$) of [Rh(COD)**1**]-BF_4: δ 59.00 (dd, $J_{(P,P)}=32.8$ Hz, $J_{(Rh,P)}=146.4$ Hz), 51.71 (dd, $J_{(P,P)}=32.8$ Hz, $J_{(Rh,P)}=151.1$ Hz)) the modest enantioselectivities in these reactions are not due to mono-coordination of **1** to the metal, but may result from the specific shape of the diphosphine.

3. Conclusion

We have reported a new synthetic approach to a rigid diphosphine ligand in ca. 28% overall yield, starting from readily available diol **2**. Preliminary asymmetric metal catalysis gave disappointing results, maybe due to an inappropriate conformation of the bicyclic backbone (absence of C_2-symmetry). Further asymmetric metal catalytic systems are currently being studied.

4. Experimental

4.1. Analysis

NMR spectra were recorded on Bruker ARX 200, AC 300 or WH 400 instruments. Chemical shifts are reported relative to the residual solvent peaks: $CDCl_3$ at 7.27 ppm (^{1}H NMR) and 77.0 ppm (^{13}C NMR). For ^{31}P NMR, 85% phosphoric acid was used as external standard. IR spectra were recorded on a Nicolet 510 or a Perkin–Elmer 281 spectrometer. Electron impact (EI) mass spectra were recorded on a Varian MAT CH 7A. High resolution mass spectra (HRMS) were recorded on a Varian MAT 711. Melting points were measured on a Büchi B-540 apparatus (Dr. Tottoli) and are uncorrected. Microanalyses were carried out by the analysis laboratory of the LMU Department of Chemistry. Solvents were distilled over drying agents under argon or nitrogen as follows: diethyl ether, DME and THF (Na/benzophenone), toluene (Na), dichloromethane (CaH_2). E.e.s were determined by GC on a 25 m×0.25 mm fused silica WCOT CP-Chirasil-DEX CB (0.25 μm) using hydrogen (84 kPa) as the mobile phase or on a 25 m×0.25 mm fused silica WCOT Chirasil-L-Val (0.12 μm) using hydrogen (48 kPa) as the mobile phase. Furthermore, e.e.s were determined by HPLC. A Chiracel OD column (Daicel Chemical Industries) was used at 21°C with *n*-heptane–2-propanol (95:5) as a mobile phase and detection by a diode array UV–Vis detector at 215 nm.

4.2. (1*R*,4*R*)-4-(Diphenylphosphinoyl)-2-cyclohexen-1-ol 5

A 500 mL flask under argon equipped with a magnetic stirrer was charged with the (*R*,*R*)-mono-protected diol **2** (21.5 g containing 15 mol% of *tert*-butyldiphenylsilanol, 55.0 mmol) and DMAP (7.45 g, 61 mmol, 1.1 equiv.) in solution in ether (250 mL). To the homogeneous solution, pure chlorodiphenylphosphine (13.4 g, 61 mmol, 1.1 equiv.) was added dropwise. The resulting suspension was stirred for 0.5 h and filtered under argon over a short pad of dry silica gel. The precipitate was washed twice with ether (60 mL). The ethereal solution was evaporated under reduced pressure and the crude product was dissolved in toluene (200 mL) and heated under argon to reflux for 36 h. After cooling to rt, the solvent was evaporated and silyl deprotection was achieved by dissolving the crude phosphine oxide in CH_3CN (250 mL) and by adding concentrated HF (aqueous 48% solution, 40 mL) at room temperature. The heterogeneous reaction mixture was vigorously stirred for 24 h, diluted with acetone–water mixture (1:1) (300 mL) and neutralised by addition of K_2CO_3 and $NaHCO_3$ until pH 7–8 was reached. The solvents were evaporated in vacuo and the solid residue was extracted several times with CH_2Cl_2. The organic phases were dried over $MgSO_4$, filtered and evaporated, yielding a crude oil (22.0 g) which was purified by chromatography on silica gel (CH_2Cl_2–Et_2O–MeOH 1:1:0 to 1:1:0.05). The amorphous deprotected alcohol **5** (15.5 g) was recrystallised from an *n*-heptane/CH_2Cl_2 mixture, affording colorless crystals (12.8 g, 77% yield), which were stored under argon at −5°C. $[\alpha]_D^{20}=+131.0$ (*c* 0.58, MeOH). Mp 193–194°C (from *n*-heptane/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.66 (m, 4H), 7.42–7.35 (m, 6H), 5.88 (m, 1H), 5.44 (m, 1H), 4.12 (m, 1H), 3.65 (m, 1H), 3.10 (m, 1H), 2.04 (m, 1H), 1.85–1.75 (m, 2H), 1.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.40 (d, $J=10.8$ Hz), 132.21–128.44 (m), 122.23 (d, $J=6.0$ Hz), 64.97 (d, $J=2.7$ Hz), 36.70 (d, $J=71.8$ Hz), 30.63 (d, $J=7.9$ Hz), 19.32 (d, $J=3.0$ Hz). ^{31}P NMR (81 MHz, $CDCl_3$): δ 33.6. IR (KBr): 3322, 1437, 1183 cm^{-1}. MS (EI): $m/z=298$ (3.9%, [M$^+$]), 279 (18.9%), 201 (100%). $C_{18}H_{19}O_2P$ (298.32): C, 72.47; H, 6.42. Found: C, 72.18; H, 6.34%.

4.3. 2-Bromophenyl(phenyl)phosphinous chloride 6

A 250 mL flask under argon was charged with 2-bromo-1-iodobenzene (12.9 mL, 28.3 g, 100 mmol) and THF (50 mL). The homogeneous solution was cooled to −30°C and isopropylmagnesium chloride (2.75 M THF solution, 35 mL, 96 mmol, 0.96 equiv.) was added dropwise within 10 min. The reaction mixture was stirred for 2 h at −30°C and dichlorophenylphosphine (13.0 mL, 17.2 g, 0.96 equiv.) was added dropwise within 10 min. The temperature (−30°C) was checked carefully during the addition of $PhPCl_2$. The reaction was stirred for 15 min at −30°C and was allowed to warm up to 0°C for 30 min. The formation of the chlorophosphine **6** was checked by ^{31}P NMR of an aliquot (δ 75.6 ppm in THF). The solvents were pumped off for 12 h and diethyl ether (150 mL) was added to the residue. After filtration under argon on a short pad of Celite and rinsing two times with diethyl ether (20 mL), the etheral solution of **6** was evaporated in vacuo. The residue was distilled at 135–140°C at 0.05 mmHg (lit.[12] 145–146°C under 0.5 mmHg), affording **6** as a colourless oil (16.5 g, 55%), which was stored under argon at −5°C. ^{31}P NMR (81 MHz, $CDCl_3$): δ 74.5. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90–7.84 (m, 1H), 7.63–7.26 (m, 8H).

4.4. (2-Bromophenyl)[(1*R*,6*R*)-6-(diphenylphosphinoyl)-2-cyclohexen-1-yl]phenylphosphine oxide 3 (diastereoisomeric mixture at phosphorus)

A 250 mL flask under argon equipped with a magnetic stirrer was charged with the allylic alcohol **5** (40 mmol, 11.93 g), DMAP (5.13 g, 42 mmol, 1.05 equiv.) and CH_2Cl_2 (40 mL). To the homogeneous solution, pure chlorophosphine **6** (12.6 g, 42 mmol, 1.05 equiv.) was added dropwise. The reaction was stirred for 0.5 h and ether (120 mL) was added to precipitate DMAP hydrochloride. After filtration under argon over a short pad of dry silica gel, the solution of diastereoisomeric monophosphinites (δ 101.3, 101.2 and 30.2 ppm by ^{31}P NMR at 81 MHz in Et_2O) was evaporated under reduced pressure and the resulting crude mixture of monophosphinites was diluted in mesitylene (100 mL). This solution was heated under argon to reflux for 2 h. After cooling to rt, the solvent was evaporated. The crude mixture of diphosphine oxides **3** (29.3 g) was purified by chromatography on silica gel (ether–CH_2Cl_2–MeOH 1:1:0 to 1:1:0.04), yielding **3** (18.2 g,

81%) as a solid amorphous (1:1) mixture after trituration in cyclohexane and filtration. Attempts to separate the two diastereoisomers were unsuccessful by chromatography or fractional crystallisation. ^{31}P NMR (81 MHz, $CDCl_3$): δ 36.5 (d, $J=46.2$ Hz) and 34.2 (d, $J=46.2$ Hz) for one diastereoisomer; δ 35.5 (d, $J=51.3$ Hz) and 34.6 (d, $J=51.3$ Hz) for the other diastereoisomer. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.11–8.07 (m, 1H), 7.89–7.19 (m, 37H), 5.90 (m, 2H), 5.50 (m, 1H), 5.28 (m, 1H), 3.16 (m, 1H), 3.10 (m, 1H), 2.62 (m, 1H), 2.15–1.95 (m, 3H), 1.82–1.70 (m, 2H), 1.60–1.50 (m, 1H). MS (EI): $m/z=560$ (3.0%, [M$^+$]), 481 (3.4% [M$^+$ −Br]), 359 (20.2%), 281 (100%), 201 (60%).

4.5. (4*R*,4a*R*,9b*S*,5*S*)-4-(Diphenylphosphinoyl)-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-benzo[*b*]phosphindole 5-oxide 7

A 1 L flask under argon equipped with a reflux condenser was charged with the diastereoisomeric mixture **3** (10.4 g, 18 mmol) and toluene (750 mL). To the homogeneous solution were added successively AIBN (0.30 g, 1.8 mmol, 0.1 equiv.) and Bu_3SnH (5.7 mL, 6.28 g, 21.6 mmol, 1.2 equiv.). The reaction mixture was heated to 80°C for 2 h. ^{31}P NMR of an aliquot showed that the reaction was complete within 2 h. The reaction mixture was cooled to room temperature and solvents were evaporated in vacuo. The crude reaction mixture was purified by chromatography on silica gel (Et_2O–CH_2Cl_2–MeOH 1:1:0 to 1:1:0.04), yielding the diphosphine oxide **7** (6.40 g) as a slightly yellow crystalline compound. The diphosphine oxide **7** was finally recrystallised from *n*-heptane/CH_2Cl_2 affording a **7**·H_2O complex (1:1) or from *n*-heptane/$CHCl_3$ mixture. This last mixture gave a **7**·$CHCl_3$ complex (1:1) (5.20–5.60 g, 48–52%) suitable for X-ray analysis. $[\alpha]_D^{20}=+40.0$ (*c* 0.66, $CHCl_3$) for the complex (1:1) with $CHCl_3$. $[\alpha]_D^{20}$ +46.8 (*c* 0.70, $CHCl_3$) for the complex (1:1) with H_2O. Mp 128–138°C (from *n*-heptane/$CHCl_3$; complex (1:1) between **7** and $CHCl_3$). Mp 161–167°C (from *n*-heptane/CH_2Cl_2; complex (1:1) between **7** and H_2O). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78–7.72 (m, 2H), 7.54–7.19 (m, 15H), 7.00–6.93 (m, 2H), 3.92 (d quint., 1H, $J=30.2$ Hz, $J=6.1$ Hz), 3.11 (dt, 1H, $J=13.4$ Hz, $J=6.4$ Hz), 2.57 (m, 1H), 2.24–2.11 (m, 3H), 1.90 (t, 1H, $J=11.9$ Hz), 1.66–1.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.06, 154.73, 132.76–125.50 (m), 41.71 (d, $J=3.1$ Hz), 37.87 (d, $J=72.9$ Hz), 34.81, 29.94 (d, $J=71.6$ Hz), 22.63 (d, $J=2.4$ Hz), 21.53. ^{31}P NMR δ (81 MHz, $CDCl_3$): 49.3 (d, $J=51.1$ Hz), 39.4 (d, $J=51.1$ Hz). IR (KBr): 3439, 2938, 1437, 1189, 1115 cm^{-1}. MS (EI): $m/z=482$ (23.4%, [M$^+$]), 281 (100%). $C_{30}H_{28}O_2P_2$·$CHCl_3$ (482.16+119.38): C, 61.90; H, 4.86. Found: C, 62.26; H, 4.75%. $C_{30}H_{28}O_2P_2$·H_2O (482.16+18.01): C, 72.04; H, 6.04. Found: C, 72.54; H, 6.02%.

4.6. (4*R*,4a*R*,9b*S*,5*S*)-4-(Diphenylphosphino)-5-phenyl-2,3,4,4a,5,9b-hexahydro-1*H*-benzo[*b*]phosphindole 1

The phosphine oxide **7** (2.48 g, 5.0 mmol, complex (1:1) with H_2O) was charged into an autoclave under argon with toluene (50 mL) and trichlorosilane (7 mL, 70 mmol, 14 equiv.) and heated for 14 h at 120°C. After cooling to rt, the reaction mixture was transferred in a 100 mL flask filled with argon. Toluene and trichlorosilane in excess were evaporated with a high vacuum pump. The residue was dissolved in toluene (25 mL) and carefully quenched with degassed 3 M KOH (15 mL). The mixture was stirred at 50°C until the organic and aqueous layers became clear. The two layers were separated and the organic phase was dried ($MgSO_4$) under argon. The resulting clear and colourless organic phase was filtered and transferred by cannulation in a second flask flushed with argon. Toluene was evaporated and the crude crystalline diphosphine **1** was washed with degassed dry methanol (2×5 mL). After filtration, traces of solvent were pumped off under high vacuum for 2 h, yielding **1** (1.96 g, 88%) as a colorless microcrystalline solid which was stored under argon. $[\alpha]_D^{20}=+53.0$ (*c* 0.80, $CHCl_3$). Mp 150–152°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–6.81 (m, 19H), 3.58–3.48 (m, 1H), 2.69–2.58 (m, 2H), 2.12–1.32 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.06, 151.95, 139.74–124.10 (m), 50.31 (dd, $J=9.7$ Hz, $J=16.1$ Hz), 43.66 (d, $J=5.5$ Hz), 33.36 (dd, $J=12.9$ Hz, $J=18.2$ Hz), 31.57, 24.42 (dd, $J=5.7$ Hz, $J=8.5$ Hz), 26.29 (d, $J=7.6$ Hz). ^{31}P NMR (81 MHz, $CDCl_3$): δ 0.6 (d, $J=34.9$ Hz), −9.7 ($J=34.9$ Hz). IR (KBr): 2923, 1433 cm^{-1}. MS (EI): $m/z=450$ (76.1%, [M$^+$]), 341 (100%), 265 (30%). HRMS (EI) calcd for $C_{30}H_{28}P_2$: 450.1667; found: 450.1661

4.7. General procedure for asymmetric hydrogenation

In a dry 50 mL Schlenk tube $Rh(COD)_2BF_4$ (3.7 mg, 1 mol%) and ligand **1** (4.5 mg, 1.1 mol%) were completely dissolved in dry methanol (10 mL) under argon. The solution was transferred via a cannula into a glass vessel, placed in a stainless steel autoclave, containing (*Z*)-α-methyl acetamidocinnamate **9** (200 mg, 0.91 mmol) under argon. The gas inlet tube was connected to a hydrogen source and argon was replaced by hydrogen by flushing three times to 10 bar pressure of hydrogen. The solution was stirred for 12 h at room temperature. The crude reaction mixture was filtered through a short silica gel column using diethyl ether as eluent. (*S*)-2-Acetylamino-3-phenyl-propionic acid methyl ester was isolated as a white solid (mp 89°C) in 58% e.e.

E.e.s and absolute configurations of the hydrogenation products were assigned by comparison with literature data.

2-Acetylamino-3-phenyl-propionic acid methyl ester:[13] GC (140°C, isothermal, column: Chirasil-L-Val): t_R (min)=12.26 (*R*), 14.47 (*S*).

3-Acetylamino-butyric acid ethyl ester:[14] GC (140°C, isothermal, column: Chirasil-DEX CB): t_R (min)=3.17 (*S*), 3.29 (*R*).

2-Methylsuccinic acid dimethyl ester:[15,17] HPLC (flow rate of 0.6 mL/min): t_R (min)=11.15 (*R*), 18.48 (*S*).

Phenylethanol:[16] HPLC (flow rate of 0.6 mL/min): *n*-alcohol: t_R (min) = 17.00; *iso*-alcohol: t_R (min) = 15.60 (*R*), 18.13 (*S*).

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