

PHANE-TetraPHOS, the First D₂ Symmetric Chiral Tetraphosphane. Synthesis, Metal Complexation, and Application in Homogeneous Stereoselective Hydrogenation

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Dedicated to Professor Franco Cozzi on the occasion of his 70th birthday

PHANE-TetraPHOS, a new D_2 symmetric tetraphosphane based on the [2.2]paracyclophane scaffold, has been synthesized and characterized. The peculiarity of this system is the presence of four homotopic diphenylphosphane groups, exchangeable through C_2 symmetry operations and consequently indistinguishable. Their spatial arrangement allows the simultaneous complexation of two metal atoms. Enantiomeric purity was attained at tetra-phosphane oxide level by fractional crystallization of the diastereomeric adducts obtained from the racemate with enantiopure dibenzoyltartaric acids. Alkaline treatment of

Introduction

Chiral tetraphosphanes have deserved too scarce consideration so far as potential ligands of transition metals for asymmetric homogeneous catalysis. This area has been worthily dominated by chiral diphosphane ligands that have been employed with enormous success for a long time, even though also chiral monophosphanes have found important specific applications.^[1] A reason for such a modest appeal could be the multiple complexation modes offered by four, generally non-equivalent, phosphorous centres which could generate different, possibly antagonist, complexes. The history of tetraphosphanes is mainly diastereomerically pure adducts followed by exhaustive P–O groups reduction with HSiCl₃ gave both PHANE-TetraPHOS antipodes in an enantiopure state. They were tested as rhodium ligands in the homogeneous enantioselective hydrogenation of some benchmark unsaturated compounds. Catalytic activity and enantiodiscrimination ability were found comparable to those exhibited by the complexes of the parent bidentate ligand PHANEPHOS, but only half a mole of precious chiral ligand was employed.

represented by achiral ligands, generally designed to "double" the catalytic activity of diphosphanes, to lower the catalyst loading and to prepare heterobimetallic complexes widening the applicative scope of a catalyst.^[2] Chirality was introduced in tetraphosphane ligands in 2003, when the group of Mikami designed a tropos tetraphosphane based on a 1,3-terphenyl backbone exhibiting a C_2 symmetric helical arrangement following double metal complexation (Figure 1).^[3] The reaction of the racemic dipalladium complex with two equivalents of an enantiopure diamine gave a one to one diastereomeric mixture of complexes. Heating the latter at 80°C caused total conversion of the less stable diastereoisomer into the more

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Figure 1. Known chiral tetraphosphanes.

stable one 1, which, applied as Lewis acid catalyst in asymmetric carbonyl-ene reaction of ethyl glyoxylate with methylenecyclohexane, showed slightly better, even though very similar, enantioselectivity and yields than those obtained by using a double molar amount of the analogous catalysts prepared from BINAP and BIPHEP.

In 2006, a P-stereogenic tetraphosphane 2 (Figure 1) combining two 1,2-bis(alkylmethylphosphino)ethane (BisP*)-like units,^[4a] was applied as Rh(I) ligand in asymmetric hydrogenation of prostereogenic C-C double bonds giving results comparable with those obtained using t-Bu-BisP-rhodium complex.^[4b] The Authors suggested that only one diphosphanerhodium unit participated to the hydrogenation catalytic cycle, underlying the crucial structural restrictions for the synchronous operation of two adjacent metal centres. As a matter of fact, when one of the rhodium atoms undergoes oxidative addition followed by coordination of the substrate, the resulting octahedral moiety creates such a steric hindrance that coordination of a second substrate molecule is inhibited. This research case demonstrates that geometrical structural parameters must be carefully considered in designing tetradentate ligands as precursors of bimetallic catalytic systems.

We developed in the past two classes of electronically tunable C_1 and C_2 symmetric diphosphanes based on atropisomeric biheteroaromatic scaffolds that were employed as chiral ligands of transition metals producing excellent results in the hydrogenation of prostereogenic C–C and C–O double bonds even at an industrial scale level.^[5] We decided to resume our work in this field by designing a new chiral tetraphosphane ligand featured by four homotopic phosphane groups, organized on a scaffold granting the complexation of two metal atoms by two selected phosphane pairs and the complete steric independence of the two units after complexation. All these structural requirements are fully satisfied by a suitably 4,7,12,15-

tetrasubstituted *p*-cyclophane, and the new tetradentate ligand **3**, which is the protagonist of the present paper, is endowed with an architecture displaying three orthogonal C_2 axes interchanging all the four phosphane groups and conferring to the ligand the unusual D_2 symmetry. The nickname we assigned to **3** is PHANE-TetraPHOS (Figure 2), considering that PHANE-PHOS **4** (Figure 2), which is a quite popular C_2 symmetric diphosphane ligand, displays the same *p*-cyclophane scaffold.^[6]

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Experimental support to the structural design of **3** was given by the single-crystal XRD analysis of the dichloropalladium complex of PHANEPHOS, showing that the planes of the two phenylene rings are perfectly parallel,^[7] suggesting that the double metal complexation in tetraphosphane **3** should easily occur without any steric constraint.

As for synthetic accessibility, *p*-cyclophane is a commercially available rather inexpensive starting material. Furthermore, its tetrabromination was expected to lead, as the main product, to the bis-pseudo-*ortho* isomer, namely the 4,7,12,15-tetrabromo-*p*-cyclophane (5), which is the natural starting material for the preparation of tetraphosphane **3** (Figure 2).^[8]

The access to PHANEPHOS is much more difficult, since dibromination of *p*-cyclophane does not afford the necessary pseudo-*ortho*-dibromo derivative **6b**, but the achiral S_2 symmetric pseudo-*para*-diastereoisomer **6a**. The latter must be submitted to thermal diastereoselective equilibration to give a 1:1 mixture of **6a** and **6b**, from which the latter was isolated by solubility difference and chromatography.^[6]



Figure 2. Comparison between synthetic routes to PHANE-TetraPHOS (±)-3 and PHANEPHOS (±)- 4.



Results and Discussion

Synthesis of (–)-3

As anticipated, the synthetic route (Scheme 1) to the tetraphosphane (\pm) -**3** involves the exhaustive bromination of commercially available [2.2]paracyclophane, which affords racemic (\pm) -**5** and the achiral constitutional isomer **7** in comparable amounts. The two isomers can be easily separated by taking advantage from the much lower solubility of the undesired isomer **7** in dichloromethane. In order to optimize the yields, we experimented several bromination methodologies: iron catalysed reaction with bromine in CH₂Cl₂ solution,^[8a] neat bromine as reagent and solvent, reaction of solid [2.2]paracyclophane with bromine vapours^[8b] and iodine-catalysed bromination in neat



Scheme 1. Synthesis and resolution of PHANE-tetraPHOS (–)-3. Reagents and conditions: (a) Br₂, l₂ (0.01 equiv.), r.t., 7 days, dark; (b) t-BuLi (4.2 equiv.), THF, -78° C, 10 min, then CIPOPh₂ (2.1 equiv.), THF, -78° C to r.t. 12 h; (c) t-BuLi (8.6 equiv.), THF, -78° C, 10 min, then CIPOPh₂ (4.6 equiv.), THF, -78° C to r.t., 12 h, then H₂O₂, r.t., 12 h; (d) (+)-DBTA (1 equiv.), CH₂Cl₂/EtOAc, 40 °C to r.t., 12 h; e) HSiCl₃ (118 equiv.), p-xilene, 140°C, 72 h.



Figure 3. X-ray structure of dibromo-diphosphinylderivative (\pm)-8; CCDC number 1972369. Ball and stick representation. Colour code: C, grey; O, red; P, dark yellow, Br, light brown and H, white.

bromine.^[8b] The best results were obtained by using the last two methodologies, affording (±)-5 in 40% and 42% yield, respectively.

Preliminary experiments for the functionalization of the paracyclophane scaffold with diphenylphosphinyl groups were based on a stepwise double substitution of the bromine atoms, effected by double lithiation of tetrabromoderivative (\pm) -**5** with *t*-BuLi, followed by addition of two equivalents of diphenylphosphinylchloride.

Chromatographic analysis demonstrated the presence of a multitude of compounds among which the most interesting one, isolated in 15% yield, was the C_2 symmetric diphosphane oxide (\pm)-**8**, whose structure was determined by single-crystal X-ray diffraction analysis (Figure 3).

Compound (±)-8 could be an interesting intermediate to obtain the 5,15-dibromo-PHANEPHOS and a series of substituted PHANEPHOS ligands endowed with different steric and electronic properties. Considering, however, the difficulties encountered in the preparation of diphosphane oxide (±)-8, we discarded the possibility of using it as intermediate to accede to tetraphosphane oxide (±)-9 and focused our attention to experiments involving the simultaneous lithiation of the four bromine atoms of (±)-5.

After several unsatisfactory attempts performed by varying lithium species, solvent, reaction times and temperature, we found that acceptable (25%) yields of (\pm) -9 were obtained when the reaction was carried out with a large excess of *t*-BuLi (8.6 eq), at -78°C; the tetra-anion was immediately quenched with chlorodiphenylphosphane. After the usual work-up, the crude reaction product was oxidized with a 30% H₂O₂ solution. Tetraphosphane oxide (\pm)-9, necessary to perform the resolution process,^(15,6) was obtained by simple treatment of the crude reaction product with ethanol and its structure was unequivocally confirmed by single-crystal X-ray diffraction analysis, after crystallization from butanol (Figure 4).

The resolution of the racemate was successfully achieved by fractional crystallization of the diastereomeric adducts obtained by reaction of (\pm) -9 with enantiopure (+)-dibenzoyl-D-tartaric



Figure 4. X-ray structure of tetraphosphane oxide (\pm) -9; CCDC number 1972368. Ball and stick representation. Colour code as in Figure 3. The butanol molecule is omitted for clarity.



acid, and subsequent alkaline decomplexation. The resolution method was very successful, as demonstrated by the HPLC



Figure 5. a: enantioselective HPLC analysis of the resolved (–)-9 (Chromatographic conditions: column, Chiralpak IA-3 100 mm×4.6 mm, 3 µm; mobile phase, dichloromethane:ethanol 20:100 (v/v); flow-rate, 1.5 mL/min; detector, CD at 280 nm). **b**: CD spectra of (+)-9 (green) and (–)-9 (red) (acetonitrile, 0.1 mg/mL).



Figure 6. a) assignment of configurational descriptors to the *pS* enantiomer; b) comparison of experimental spectra of (+)- and (-)-9 and calculated CD spectrum for *pS* enantiomer.

analysis on a chiral stationary phase of the levorotatory phosphane oxide (Figure 5a), which showed an enantiomeric excess higher than 99% ($[\alpha]_D^{25} = -48.0^\circ$, c = 1% in CH₂Cl₂). Treatment of the mother liquors, after alkaline decomplexation, with (–)-dibenzoyl-L-tartaric acid and crystallization of the adduct, gave the dextrorotatory antipode. The CD spectra of both the antipodes are perfectly specular (Figure 5b).

Before discussing the assignment of the absolute configuration to the antipodes of **9**, it is useful to introduce a short recall of the CIP rules concerning the attribution of the configurational descriptors pS and pR to such high symmetry chiral molecules. Firstly, the stereogenic plane must be individuated that, in this case, is indifferently one of the two homotopic planes containing the aromatic ring, two phosphorous atoms and two methylene groups. Secondly, the so called "pilot atom", which is the first prioritary atom out of the plan must be chosen; in the present case it is indifferently one of the two equivalent methylene carbons of the cyclophane bridge, indicated as *P* in Figure 6a.

The last step is the check of the clockwise (pR) or counterclockwise (pS) sequence, as seen from the pilot atom *P*, starting from the atom directly connected to it (indicated as **a** in Figure 6a) and moving along the two following atoms (**b** and **c**) according to CIP priority rules.

The CD spectrum for the *pS* enantiomer of tetraphosphane oxide **9** was simulated by DFT calculations (see details in Experimental Section) and compared to the equivalent spectra registered for the enantiomers of **9** separated by enantioselective HPLC. A good matching was found between the CD spectrum of the second-eluted enantiomer and the calculated one. (Figure 6b); thus, the *pS* configuration was assigned to the second-eluted enantiomer of **9**, and the *pR* configuration to the first-eluted one.

The reduction of enantiopure (–)-**9** into the corresponding phosphane (–)-**3**, was successfully performed using trichlorosilane as reducing agent in refluxing *p*-xylene solution. The complete reduction of the four diphenylphosphino groups required prolonged reaction times (three days) at 140 °C and a large excess of HSiCl₃, added in three portions distributed along the whole reaction time. The ³¹P NMR spectrum of phosphane **3** displayed a singlet at –1.1 ppm confirming the D_2 2 symmetry of the molecule.

Rh complexes of 3 and enantioselective catalytic hydrogenation tests

The preliminary complexation experiments performed with (\pm) -**3** using two equivalents of bis(benzonitrile)palladium(II) chloride gave such an insoluble material that we could get the proof that the expected bimetallic complex was formed only by mass spectrometry analysis. Thus, we redirected our investigation to enantiopure Rh(I) complexes (Scheme 2).

The reaction of **3** with one equivalent of $[Rh(COD)_2]BF_4$ gave the mononuclear rhodium complex **10**, as demonstrated by the ³¹P NMR showing a singlet at -1.7 ppm corresponding to the free phosphane groups, and a doublet at 33.1 ppm related to Full Papers doi.org/10.1002/ejoc.202100109





Scheme 2. Rhodium complexes of (\pm) -3.

the two chelating phosphorous atoms, characterized by the typical Rh-P coupling constant (J = 147.0 Hz).

The neat formation of the mono rhodium complex **10** is of great interest, since it demonstrates the feasibility of inserting two *quasi*-homotopic different metals onto the two phosphane couples of **3**, thus pathing the access to a series of heterobimetallic catalysts. Unfortunately, preliminary experiments in this direction have been, at least for the moment, unsuccessful, since, by adding one equivalent of bis-benzonitrilepalladium dichloride to a solution of complex **10**, the precipitation of an intractable highly insoluble material, impossible to characterize, was again observed.

By adding a second equivalent of $[Rh(COD)_2]BF_4$ to complex **10**, both the ³¹P NMR signals immediately disappeared and the contemporary growth of a new a doublet at 27.5 ppm confirmed the formation of the binuclear Rh complex **11**. The same complex was formed also by direct addition of two equivalents of $[Rh(COD)_2]BF_4$ to a solution of **3**.

The Rh(COD)OTf complex of the (–)-PHANEPHOS ((–)-12),^[6a] and the bis Rh(COD)OTf complex of (–)-3 ((–)-13) were prepared *in situ* to compare the performances of (–)-PHANE-TetraPHOS (–)-3 with those exhibited by (–)-PHANEPHOS (–)-4 in the asymmetric homogeneous hydrogenation of some benchmark unsaturated compounds (Figure 7). The two complexes have been tested under identical experimental conditions, with the sole difference that half a mole of complex 13 was used in order to have identical metal amounts in solution (Table 1).

The results of this preliminary catalytic screening, summarized in Table 1, show that the performances of both the complexes (–)-12 and (–)-13 are similar. The enantioselection levels are nearly identical, while a moderate drop in kinetics was observed in some cases (Table 1, entry 4 and 5) when the binuclear complex (–)-13 was used.



Figure 7. Metal complexes (–)-12 and (–)-13 used for comparison and substrates.

Table 1. Comparison of catalytic activity and enanatioselectivity of complexes (–)-12 and (–)-13. $^{\rm [a]}$					
Entry	S	Conv. [%] ^[b] (–)- 12	ee [%] ^[c] (—)- 12	Conv. [%] ^[b] (–)- 13	ee [%] ^[c] (—)- 13
1 2 3 4 5	14 15 16 17 18	100 100 100 98 96	> 99 (R)-(-) 79 (R)-(-) 31 (S)-(-) 22 (R)-(+) 14 (R)-(+)	100 100 100 70 75	> 99 (R)-(-) 78 (R)-(-) 32 (S)-(-) 22 (R)-(+) 14 (R)-(+)
6	19	3	7 (R)-(+)	2	8 (R)-(+)

[a] Experimental conditions: S/C (–)-12=100 (1% mol); S/C (–)-13=200 (0.5% mol); solvent: MeOH; temperature: 25 °C; hydrogen pressure: 1 atm; reaction time: 1 h. [b] Determined by GC for 14, 16, 17, 18, 19 and by ¹H NMR for 15. [c] Determined by GC on CSP for 14, 16, 17, 18, 19 and by HPLC on CSP for 15.

Conclusions

The challenge of the project was the design, the synthesis and the investigation of the complexation properties of PHANE-TetraPHOS (3), an unusual tetradentate ligand in which all four donor atoms are homotopic. Keystone to satisfy this requirement is the D_2 molecular symmetry and PHANE-TetraPHOS, based on the [2,2]-paracyclophane scaffold, is the first example of such a high symmetry chiral tetraphosphane. It was synthesized according to a rather simple scheme and both antipodes were obtained in an enantiopure state through a classical sequence involving tetraphosphane oxide 9. The 3D properties of the new molecules are well depicted by X-ray diffraction analysis of 9. The complexation ability of 3 to was investigated. While mono- and bimetallic complexes of Pd are fully insoluble materials, the formation of mono- and birhodium complexes has been investigated by ³¹P NMR spectrometry. A preliminary screening of the catalytic activity and stereoselection ability of the binuclear Rh complex (-)-13 was carried out in the C-C double bond hydrogenation of some standard (pro)¹-chiral substrates in parallel with the corresponding mononuclear PHANEPHOS complex (-)-12,



maintaining identical Substrate/Rh ratio. Similar enantioselection performances were observed for the two catalysts demonstrating that the new D_2 -symmetric PHANE-TetraPHOS mirrors the structurally related C_2 -symmetric PHANEPHOS. It is evident, however, that in the former case, the amounts of the precious ligand are halved. Research would deserve further investigation mainly directed to the preparation of new more soluble bi- and hetero-bimetallic complexes.

Experimental Section

All reactions utilizing air- and moisture-sensitive reagents were performed in dried glassware under dry argon or nitrogen. Dry solvents were used as received and stored under inert gas. All reagents, if not otherwise specified, were used as received and, if necessary, stored under inert gas. Macherey-Nagel Alugram® sil G/ UV 254 pre-coated plates were used for TLC analysis. Column chromatography was performed on Macherey-Nagel MN Kieselgel silica gel. Melting points were determined with a Büchi B-540 instrument. ¹H, ¹³C and ³¹P NMR spectra were recorded with Bruker AC300, AC200 or AV400 spectrometers. Chemical shifts (δ) are expressed in parts per million (ppm), and coupling constants are given in Hz. Splitting patterns are indicated as follows: s = singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br.=broad, dd= doublet of doublets. Mass analyses were performed by using a VG 7070 EQ-HF instrument. Specific rotations were measured at five wavelengths (589, 578, 546, 436 and 365 nm) by using a Perkin-Elmer polarimeter model 241 equipped with an Na/Hg lamp. The volume of the cell was 1 mL, and the optical path was 10 cm. The system was set at a temperature of 20°C. Circular dichroism (CD) spectra were recorded by using a Jasco J-700 spectropolarimeter. The spectra were average-computed over three instrumental scans, and the intensities are presented in terms of ellipticity values (mdeg). The analytical HPLC apparatus consisted of a Perkin-Elmer (Norwalk, CT, USA) 200 LC pump equipped with a Rheodyne (Cotati, CA,USA) injector, a 5-µL sample loop, an HPLC Dionex CC-100 oven (Sunnyvale, CA, USA) and a Jasco (Jasco, Tokyo, Japan) Model CD2095 Plus UV/CD detector. Data were processed using Clarity software (DataApex, Prague, The Czech Republic). GC analyses of the products of the hydrogenation tests were performed by using a Dani GC1000 instrument. HPLC analysis of the product of the hydrogenation of methyl (Z)-2-acetamidocinnamate 15 was performed by using a Waters 1525 binary HPLC pump coupled with a Waters 2487 UV detector.

4,7,12,15-tetrabromo-[2.2]-paracyclophane (±)- (5) and **4,5,15,16-tetra-bromo[2.2]paracyclophane** (7).^[8b] [2.2]Paracyclophane (5 g, 24 mmol) was slowly added in small portions to a mixture of Br₂ (15 mL, 295 mmol) and I₂ (75 mg, 0.3 mmol). The solution was kept in the dark and left under stirring for one week at r.t.. The mixture was dropped into NaOH_(aq) (20%, 150 mL) at 0 °C. The precipitate was collected by filtration, washed with hot EtOH (3×25 mL), and dried in vacuo to yield a mixture of (±)-5 and 7 in equal amount. Dichloromethane was added to the residue, pure 7 was recovered by filtration (4.5 g, 36%). The dichloromethane filtrate was concentrated under reduced pressure to afford (±)-5 as white solid (5.2 g, 42%).

(±)-5. ¹H NMR (400 MHz, CDCl₃) δ 7.20 (s, 4H, Ar–H), 3.29-3.18 (m, 4H, CH₂), 3.04-2.93 (m, 4H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 140.3 (C-4,7,12,15), 134.4 (C-5,8,13,16), 125.3 (C-3,6,11,14), 32.7 (C-1,2,9,10).

7. ¹H NMR (400 MHz, CDCl₃) δ 6.99 (s, 4H, Ar–H), 3.41-3.30 (m, 4H, CH₂), 3.16-3.05 (m, 4H, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ 140.7 (C-4,5,15,16), 129.3 (C-3,6,11,14), 128.6 (C-7,8,12,13), 34.5 (C-1,2,9,10).

4,12-Dibromo-7,15-bis(diphenylphosphinyl)[2.2]

paracyclophane (\pm) - (8). t-BuLi (1.6 M solution in pentane, 2.5 mL, 4.0 mmol) was added dropwise to a stirred solution of (\pm) -5 (530 mg, 1.0 mmol) in dry THF (30 mL) at -78 °C at a rate such that the temperature remains below -70 °C. Diphenylphosphinic chloride (400 µL, 2.1 mmol) was added via a syringe over 15 minutes and the reaction mixture was left warming to r.t. overnight, under vigorous stirring. Water (25 mL) was added to the suspension. The organic layer was separated, the aqueous phase was extracted with AcOEt (3×20 mL), the combined organic layers were washed with NaOH $_{\rm (aq)}$ (32%, 50 mL), dried (Na₂SO₄) and concentrated in vacuo. Chromatography (SiO₂, AcOEt/Exane 1/1, $R_{\rm f}$ = 0.22) afforded (±)-8 (110 mg, 15%). White solid; m.p. 270-275 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.75-7.32 (m, 12H, POPh₂-H 5-H 13-H), 7.24 (d, J = 14.0, 2H, 8-H 16-H), 3.42-3.31 (m, 2H, CH₂), 3.26-3.17 (m, 2H, CH₂), 3.04-2.85 (m, 4H, CH₂); ³¹P NMR (121 MHz, CD_2CI_2) δ 23.9; MS (EI): m/z = 766 [M]⁺.

(±)-4,7,12,15-Tetra(diphenylphosphinyl)[2.2]paracyclophane

(\pm)-(9). t-BuLi (1.7 M solution in pentane, 5 mL, 8.6 mmol) was added dropwise to a stirred solution of (\pm) -5 (530 mg, 1.0 mmol) in dry THF (30 mL) at -78 °C at a rate such that the temperature remains below -70 °C. Chlorodiphenylphosphine (848 μ L, 4.6 mmol) was added via a syringe over 15 minutes and the reaction mixture was left warming to r.t. overnight, under vigorous stirring. Water (25 mL) was added to the suspension. The organic layer was separated, the aqueous phase was extracted with CH_2Cl_2 (3×25 mL), the combined organic layers were concentrated in vacuo. CH₂Cl₂ (15 mL), EtOH (15 mL), and H_2O_2 (30% (w/w) in H_2O_1 1 mL) were added to the residue, the resulting solution was stirred overnight at r.t.. The solution was dried (Na₂SO₄) and concentrated under reduced pressure. Crystallization (EtOH) afforded (±)-9 (257 mg, 25%). White solid; m.p. 354-355 °C; IR (ATR): 3054, 2935, 2857, 1590, 1573, 1483, 1436, 1348, 1311, 1186, 1134, 1111, 1071, 1028, 998, 964, 914, 853, 751, 717, 694, 618, 571, 559 cm⁻¹; ¹H NMR (300 MHz, CD₂Cl₂) δ 7.77-7.31 (m, 44H, Ar-H), 3.18-3.07 (m, 4H, CH₂), 2.82-2.71 (m, 4H, CH₂); ¹³C NMR (75 MHz, CD₂Cl₂) δ 146.5–146.1 (m, C-3,6,11,14), 139.5-139.0 (m, C-5,8,13,16), 134.4 (dd, J=281.5, 103.5 Hz, C-4,7,12,15), 134.4 (dd, J=102.1, 4.0 Hz, C-1 POPh₂), 133.1-131.0 (m, C-2,6 POPh₂), 132.1 (d, J=21.1 Hz, C-4 POPh₂), 129.0-128.7 (m, C-3,5 POPh₂), 35.7 (d, J=3.5 Hz, (C-1,2,9,10); ³¹P NMR (121 MHz, CD_2CI_2) δ 24.6; MS (EI): m/z = 1008 [M]^{+.}

Resolution of (±)-4,7,12,15-tetra(diphenylphosphinyl)[2.2] paracyclo-phane (\pm)-9. A solution of (+)-dibenzoyl-D-tartaric acid (0.57, 1.6 mmol) in a mixture of CH₂Cl₂ (15 mL) and AcOEt (15 mL) at 40 °C was added rapidly to a solution of (\pm) -9 (1.6 g, 1.6 mmol) in CH₂Cl₂ (50 mL) at 40 °C under vigorous stirring. The reaction mixture was allowed to cool slowly overnight. The white precipitate was filtered, dissolved in dichloromethane (50 mL) and washed with 1 M aqueous sodium hydroxide (3×50 mL) and water (50 mL). The organic layer was dried (MgSO₄) and concentrated to afford (-)-9 as white solid (520 mg, 65%). The enantiomeric purity of (-)-9 was determined to be >99% by HPLC analisys (Chiralpak IA-3, dichloromethane:ethanol 20:100, 1.5 ml/min, detector CD at 280 nm) (+)-9 $t_1 = 1.0$ min, (-)-9 $t_2 =$ 1.6 min, $\left[\alpha\right]_{25}{}^{D}\!=\!-48^{\circ}$ (c 1, DCM). The mother liquors of the first resolution were washed with 1 M aqueous sodium hydroxide ($3 \times$ 50 mL) and water (50 mL). The organic layer was dried (MgSO₄), concentrated and treated with (-)-dibenzoyl-L-tartaric acid as well as done before to afford (+)-9 as white solid (488 mg, 61%): $[\alpha]_{25}^{D} = +48^{\circ}$ (c 1, DCM).

(-)-4,7,12,15-tetra(diphenylphosphanyl)[2.2]paracyclophane

(-)-3. Trichlorosilane (1 mL, 9.9 mmol) was added to a suspension of (-)-9 (175 mg, 0.17 mmol) in *p*-xilene (10 mL, degassed), under Ar atmosphere, and heated to 140 °C overnight. At 24 hours intervals two further aliquots of HSiCl₃ (1 mL, 9.9 mmol) were added. The reaction mixture was cooled to -10 °C and quenched by the addition of NaOH_(aq) (32%, 10 mL, degassed) (exothermic!). The organic layer was separated, and the aqueous phase was extracted with CH₂Cl₂ (3×10 mL, degassed). The combined organic layers were dried (Na₂SO₄) and the solvent was removed in vacuo. MeOH (5 mL, degassed) was added to the residue and the white precipitate was collected to give (-)-3 as white solid (103 mg, 63%). ¹H NMR (300 MHz, CD₂Cl₂) δ 7.80–7.21 (m, 42H, Ar–H), 6.72 (dd, J=9.4, 5.8 Hz, 2H, Ar–H) 2.95–2.76 (m, 4H, CH₂), 2.66–2.47 (m, 4H, CH₂); ³¹P NMR (121 MHz, CD₂Cl₂) δ -1.0; MS (EI): m/z=944 [M]⁺.

(–)-[(COD)Rh(PHANEPHOS)]OTf (–)-(12). PHANEPHOS (–)-4 (50 mg, 87 µmol) and [Rh(COD)₂]OTf (41 mg, 87 µmol) were placed in a Schlenk tube. After three argon-vacuum cycles, dry dichloromethane (2 mL, degassed) was added, and the mixture was left for 30 minutes under stirring. The solvent was removed under reduced pressure, dry MTBE (2 mL, degassed) was added to the residue, and the flask was placed in a sonicator for 15 minutes. After vigorous stirring for a further 30 minutes, the yellow precipitate was filtered, dried in vacuum and directly used for asymmetric hydrogenation tests.

(-)-{[(COD)Rh]₂(PHANE-TetraPHOS)}(OTf)₂ (-)-(13). (-)-3 (50 mg, 53 μ mol) and [Rh(COD)₂]OTf (50 mg, 106 μ mol) were placed in a Schlenk tube. After three argon-vacuum cycles, dry dichloromethane (2 mL, degassed) was added, and the mixture was left for 30 minutes under stirring. The solvent was removed under reduced pressure, dry MTBE (2 mL, degassed) was added to the residue, and the flask was placed in a sonicator for 15 minutes. After vigorous stirring for a further 30 minutes, the orange precipitate was filtered, dried in vacuum and directly used for asymmetric hydrogenation tests.

General procedure for asymmetric hydrogenations. A solution of the substrate (0.36 M) in dry MeOH was deossigenated with flowing argon for ten minutes. The catalyst was then added (ratio stated in the text), three vacuum hydrogen cycles were applied, and the mixture was left under vigorous stirring for 1 hour. The solution was then directly injected in the gas chromatograph or filtrate through a short pad of silica gel when HPLC analysis was performed.

Methyl 2-(acetylamino)propanoate. Analysed by GC. CSP: MEGA-DEX DACTBS β (25 m×0.25 mm i.d.); carrier gas: hydrogen; flow: 1 mLmin⁻¹; inlet temperature: 222 °C; initial temperature: 140 °C; time isotherm: 6 min; gradient: 8 °Cmin⁻¹; final temperature: 200 °C; detector temperature: 250 °C; retention times [min]: 3.7 (substrate 14), 4.7 [(-)-(*R*)], 5.3 [(+)-(S)].

Methyl 2-acetamido-3-phenylpropanoate. Analysed by HPLC. CSP: Chiracel[®] AD–H; eluent mixture: hexane/*i*-PrOH, 9:1; flow rate: 0.5 mLmin⁻¹; retention times [min]: 17.1 [(–)-(*R*)], 21.5 [(+)-(*S*)], 42.0 (substrate **15**).

Dimethyl 2-methylenesuccinate: Analysed by GC. CSP: MEGADEX DACTBS β (25 m×0.25 mm i.d.); carrier gas: hydrogen; pressure: 1 bar; inlet temperature: 222 °C; initial temperature: 60 °C; time isotherm: 10 min; gradient: 2 °C min⁻¹; final temperature: 200 °C; detector temperature: 250 °C; retention times [min]: 19.5 [(-)-(*R*)], 20.1 [(+)-(S)], 23.3 (substrate **16**).

N-(1-phenylethyl)acetamide: Analysed by GC. CSP: MEGADEX DACTBS β (25 m \times 0.25 mm i.d.); carrier gas: hydrogen; flow:

1.3 mLmin⁻¹; inlet temperature: 222 °C; initial temperature: 145 °C; time isotherm: 15 min; gradient: 8° Cmin⁻¹; final temperature: 200 °C; detector temperature: 250 °C; retention times [min]: 12.8 [(+)-(*R*)], 13.4 [(-)-(*S*)], 16.1 (substrate **17**).

1-Phenylethyl acetate: Analysed by GC. CSP: MEGADEX DACTBS β (25 m×0.25 mm i.d.); carrier gas: hydrogen; pressure: 0.55 bar; inlet temperature: 222 °C; initial temperature: 80 °C; time isotherm: 25 min; gradient: 20 °Cmin⁻¹; final temperature: 200 °C; detector temperature: 250 °C; retention times [min]: 22.8 [(–)-(S)], 23.9 [(+)-(R)], 28.3 (substrate **18**).

Methyl 3-(acetylamino)-2-benzylpropanoate: Analysed by GC. CSP: MEGADEX DACTBS β (25 m×0.25 mm i.d.); carrier gas: hydrogen; flow: 1.4 mLmin⁻¹; inlet temperature: 222°C; initial temperature: 170°C; time isotherm: 30 min; gradient: 10°Cmin⁻¹; final temperature: 200°C; detector temperature: 250°C; retention times [min]: 22.4 [(+)-(*R*)], 23.0 [(-)-(*S*)], 24.1 (substrate **19**).

Single crystal X-Ray diffraction analysis for 8 and 9. The single crystal data diffraction of 8 and 9 were collected at Bruker SMART APEX II CCD area detector diffractometer, equipped with a Bruker KRYOFLEX low temperature device and graphite monochromator, Mo–K α radiation (λ =0.71069 Å). Cell refinement and data reduction were done with Bruker SAINT. Structure solution was performed with SHELXL and Fourier analysis and refinement were performed by the full-matrix least-squares methods based on F^2 implemented in SHELXL-2014;^[9] absorption correction was performed based on multi-scan procedure using SADABS.^[10] Compound 9 crystallized as butanol solvate. The disordered butanol molecule was modelled over two positions fixing at 0.5 the atom site occupancy factor. Pictures were prepared using Mercury^[11] software. Essential crystal and refinement data are reported in Table S1 of supporting information.

Simulation of the CD spectra for the (pS) enantiomer of the tetraphosphane oxide 9. The chiroptical properties of the enantiomers of 9 were estimated by molecular modelling calculations. As the first step, the structure of the (pS)-9 enantiomer was optimized and submitted to conformational search, performed at the molecular mechanics level of theory by means of the MMFF94 force field, using the computer program SPARTAN 10v1.1.0 (Wavefunction Inc., 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, USA). This afforded just one conformation inside an energy window of $8 \text{ kcal} \times \text{mol}^{-1}$, perfectly consistent with the one obtained through X-ray analysis. Next, such a structure was subjected to assessment of the Electronic Circular Dichroism (CD) spectrum by resorting to the Amsterdam Density Functional (ADF) package v. 2007.01. The set options were single point calculation at the BLYP level of theory, employing the TZ2P large core basis set; 50 singlet excitations; diagonalization method: Davidson; velocity representation; scaling factor 0.80; peak width 8.0.

Deposition Numbers 1972369 (for 8), and 1972368 (for 9) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

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