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DIOPHEP, a chiral diastereoisomeric bisphosphine ligand: synthesis and applications in asymmetric hydrogenations

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ABSTRACT

Novel optically active diphosphine ligands, known as DIOPHEP, have been designed and synthesized starting from a derivative of tartaric acid. The ligands conjugate the sp^3 chirality of the precursor of DIOP with the atropisomeric chirality of a biaryl scaffold. The stereorecognition abilities of DIOPHEP-Ru complex catalysts have been investigated in the asymmetric catalytic hydrogenation of some standard substrates suggesting a close relationship between dihedral angles and enantioselectivity.

1. Introduction

Metal complexes and chiral ligands have become leading auxiliaries in the field of organic synthesis: reactions such as catalytic asymmetric hydrogenations, hydroformylations, hydrocyanations and isomerizations are now recognized as effective alternatives in strategies for the preparation of compounds, which were believed to be impossible to carry out by conventional stereoselective organic transformations.[1–3]

The greater part of the transition metals known as excellent catalysts for asymmetric synthesis has optically active diphosphine ligands as a source of chirality but, in spite of the great variety of chiral ligands available, the development of new chiral ligands still plays a crucial role in the development of catalysts characterized by high enantioselectivity, diastereoselectivity, productivity and process robustness.[4]

Since the pioneering works of Kagan on DIOP, the first example of chelating diphosphines based on sp^3 stereogenic carbon atoms,[5] over the past 20 years a large amount of success has been achieved by the use of atropisomeric chiral diphosphine ligands derived from di-aryl or di-heteroaryl frames; ligands such as BINAP,[6] BIPHEMP,[7] MeO-BIPHEP[7] or BITIOP[8] and Rh(I) or Ru(II) give catalysts able to reduce C=C and C=O double bonds with an ee% higher than 99%.

Many other diphosphines showing a C_2 axial chirality have been developed up to now,[9] but most of these ligands are only obtained in an enantiomerically pure form after tedious and somewhat difficult resolution steps, usually based on the separation of the diastereoisomeric adducts between the phosphorus oxides and DBTA;[10] when the ligands are not basic enough to react with the resolving agent however, they cannot be resolved with this method[10a,11] drastically reducing the synthetic opportunities connected, for instance, with the use of a large range of aromatic frames containing nitrogen atoms.

Recently different approaches based on the synthesis of biaryl diphosphines as mixtures of diastereoisomers were explored. Enev et al.[12a] obtained a bis-steroidal phosphine in a sequence of stereoselective reactions on diastereopure (*R*)- or (*S*)-4,4′-bis(3-hydroxyestra-1,3,5(10),6,8-pentaene). Chan et al.[12b] prepared a biaryl phosphine, known as PQ-Phos, in which the two aryl rings are tethered by a chain bearing two stereogenic carbon atoms; the chirality on the chain and the axial chirality give rise to a couple of diastereoisomers that can more or less be easily separated by chromatography, avoiding time consuming resolution procedures. By increasing or decreasing the length of the chain, it is possible to adjust the dihedral angles of the diaryl scaffold with marked effects on the enantioselectivity of asymmetric catalysis. Subtle changes in the conformation of the ligands and the variation of the dihedral angles of the diphosphine can modify the chiral array of the substituents on the phosphorus atoms, that is, the chirality transmitters (usually aryl groups) increasing or decreasing the chiral recognition of prochiral substrates; these effects can clearly be seen with tunaphos,[13] a family of ligands characterized by variable dihedral angles and restricted rotations prepared by bridging the aryl scaffold with carbon chains of variable length.

Herein, we report the synthesis and applications of chiral chelating diastereoisomeric diphosphines in which the bi-aryls are bridged with a chiral chain derived from (*S*,*S*)-(−)-2,3-O-isopropilidene-1,4-di-*O*-tosyl-D-threitol (Fig. 1), the same chiral starting material of DIOP; in our aims these ligands should be the blending of the two families of diphosphines, those based on stereogenic sp^3 carbon atoms and those based on axial chirality.

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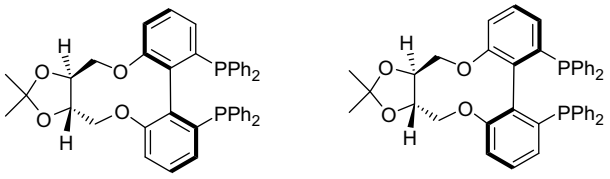


Figure 1.

2. Results and discussion

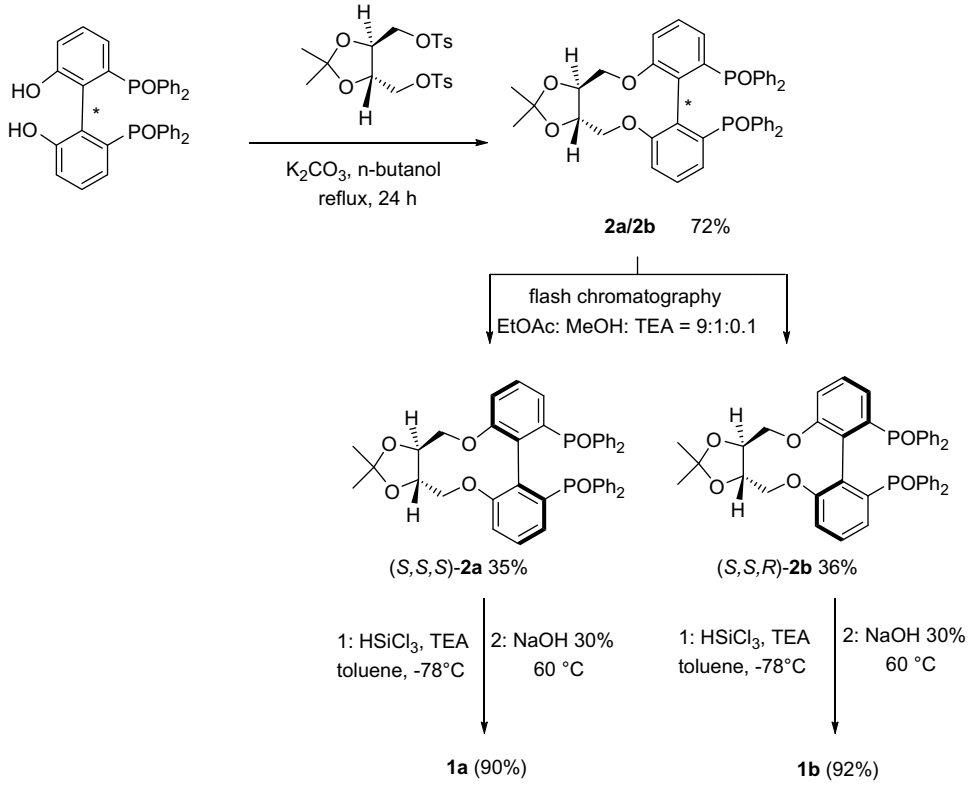
The preparation of the ligands is shown in Scheme 1: racemic HO-BIPHEP[14] oxide reacts with *S,S*-2,3-*O*-isopropylidene-1,4-di-*O*-tosyl-D-threitol in presence of K_2CO_3 to give an almost equimolar mixture of diastereoisomers (+)-(*S,S,S*$_{ax}$)-DIOPHEPO **2a** and (−)-(*S,S,R*$_{ax}$)-DIOPHEPO **2b** in 72% yield. Flash chromatography with ethyl acetate/methanol/triethylamine = 9:1:0.1 on silica gel gives **2a** (34%) and **2b** (35%) in an almost enantiomerically pure form. Reduction of the isolated oxides **2a** and **2b** with $HSiCl_3/Et_3N$ in toluene at 0 °C followed by treatment with aq NaOH 30% at 60 °C affords the desired diastereoisomeric diphosphines (*S,S,S*$_{ax}$)-DIOPHEP **1a** and (*S,S,R*$_{ax}$)-DIOPHEP **1b** enantiomerically and chemically pure.

The CD spectra of the diastereoisomeric diphosphines (*S,S,S*$_{ax}$)-DIOPHEP **1a** and (*S,S,R*$_{ax}$)-DIOPHEP **1b**, of (+)-(*S,S,S*$_{ax}$)-DIOPHEPO **2a** and (−)-(*S,S,R*$_{ax}$)-DIOPHEPO **2b** and of the corresponding rhodium complexes [((*S,S,S*$_{ax}$)-DIOPHEP **1a**)Rh(COD)]$^+ClO_4^-$ **(+)-3a** and [(*S,S,R*$_{ax}$)-DIOPHEP **1b**)Rh(COD)]$^+ClO_4^-$ **(−)-3b**, prepared according to standard procedure by ligand exchange from $[Rh(COD)_2]^+ClO_4^-$, are reported in Figure 2; the CD spectra are recorded in CH_2Cl_2 and plotted as mDeg/*A* where *A* is the UV absorption of the solutions at 296 nm, because in this way it is possible to compare certain spectra of chiral compounds when very large molar extinction coefficients are involved.

Despite the diphosphines, the oxides and the Rh(I) complexes being couples of diastereoisomers, the CD spectra are almost mirror images, quite similar to those reported for (*R*)- or (*S*)-BINAP[15] and (*R*)- or (*S*)-MeO-BIPHEP[14a] which are really couples of enantiomers; this is not unexpected because the CD active electronic transitions in 270–300 nm are essentially due to the biaryl chromophores which, locally, can be considered in enantiomeric relationship. The small differences in the CD intensities probably reflect the real diastereoisomeric nature of the ligands.

Unfortunately, in absence of suitable crystals for an X-ray structural determination, the absolute configuration of the biaryl scaffold can be inferred only by the results of the catalytic activity; comparing the absolute configuration of reduction products obtained with the Ru(II) complexes of BITIOP, BINAP and BIPHEMP with those reported herein (vide infra), it is possible to assign an (*S*)-configuration to the **(+)**-DIOPHEP **1a** and, obviously, an opposite (*R*)-configuration to **(−)-1b** diastereoisomer.

It is well known that one of the main factors in determining asymmetric control using chelating diphosphine ligands is the natural bite angle (β_n)[16] of metal complexes. In biaryl diphosphines, the natural bite angle (β_n) is strictly related to the dihedral angle (θ) of the biaryl backbone. In the asymmetric hydrogenation, in particular the influence of θ on the enantioselectivity has recently been described by Zhang et al.,[13] Saito et al.[17] and Genêt et al.[18] The dihedral angles of biphenyl systems are expected to affect the steric bulk of the diphenyl-phosphino group. Clearly this hypothesis is based on simple steric considerations and does not envisage the electronic properties of complex or metal valence. A simple inspection of molecular models indicates that the dihedral angle (θ) of (*S,S,S*$_{ax}$)-DIOPHEP **1a** is higher than that of (*S,S,R*$_{ax}$)-DIOPHEP **1b** when coordinated to a metal; a coarse measure gives about 70°



Scheme 1. Synthesis of (*S,S,S*$_{ax}$)-DIOPHEP **1a** and (*S,S,R*$_{ax}$)-DIOPHEP **1b**.

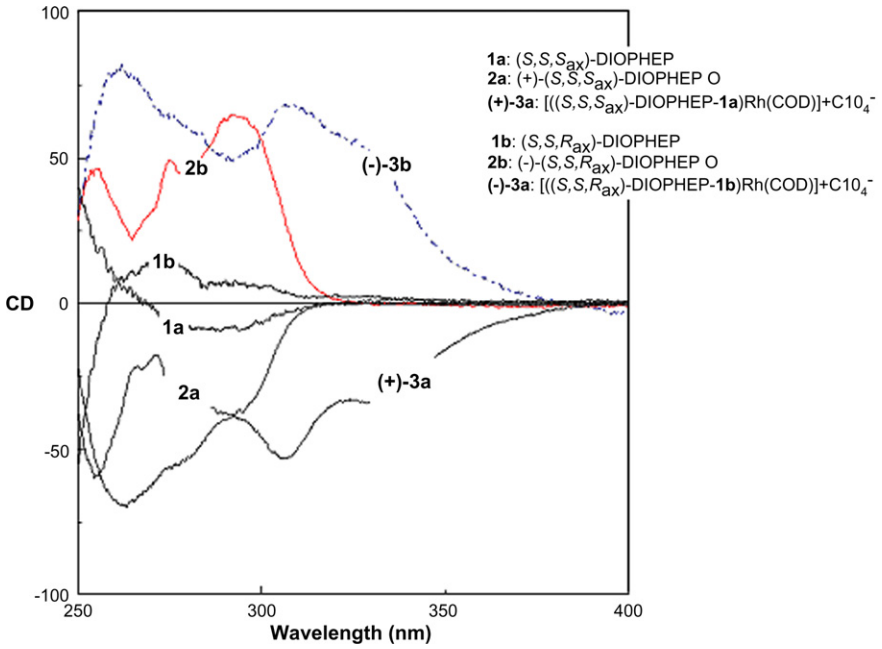


Figure 2. CD spectra of **1a**, **1b**, **2a**, **2b**, (+)-**3a** and (−)-**3b**.

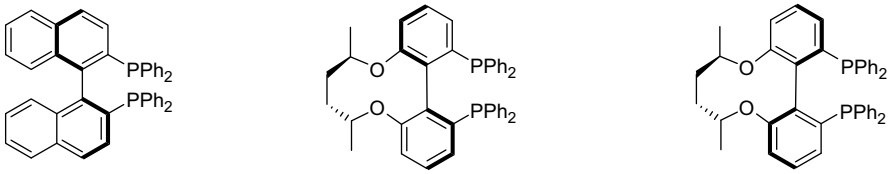
for **1a** and 60° for **1b**, enough to confirm that the bite angles β_n must be rather different, and as a consequence, the complexes derived from the two diastereoisomers should show different behaviours in asymmetric hydrogenations. These preliminary considerations are supported by a more accurate computational investigation. We calculated the dihedral angles and the bite angles of both diastereoisomeric metal complexes of DIOPHEP **1a** and **1b**. Moreover, we refined our theoretical approach calculating the 'flexibility range' of the complexes.

According to reported methods, we performed calculations at molecular mechanics level using the MM+ force field, (an implemented version of Allinger MM2[19] force field included in the HYPERCHEM® molecular modelling program),[20] specifically developed for small and middle sized organic molecules. Minimizations were performed on the diphosphine–metal fragment without incorporation of other ligands at the metal centre. A 'metal dummy atom' (M) was used to direct the lone pairs of the phosphine ligands. The M–P distance was fixed at 2.315 Å, an average length of the M–P bond in Rh and Ru complexes (force constant 100,000 kcal mol^{-1} Å^{-1}), whilst the force constant of P–M–P bond angle was imposed to 0 kcal mol^{-1} deg^{-1} in order to eliminate any contribution of the metal. Best conformations are obtained towards an accurate conformational search. The flexibility range of each complex was calculated towards a sequence of geometry optimization, with the bite angle fixed at given values using restraints (force constant 100,000 kcal mol^{-1} Å^{-1}) and energies were evaluated by subsequent single point calculation without restraints. All energy minimizations were carried out with a Polak-Ribiere algorithm (RMS gradient 0.015 kcal mol^{-1} Å^{-1}), assuming the molecules in the gas phase.

As underlined by Van Leeuwen[21] in evaluating these geometrical parameters, it is more important to calculate a correct 'trend' rather than perfect geometries. Moreover, in order to correctly compare the bite and dihedral angles of different metal-complexes, all ligands in a series should be modelled under identical conditions, using the same program, the same force field and the same parameter set. As a consequence, with the double aim of validating the calculation method and to compare the geometric features amongst our phosphines and some well-known ligands, we optimized the geometry and calculated the flexibility range of the metal complexes of two diphosphines, BINAP and Hex-PQ-Phos (Fig. 3).

We focused our attention on BINAP for its obvious pivotal and reference role in asymmetric hydrogenation with Ru(II) complexes and Hex-PQ-Phos diphosphines recently developed by Chan et al.[12b,22] These ligands are diastereoisomers in which the biaryl scaffold is tethered by a chiral chain of 4 carbon atoms where the diphosphines are more comparable to those reported in the present paper because they fulfil contemporary to two conditions: a chain and stereogenic atoms on it.

Calculated dihedral angles (θ) and bite angles (β_n) are summarized in Table 1; from these results we can foresee some consequences regarding the potential selectivity of ligands **1a** and **1b**: (a) the activity of **1a,** whose calculated metal complex display



(*S*)-BINAP (*R*,*R*,*S*$_{ax}$)-Hex-PQ-Phos (*R*,*R*,*R*$_{ax}$)-Hex-PQ-Phos

Figure 3.

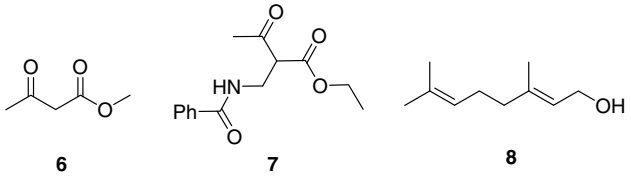
Table 1
Calculated dihedral and bite angle of diphosphine ligands

Ligand	E MM+ (kcal/mol)	θ (°)	β_n (°)
(*S*)-BINAP	44.6	71.5	98.6
(*R*,*R*,S_{ax})-Hex-PQ-Phos	78.3	73.0	101.1
(*R*,*R*,R_{ax})-Hex-PQ-Phos	83.1	55.5	90.6
(+)-(*S*,*S*,S_{ax})-**1a**	81.2	72.7	100.7
(−)-(*S*,*S*,R_{ax})-**1b**	82.8	61.4	93.0

the broader dihedral and bite angle, is similar to BINAP and to (*R*,*R*,S_{ax})-Hex-PQ-Phos because they have comparable values of critical angles and an almost super-imposable flexibility range (Fig. 4); (b) on the other hand the metal complex of **1b** shows rather lower calculated geometrical parameters.

The ligands have been tested in the Ru-catalyzed hydrogenations of some selected substrates, in particular in the reduction of methyl 3-oxobutanoate **6**, ethyl 2-(benzamidomethyl)-3-oxobutanoate **7** and geraniol **8**; the complex [Ru(*p*-cymene)I]$^+$I$^-$ has been chosen as a catalyst precursor due to the good results obtained in the reduction of **7**, a valuable intermediate in the synthesis of azetidinone which is in turn the precursor of Carbapenem;[23] the asymmetric hydrogenations of ketones were carried out in CH_2Cl_2/MeOH, (7:3 v/v) at 60 °C and at 50 atm H_2; the reduction of geraniol was carried out in MeOH at 20 °C and 100 atm H_2; the results are summarized in Table 2.

Table 2
Catalyzed reduction of β-ketoesters **6** and **7** and of geraniol **8**



6 **7** **8**

Entry	Substrate	Ligand	de%	ee%
1	**6**	(+)-**1a**		95.2 (*S*)
2	**6**	(−)-**1b**		79.1 (*R*)
3	**7**	(+)-**1a**	56% (syn)	94.1(2*R*,3*S*)
4	**7**	(−)-**1b**	65% (syn)	73.7 (2*S*,3*R*)
5	**8**	(+)-**1a**		97.0 (*R*)
6	**8**	(−)-**1b**		65.2 (*S*)

The ligand (*S*,*S*,S_{ax})-DIOPHEP **1a** gave the highest enantioselectivities, always more than 94% either in the reduction of β-ketoesters, (entries 1 and 3) or in the reduction of geraniol (entry 5), whilst the diastereoisomer (*S*,*S*,R_{ax})-DIOPHEP **1b** gave enantioselectivities lower that 80% (entries 2, 4 and 6). These results could be the result of the higher critical angles (β_n and θ) of (*S*,*S*,S_{ax})-DIOPHEP **1a** to the higher enantioselectivity making it rather similar to BINAP and to (*R*,*R*,S_{ax})-Hex-PQ-Phos which have analogous values of β_n and θ and an almost super-imposable flexibility range; in our hands, the BINAP and [Ru(*p*-cymene)I]$^+$I$^-$ catalyst precursor gave enantioselectivities clustered around 95–97% ee in the reduction of substrates **6, 7** and **8** whilst (*R*,*R*,S_{ax})-Hex-PQ-Phos gives (*S*)-**6** in 99% ee.[20]

The confirmation of a strict relationship between the calculated dihedral angle of the diphosphine when coordinated to a metal and the enantioselectivity would come from the stereodifferentiating ability of (*R*,*R*,R_{ax})-Hex-PQ-Phos. We have calculated for (*R*,*R*,R_{ax})-Hex-PQ-Phos a θ angle of 55.5° and a β_n of 90.6° lower than that of (*R*,*R*,R_{ax})-Hex-PQ-Phos and even that of (*S*,*S*,R_{ax})-DIOPHEP **1b**; unfortunately no data are available for this ligand which apparently has not been synthetized. It is likely that the different stereodifferentiating abilities of (*S*,*S*,S_{ax})-DIOPHEP **1a** and (*S*,*S*,R_{ax})-DIOPHEP **1b** should be due also to the presence of the fused oxolane ring which dictates a conformational rigidity of the biaryl scaffold. The different dihedral angles in (+)-**1a** and (−)-**1b** impose a more or less pronounced equatorial/axial disposition of the phenyl groups of the diphosphine. It is worth mentioning that this axial/equatorial disposition of the phenyl groups, giving them the role of chirality transmitters, generates the C_2 symmetry at the metal which in turn determines the stereodifferentiation on the incoming prochiral substrate.

3. Experimental

All chemicals and solvents are commercially available and were used after distillation or treatment with drying agents. Silica gel F_{254} thin-layer plates were employed for thin-layer chromatography (TLC). Silica gel 40–63 μm/60A was employed for flash column chromatography. Proton NMR spectra were recorded at room temperature in $CDCl_3$ at 500 MHz, with residual solvents as the internal reference. ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ at 125.7 MHz, with residual solvents as the internal reference. The APT or DEPT sequences were used to distinguish the methine and methyl carbon signals from those due to methylene

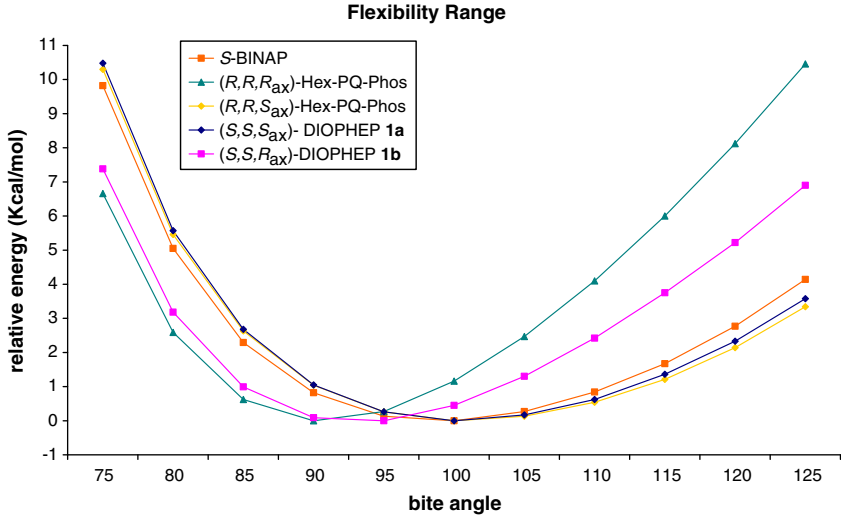


Figure 4. Flexibility range of different diphosphines.

and quaternary carbons. Two-dimensional NMR experiments were used, where appropriate, to aid in the assignment of structures. HPLC analyses were performed with Merck-Hitachi 7100 pump, loop 20 μL, detector HP 1050 DAD. Optical rotations were measured on a Perkin Elmer R241 polarimeter. The (*RS*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) was prepared according to previously reported procedures.[14]

3.1. Synthesis of (*S,S,S*$_{ax}$)-DIOPHEPO 2a and (*S,S,R*$_{ax}$)-DIOPHEPO 2b

A well stirred suspension of (*R,S*)-(6,6′-dihydroxybiphenyl-2,2′-diyl)bis(diphenylphosphine oxide) (0.6 g, 1.03 mmol), (*S,S*)-(−)-2,3-*O*-isopropylidene-1,4-di-*O*-tosyl-threitol (0.48 g, 1.03 mmol) and K_2CO_3 (0.35 g, 2.56 mmol) in dry butanol (18 mL) was heated at 140 °C for 20 h. Then, the solvent was evaporated under reduced pressure, and the crude mixture was taken up in ethyl acetate (100 mL) and water (150 mL). The organic layer was separated and the aqueous phase was extracted twice with ethyl acetate (100 mL × 2). The combined organic phases were dried over anhydrous sodium sulphate, filtered and concentrated under vacuum. The crude product was purified by flash chromatography on silica gel using ethyl acetate/2-propanol (9:1) as eluent to give 0.53 g of a 1:1 mixture of diastereoisomeric (*S,S,S*$_{ax}$)-DIOPHEPO **2a** and (*S,S,R*$_{ax}$)-DIOPHEPO **2b** (combined yield 71%). Finally, the two diastereoisomers were separated by flash chromatography performed with a mixture of chloroform and 2-propanol (97:3) containing 0.5% of triethylamine, yields progressively (*S,S,S*$_{ax}$)-DIOPHEPO **2a** (0.25 g) and (*S,S,R*$_{ax}$)-DIOPHEPO **2b** (0.26 g).

(*S,S,S*$_{ax}$)-DIOPHEPO **2a**: ^{1}H NMR (500 MHz), $CHCl_3$, δ (ppm) 1.35 (s, 6H, CH_3), 3.58 (dd, 1H, CH_2, J = 11.2, 11.7), 4.02 (m, 1H, CH), 4.53 (dd, 1H, CH_2, J = 3.7, 11.7), 6.85 (dd, 1H$_{arom}$, J = 7.7, 13.3), 7.06 (d, 1H$_{arom}$, J = 8.3), 7.20 (tdd, 1H$_{arom}$, J = 3.3, 7.7, 8.3), 7.32 (m, 4H$_{arom}$), 7.39 (m, 2H$_{arom}$), 7.49 (m, 2H$_{arom}$), 7.74 (m, 2H$_{arom}$); ^{13}C NMR (500 MHz), $CHCl_3$, δ (ppm) 27.2 (CH_3), 69.8 (CH_2), 76.6 (CH), 110.1 (C), 116.3, 126.4 (d), 127.4 (d), 127.8 (d), 128.1 (d), 130.8, 131.0, 132.3 (d), 132.8 (d) (C_{sp^2}—H), 133.4, 133.6, 133.9, 134.2, 134.5, 134.8 (m, quaternary C_{sp^2}, signals complicated by C–P coupling), 154.7 (d, quaternary C_{sp^2}); ^{31}P (500 MHz), $CHCl_3$, δ (ppm) 28.5; APCI(+)-MS m/z (relative intensity): 713 (M+, 100); HPLC analysis was performed on a LiChrospher RP-18E column (125 × 4 mm), mobile phase methanol/water 70:30, flow rate 0.8 mL/min, T 30 °C, detection wavelength 210 nm.

(*S,S,R*$_{ax}$)-DIOPHEPO **2b**: ^{1}H NMR (500 MHz), $CHCl_3$, δ (ppm) 1.33 (s, 6H, CH_3), 3.73 (m, 1H, CH), 3.98 (dd, 1H, CH_2, J = 11.0, 11.4), 4.24 (dd, 1H, CH_2, J = 2.4, 11.0), 6.80 (dd, 1H$_{arom}$, J = 7.7, 14.3), 7.10 (d, 1H$_{arom}$, J = 8.1), 7.24 (tdd, 1H$_{arom}$, J = 3.3, 7.7, 8.1), 7.30 (m, 4H$_{arom}$), 7.38 (m, 2H$_{arom}$), 7.45 (m, 2H$_{arom}$), 7.72 (m, 2H$_{arom}$); ^{13}C NMR (500 MHz), $CHCl_3$, δ (ppm) 27.0 (CH_3), 73.8 (CH_2), 80.2 (CH), 108.5 (C), 118.1, 126.3 (d), 127.4 (d), 127.8 (d), 128.5 (d), 130.7, 131.0, 132.3 (d), 132.7 (d) (C_{sp^2}—H), 133.3, 133.8, 133.9, 134.2, 134.3, 134.8 (m, quaternary C_{sp^2}, signals complicated by C–P coupling), 157.5 (d, quaternary C_{sp^2}); ^{31}P (500 MHz), $CHCl_3$, δ (ppm) 28.3; APCI(+)-MS m/z (relative intensity): 713 (M+, 100); HPLC analysis was performed on a LiChrospher RP-18E column (125 × 4 mm), mobile phase methanol/water 70:30, flow rate 0.8 mL/min, T 30 °C, detection wavelength 210 nm.

3.2. Reduction of (*S,S,S*$_{ax}$)-DIOPHEPO 2a to (+)-(*S,S,S*$_{ax}$)-DIOPHEP 1a

$HSiCl_3$ (0.407 mL, 4.04 mmol) was carefully added under nitrogen at 0 °C to a mixture of (*S,S,S*$_{ax}$)-DIOPHEPO **2a** (0.144 g, 0.202 mmol) and dry triethylamine (0.558 mL, 4.04 mmol) in dry and degassed toluene (12 mL). The mixture was stirred and refluxed overnight. Then the solution was cooled to 0 °C and a deoxygenated 30% sodium hydroxide solution (10 mL) was added carefully. The resulting mixture was then stirred at 60 °C until the organic and aqueous layers became clear. The organic layer was transferred via cannula to a Schlenk tube where, under nitrogen, was washed with degassed saturated NaCl solution (15 mL), then with degassed water (15 mL), and finally dried over anhydrous Na_2SO_4 and concentrated under vacuum to give a crude product. The crude product was washed with pentane (3 mL) to afford 100.0 mg of pure (+)-(*S,S,S*$_{ax}$)-DIOPHEP **1a** as a white solid (73% yield). (+)-(*S,S,S*$_{ax}$)-DIOPHEP **1a**: ^{1}H NMR (500 MHz), $CHCl_3$, δ (ppm) 1.28 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.56 (t, 1H, CH_2, J = 11.4), 4.08 (m, 1H, CH), 4.54 (dd, 1H, CH_2, J = 3.7, 11.4), 6.74 (d, 1H$_{arom}$, J = 7.64), 6.90 (d, 1H$_{arom}$, J = 8.2), 7.12 (m, 2H$_{arom}$), 7.17 (m, 3H$_{arom}$), 7.29 (m, 4H$_{arom}$), 7.46 (m, 2H$_{arom}$); ^{31}P (500 MHz), $CHCl_3$, δ (ppm) −11.82; APCI(+)-MS m/z (relative intensity): 681 (M+, 100); $[\alpha]_D$ = +54.5 (c 0.33 in CH_2Cl_2).

3.3. Reduction of (*S,S,R*$_{ax}$)-DIOPHEPO 2b to (−)-(*S,S,R*$_{ax}$)-DIOPHEP 1b

Reduction of (*S,S,R*$_{ax}$)-DIOPHEPO **2b** (100 mg, 0.13 mmol) performed as described above for the preparation of (+)-(*S,S,S*$_{ax}$)-DIOPHEP **1a** afforded (−)-(*S,S,R*$_{ax}$)-DIOPHEP **1b** as a white solid (88.1 mg, 92% yield).

(−)-(*S,S,R*$_{ax}$)-DIOPHEP **1b**: ^{1}H NMR (500 MHz), $CHCl_3$, δ (ppm) 1.26 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.70 (m, 1H, CH), 4.06 (t, 1H, CH_2, J = 10.7), 4.28 (dd, 1H, CH_2, J = 1.9, 10.7), 6.63 (d, 1H$_{arom}$, J = 7.8), 6.86 (d, 1H$_{arom}$, J = 8.2), 7.14 (m, 2H$_{arom}$), 7.20 (m, 3H$_{arom}$), 7.29 (m, 4H$_{arom}$), 7.44 (m, 2H$_{arom}$); ^{31}P (500 MHz), $CHCl_3$, δ (ppm) −9.50; APCI(+)-MS m/z (relative intensity): 681 (M+, 100); $[\alpha]_D$ = −45 (c 0.1 in CH_2Cl_2).

3.4. Preparation of [Ru(*p*-cymene) ((*S,S,S*$_{ax}$)-DIOPHEP 1a)I]$^+$I$^-$ complex

To a Schlenk tube charged with (*S,S,S*$_{ax}$)-DIOPHEP **1a** (PM = 680; 13.6 mg; 0.02 mmol) and red brown diiodo(*p*-cymene)Ruthenium(II) dimer (PM = 978.19; 8.8 mg; 0.009 mmol) was added freshly distilled argon-degassed DMF (4 mL). The mixture was stirred at 100 °C for 2 h. The resulting brown solution was cooled to 50 °C and concentrated under reduced pressure to give [Ru(*p*-cymene) ((*S,S,S*$_{ax}$)-DIOPHEP **1a**)I]$^+$I$^-$ complex. The residue was left under vacuum for 2 h; the ruthenium complex was utilized without other purification in the enantioselective reduction reactions. ^{31}P NMR (300 MHz) $CDCl_3$ δ (ppm): 53.26–52.97 (d), 61.73–61.44 (d); FAB+ 908 (M−127 (−I) = 781).

3.5. Preparation of [Ru(*p*-cymene)((*S,S,R*$_{ax}$)-DIOPHEP 1b)I]$^+$I$^-$ complex

The complex was prepared as [Ru(*p*-cymene) ((*S,S,S*$_{ax}$)-DIOPHEP **1a**)I]$^+$I$^-$, described above.

^{31}P NMR (300 MHz) $CDCl_3$ δ (ppm): 51.3–51.01 (d), 62.6–62.32 (d); FAB+ 908 (M−127 (−I) = 781).

3.6. General procedure for the hydrogenation of methyl 3-oxobutanoate 6

In a Schlenk tube sealed with a rubber septum under an argon atmosphere, the substrate (1 equiv) was added to the [Ru(*p*-cymene)I(DIOPHEP)]$^+$I$^-$ **3** (0.01 equiv), followed by 20 mL of distilled methanol. The solution was stirred for 30 min and then transferred to an autoclave with a cannula. The stainless steel autoclave (200 mL), equipped with temperature control and magnetic stirrer, was purged five times with hydrogen before use. After the transfer of the reaction mixture, the autoclave was pressurized

at 50 atm and then warmed at 60 °C. At the end of the reaction, the autoclave was vented, the catalyst was removed by filtration on a short pad of cellulose and the solvent was evaporated. The conversion was determined by ^{1}H NMR. The enantiomeric excess of the product was determined by GC on a chiral stationary phase column (MEGA DAcTButSilBETA (25 m, internal diameter 0.35 mm).

3.7. General procedure for hydrogenation of ethyl-2-(benzamidomethyl)-3-oxobutanoate 7

In a Schlenk tube sealed with a rubber septum under an argon atmosphere, the substrate (1 equiv) was added to the [Ru(p-cymene)I(DIOPHEP)I]$^+$I$^-$ **3** (0.01 equiv), followed by 20 mL of a mixture of CH_2Cl_2 and methanol (7:3 v/v). The solution was stirred for 30 min and then transferred to an autoclave with a cannula. The stainless steel autoclave (200 mL), equipped with temperature control and magnetic stirrer, was purged five times with hydrogen before use. After the transfer of the reaction mixture, the autoclave is pressurized at 50 atm and then warmed at 60 °C. At the end of the reaction, the autoclave was vented, the catalyst was removed by filtration on a short pad of cellulose and the solvent was evaporated. The conversion was determined by ^{1}H NMR. The diastereoisomeric excess and enantiomeric excess of the product were determined by HPLC on a chiral stationary phase column (Diacel Chiralcel OD®, *n*-hexane/isopropanol = 9:1; flow rate 0.6 mL/min, λ = 230 nm).

3.8. General procedure for hydrogenation of geraniol 8

In a Schlenk tube sealed with a rubber septum under an argon atmosphere, the substrate (1 equiv) was added to the [Ru(*p*-cymene)I(DIOPHEP)I]$^+$I$^-$ **3** (0.01 equiv), followed by 20 mL of methanol. The solution was stirred for 30 min and then transferred to an autoclave with a cannula. The stainless steel autoclave (200 mL), equipped with temperature control and magnetic stirrer, was purged five times with hydrogen before use. After the transfer of the reaction mixture, the autoclave was pressurized at 100 atm and stirred at room temperature. At the end of the reaction, the autoclave was vented, the catalyst was removed by filtration on a short pad of cellulose and the solvent was evaporated. The conversion was determined by ^{1}H NMR. The enantiomeric excess of the product was determined by GC on a chiral stationary phase column (MEGA DAcTButSilBETA (25 m, internal diameter 0.35 mm).

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