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Chirality in the Absence of Rigid Stereogenic Elements: The Absolute Configuration of Residual Enantiomers of C_3-Symmetric Propellers

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Abstract: Two new tris(aryl)phosphane oxides existing as configurationally stable residual enantiomers have been synthesised and their racemates resolved by semipreparative HPLC on a chiral stationary phase (CSP HPLC). One of them, recognised as a conglomerate, could be resolved by fractional crystallisation at a preparative scale level. In this case, the absolute configuration of the propeller-shaped molecule was determined by anomalous X-ray scattering. The problem of the correlative assignment of the absolute configuration to all known C_3-symmetric three-bladed propeller-shaped molecules existing as stable residual enantiomers is discussed. The configurational stability of the new chiral phosphane oxides and of the corresponding phosphanes was evaluated by CD signal decay kinetics and dynamic ^{1}H NMR spectroscopy. The racemisation barriers in phosphanes were found about 10 kcal mol^{-1} lower than those found for the corresponding oxides, though geometry and inter-ring gearing would be very similar in the two series. Configurational stability of residual tris-(aryl)phosphanes was found to be influenced by the electronic availability of the phosphorus centre, as evaluated by electrochemical CV experiments.

Keywords: chirality · phosphane oxides · phosphanes · residual enantiomers

Introduction

Three-bladed molecular propellers have attracted considerable attention[1] since Mislow described their fascinating stereodynamics, discovering a novel type of stereoisomerism that he named residual.[2] Differentiation of the edges of the blades and strict correlation of the rings motions are the conditions for the existence of residual stereoisomers in these systems. If satisfied, the fastest stereoisomerisation mechanism, the so called M_1 (or two-ring flip) mechanism, does not interconvert all possible stereoisomers generated by helicity and the three simple blade-hub rotors. In the case of C_3-symmetric systems bearing three identical blades, two non-interconverting subgroups (the residual enantiomers), each one constituted by four quickly interconverting stereoisomers, are generated. Elguero first isolated the configurationally stable ($\Delta G^{\neq} = 28.5$ kcal mol^{-1} at 70 °C) residual antipodes of tris-[1-(2-methyl)benzimidazolyl]methane (**1**).[3] We have substantially enlarged the family of the resolvable C_3-symmetric propellers devoid of any rigid stereogenic element by investigating compounds **2** and **3a–d** and shedding some light on the electronic and steric parameters controlling their configurational stability.[4] We focused our attention onto phosphorus-centred systems, since the possibility of acceding to a class of nonconventional chiral tris-(aryl)phosphanes seemed to us a very exciting challenge considering that hindered tris(aryl)phosphanes are the promoters of choice in several specific reactions.[5]

The use of a phosphorus atom as the hub makes the attainment of the configurational stability difficult, since C–P

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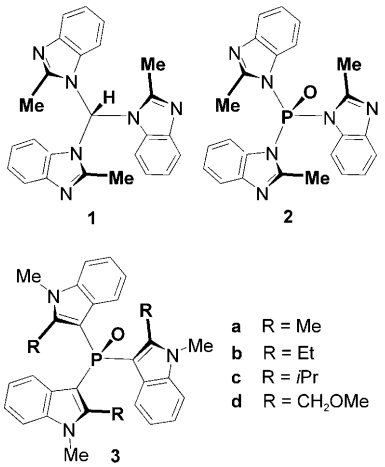
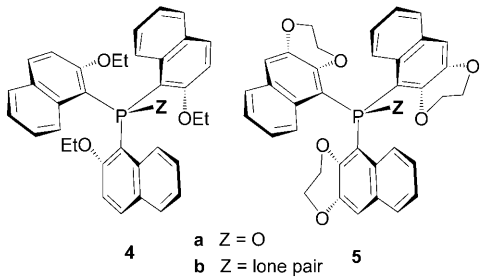


bonds are much longer (1.78 Å) than C–C (1.54 Å) and C–N bonds (1.45 Å) and the P atom in phosphanes can undergo pyramidal inversion. In any case, an accurate design of the blades and of their substituents is mandatory to stabilise the residual enantiomers by improving the efficacy of the correlated rotation of the rings. Indeed, we found that in phosphane oxides (**3a–c**) configurational stability is enhanced by increasing the size of the *ortho* groups.[6] Unfortunately the P atom is so hindered in the most stable system **3c** that its reduction to phosphane is extremely difficult. We felt forced to revise the design of the blades resorting to phosphane oxides **4a** and **5a** and to the corresponding phosphanes **4b** and **5b**.



The naphthalene ring offers a wider contact surface and a more favourable arrangement of the *ortho* substituents than benzocondensed five-membered systems to produce an efficient engagement of the blades. Thus, *ortho* substituents less sterically demanding than the isopropyl group could be selected. A further advantage is that a direct, simple access to phosphanes could be envisaged not involving the phosphane oxides as intermediates.

This paper reports the synthesis of **4** and **5**, the resolution of **4a** and **5a**, performed on a preparative scale in the latter case, the structural characterisation of all compounds, and the evaluation of their configurational stability. However, the key item of the paper is that we found a solution to a problem that, even though considered in the past,[3] has not been solved so far, namely, the assignment of the absolute configuration to propeller-shaped residual enantiomers.

Results and Discussion

Synthesis of phosphanes and phosphane oxides 4 and 5: The synthesis of racemic **4b** and **5b** was achieved by heating to reflux a solution of 1-(2-ethoxynaphthyl)- or 1-(2,3-ethylenedioxynaphthyl)magnesium bromide in THF with PCl_3. 1-Bromo-2,3-ethylenedioxynaphthalene was prepared by reaction of known 2,3-ethylenedioxynaphthalene[7] with *N*-bromosuccinimide (NBS) in DMF and separated from some 1,4-dibromo-2,3-ethylenedioxynaphthalene, formed as by-product, by fractional crystallisation. Oxidation of **4b** and **5b** with hydrogen peroxide gave phosphane oxides **4a** and **5a**. All compounds were fully characterised on the basis of their analytical and spectral data. The ^{1}H NMR spectra of all compounds revealed the presence of a single C_3-symmetric enantiomeric pair in solution at room temperature.

X-ray diffraction (XRD) analysis: In agreement with the ^{1}H NMR spectra, XRD data collected on the racemates showed that the C_3-symmetric *Maaa* and *Paaa* conformers[8] are present in all the cases. (Figure 1a–d) Interestingly, bond lengths and angles in phosphanes and phosphane oxides are comparable: the phosphorus atom displays a nearly perfect tetrahedral arrangement, suggesting that the three bulky substituents do not force the molecule to flatten, unlike

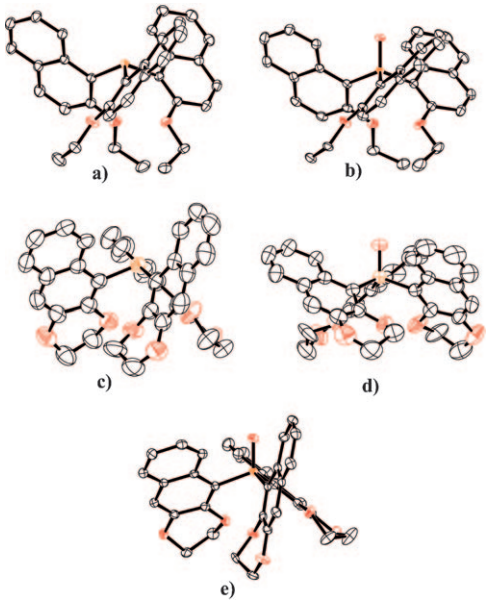


Figure 1. ORTEP projections from XRD data: atomic displacement parameters at 50% probability level. a) (±)-**4b**, 123 K; b) (±)-**4a**, 123 K; c) (±)-**5b**, room temperature; d) (±)-**5a**, room temperature; e) enantiopure (−)-**5a**, 90 K. The dioxene rings are partially [(−)-**5a** and (±)-**5a**] or totally [(±)-**5b**] disordered: only one model is presented. A solvating, disordered $CHCl_3$ molecule is present in the (±)-**5b** structure, while (±)-**4a** contains ordered CH_2Cl_2 and $CHCl_3$ molecules (omitted along with H atoms).

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some hindered tris(aryl)phosphanes in which the cone angle exceeds 110°.[9] The mean P–C bond length is 1.822 Å in **4a**, 1.826 Å in **4b**, 1.818 Å in **5a** and 1.839 Å in **5b**. The mean C-P-C angle is 109.98° in **4a**, 108.73° in **4b**, 108.81° in **5a** and 106.08° in **5b**.

Resolution of the residual racemates: Analytical and semi-preparative resolution of **4a** and of **5a** was achieved by CSP HPLC (Figure 2), while attempts to resolve phosphanes were unsuccessful. The dextrorotatory enantiomers were eluted first, as already observed in the case of **1**, **2**, **3b** and **3c**.[4] The CD spectra of the resolved antipodes are reported below.

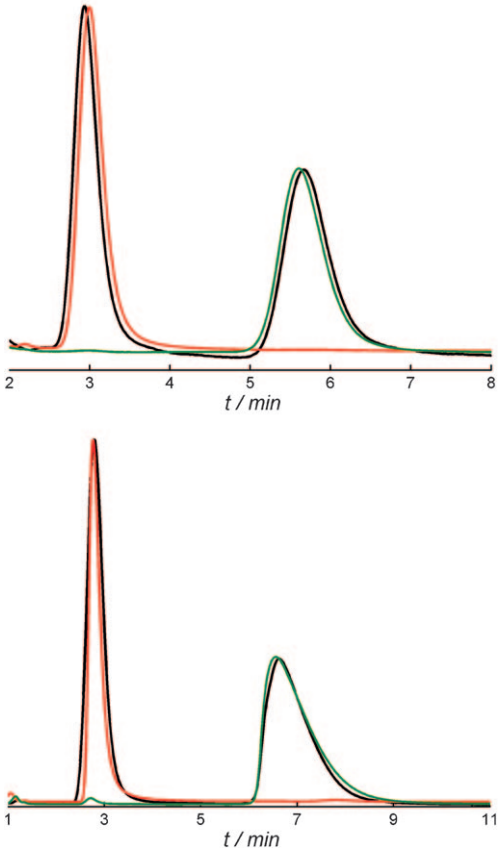

Figure 2. Top: CSP HPLC chromatograms of (±)-**4a** (black curve) and of resolved antipodes (red and green curves). Bottom: CSP HPLC chromatograms of (±)-**5a** (black curve) and of resolved antipodes (red and green curves).

Crystallisation of **5a** from CH_2Cl_2 at 4°C in the presence of optically active quartz powder gave a crop of chiral needlelike crystals (space group $P2_12_12_1$) enriched in the (+)-enantiomer, while a solid enriched in the (−)-enantiomer was recovered from the mother liquor. Several seed-induced crystallisations of the enriched solids gave (+)- and (−)-**5a** in 98.0 and 96.5% *ee* ($[\alpha]_D^{25} = +444°$ and $-432°$, $c = 1\%$ in CH_2Cl_2). This resolution process could be extended to a preparative scale and several hundreds of milligrams of both the antipodes were made available.

Anomalous XRD scattering experiments[10] carried out on (−)-**5a** allowed us to assign for the first time the absolute configuration to the residual enantiomers of propeller-shaped molecules. In this case, (−)-**5a** assumes a distorted C_1 *Paaa* conformation, with one naphthodioxene ring nearly orthogonal to the reference plane. (Figure 1e)

Evaluation of the configurational stability of the residual enantiomers: The racemisation kinetics of **4a** ($MeCN/H_2O$ 35:65) and **5a** (MeCN) was followed by CD decay kinetic measurements at temperatures ranging from 60 to 82°C. The racemisation barrier $\Delta G^{\neq}$ (25°C) was found to be 28.1 ± 0.2 kcal mol^{-1} for **4a** and 26.7 ± 0.6 kcal mol^{-1} for **5a**; these values are quite high for three-bladed phosphorus-centred residual enantiomers.

The configurational stability of phosphanes **4b** and **5b** was assessed by dynamic NMR spectroscopy, the sole technique available in these cases. In the ^{1}H NMR spectrum the methylene multiplet of the ethoxy group of **4b** starts coalescing at 50°C and a sharp quartet is observed at 100°C. The methylene signals in the ^{1}H NMR spectrum between 27°C and 100°C were simultaneously fitted to a dynamic model.[11] The procedure gave very good agreement between experimental data and the theoretical model and provided an enantiomerisation barrier of 18.1 ± 0.1 kcal mol^{-1} at 25°C, about 10 kcal mol^{-1} lower than that exhibited by the corresponding phosphane oxide **4a**. (Figure 3a)

A quite similar behaviour was shown by the dioxene ring signals of **5b**, which start coalescing at 70°C to give two trip-

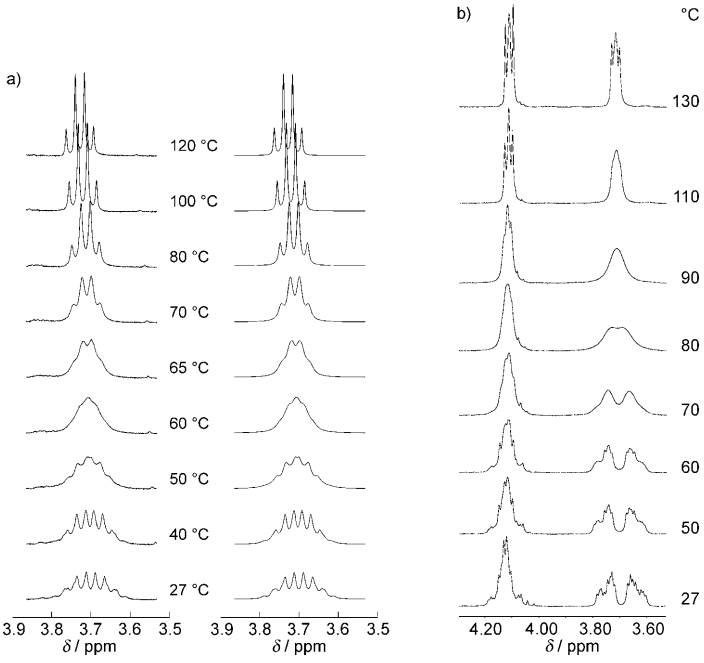

Figure 3. a) Variable-temperature ^{1}H NMR ([D$_6$]DMSO) of the methylene protons of **4b**, left: experimental, right: best-fit. b) Variable-temperature ^{1}H NMR ([D$_6$]DMSO) of the ethylenedioxy protons of **5b**.

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lets at about 130 °C, indicating that dioxene ring flipping and enantiomerisation are quite fast processes at this temperature (Figure 3b). In this case the signal pattern was too complex to be fitted to a dynamic line-shape model, but a barrier of about 20 kcal mol^{-1}, slightly higher than that exhibited by **4b**, looks reasonable for this compound.

The much lower configurational stability of phosphanes **4b** and **5b** in comparison with the phosphane oxides **4a** and **5a** is in agreement with the observations previously reported in the case of the indole-based phosphane oxide **3b** and the corresponding phosphane.[4]

On the basis of the XRD data, showing that the engagement of the blades is very similar in the couples **4a**/**4b** and **5a**/**5b**, one could suggest that such a large difference in configurational stability is due to phosphorus inversion, even though theoretical calculations at the DFT-B3LYP/cc-pVDZ level carried out for the tris[3-(2-ethyl-1-methyl)indolyl]phosphane[4] (the phosphane corresponding to phosphane oxide **3b**) showed that the barrier of the M_0 mechanism is about 13 kcal mol^{-1} lower than in **3b**.

In any case, we are forced to consider the possibility that the phosphorus inversion process is responsible for the modest configurational stability of phosphanes in view of the fact that, to the best of our knowledge, no data on the inversion barrier is available in the literature for tris(aryl)phosphanes, even though a 20 kcal mol^{-1} barrier looks quite low in comparison with the free energy barriers of about 30 kcal mol^{-1} (at 130 °C) found for bis(aryl)phosphanes.[12] However, the completely different steric and electronic characteristics of tris(aryl)phosphanes could play an important and unexpected role on phosphorus inversion attitude. The *ortho* substitution of tris(aryl)phosphanes is known to produce peculiar effects on the phosphorus electronic density,[13] which in turn affects the energy barrier for the inversion process.[12,14] In this light, preliminary CV experiments were carried out in the case of **4b**, **5b** and tris(indolyl)phosphane corresponding to **3b**.[4]

The results of these experiments confirmed that there is a relationship between the configurational stability of tris(aryl)phosphanes and their electrochemical oxidation peak potential (E_p/V), which is one of the most convenient and reliable parameters to quantitatively evaluate the electronic properties of a donor phosphorus ligand (the higher the E_p value, the lower its electronic availability).[15] We found that the enantiomerisation barrier progressively decreases from **5b** ($\Delta G^{\neq} \approx 20$ kcal mol^{-1}) to **4b** ($\Delta G^{\neq} = 18$ kcal mol^{-1}) and to the tris[3-(2-ethyl-1-methyl)indolyl]phosphane ($\Delta G^{\neq} \approx 10$ kcal mol^{-1}) with a parallel decrease in the E_p (0.81 V for **5b**, 0.69 V for **4b** and 0.41 V for the indolic phosphane, vs. SCE). This trend is opposite to that described for bis(aryl)phosphanes,[12] suggesting that phosphorus electronic density could play a bivalent role on the racemisation of the residual enantiomers of tris(aryl)phosphanes by affecting both phosphorus inversion and M_0 mechanism barriers.

Proposal for stereogenicity descriptors for propeller-shaped residual enantiomers: The problem of assigning stereogenicity descriptors to propeller-shaped residual enantiomers has never been considered. In our opinion, this is mainly because only one example was known until very recently and the anomalous X-ray diffraction analysis was not successful in that case.[3] As a consequence, the need for differentiating two residual enantiomers through abbreviations was not felt as a necessity. The problem is not trivial since it refers to systems devoid of rigid stereogenic elements, while the classical descriptors of the Cahn–Ingold–Prelog (CIP) rules apply to molecules for which a stiff model of the stereogenic core can be created (centre, axis, plane, helix or a suitably substituted double bond).

In the case of C_3-symmetric three-bladed propellers each residual enantiomer is not constituted by a single stereoisomer, but by a group of conformers displaying both *P* and *M* helicity [Eqs. (1) and (2)] even though only one of them is generally found in crystals of a single enantiomer.

$$Psss \rightleftharpoons Mssa \rightleftharpoons Psaa \rightleftharpoons Maaa \quad (1)$$

$$Msss \rightleftharpoons Pssa \rightleftharpoons Msaa \rightleftharpoons Paaa \quad (2)$$

Thus, it is evident that simple *P* and *M* labels cannot define the absolute configuration of residual antipodes even though they must contribute to coining the appropriate descriptors.

A sub-rule is needed, which should establish a relationship between the helicity and the orientation of all the labelled edges above or below the reference plane in a specific enantiomer.

We suggest to assign to a residual enantiomer the descriptor P_{res} or M_{res}, in which *res* as subscript means residual, corresponding to the helicity shown by the *sss* stereoisomer (according to the sequence rules *syn* precedes *anti*),[16] independently on which stereoisomer is present in the crystalline structure. This rule works even in the cases where more than one stereoisomer is present in the single crystal of a pure residual enantiomer, like in the case of **1**, in which two diastereoisomers (*sss* and *ssa*) displaying opposite helicity are present in the crystal lattice.

In the case of (−)-**5a**, XRD data showed that only the *Paaa* conformer is present in the crystal. The *Paaa* conformer belongs to the group of conformers in which the *sss* diastereoisomer displays *M* helicity [Eq. (2)]. Then, the absolute configuration of (−)-**5a** is M_{res}.

According to this rule, all the stereoisomers **1**, **2** and **3** as are the P_{res} enantiomers, since they display *P* helicity and the *sss* conformation of the blades [Eq. (1)]. The rule works also in the case of maximally labelled C_1-symmetric propellers.

Correlative assignment of the absolute configuration to configurationally stable residual enantiomers of C_3 propellers: Since we succeeded in determining the absolute configuration of (−)-**5a** and (+)-**5a**, we now set out to correlatively

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assign the absolute configuration to all known residual enantiomers of C_3 propellers.

Indeed, in the absence of X-ray anomalous scattering data, the analogy of the CD curves and the chromatographic elution order under the same experimental conditions are considered as reliable correlative methods for assigning the absolute configuration to the antipodes belonging to a series of structurally similar substrates.[17] We will also consider the relationship between the sign of the optical rotation and the elution order. We assume that this correlative method, which is successfully employed in the case of chiral systems endowed with rigid stereogenic elements, can be applied also to residual enantiomers stable enough to be subjected to CD and α_D measurements in solution at room temperature (**1**, **2**, **3b**, **3c**, **4a** and **5a**). The CD curves, the sign of the optical rotation at 589 nm and the CSP HPLC elution order from the same column under very similar experimental conditions are reported in Figure 4.

As reported above, the dextrorotatory residual enantiomer of **5a** has absolute configuration P_{res}. It is the first eluted one and its CD spectrum shows two ellipticity minima at 210 and 225 nm and a maximum at 245 nm.

The enantiomers of **4a**, which are structurally very similar to and share the same preferred blade conformation (*aaa*) with the enantiomers of **5a**, show a convincing parallelism between elution order, shape of the CD curves, and optical rotation sign. Indeed, the first eluted antipode of **4a** is dextrorotatory and its CD spectrum features an ellipticity minimum at 225 nm and a maximum at 240 nm. Thus, we can reliably assign the absolute configuration P_{res} to the dextrorotatory enantiomer of **4a**.

Also for the two indole-based systems **3b** and **3c**, the first eluted enantiomers are dextrorotatory, as for **4a** and **5a**. The CD spectra of the two indole-based systems **3b** and **3c** are expectedly very similar to each other, suggesting that (+)-**3b** and (+)-**3c** possess the same absolute configuration. At variance with (+)-**4a** and (+)-**5a**, (+)-**3b** and (+)-**3c** show ellipticity maxima at 215 and 275 nm (the latter of modest intensity) and a minimum at 230 nm. This different behaviour could be interpreted on the basis of the observation that the preferred conformation of phosphane oxides **4a** and **5a** is *aaa*, whereas in the case of the three indole bladed systems **3a–c**, the preferred conformation is *sss*. Total edge exchange through three subsequent M_1 stereomerisation steps inside a single residual enantiomer involves the reversal of the helicity [Eqs. (1) and (2)] and, by consequence, also of the CD behaviour. Thus, it is not surprising that first-eluted (+)-**3b** and (+)-**3c**, with the preferred *sss* blade conformation, show a CD spectrum opposite to that exhibited by (+)-**4a** (*aaa*). On account of this reasoning, we assign the absolute configuration P_{res} to the first-eluted (+)-**3b** and (+)-**3c**. As for **3a**, we only know the ellipticity sign at 230 and 280 nm, which agree with those of **3b** and **3c**. Then, also in this case, we can assign the P_{res} absolute configuration to the first-eluted antipode of **3a**.

By comparing the CD spectra of compounds **1** and **2** it appears that the nature of the central atom does not substan-

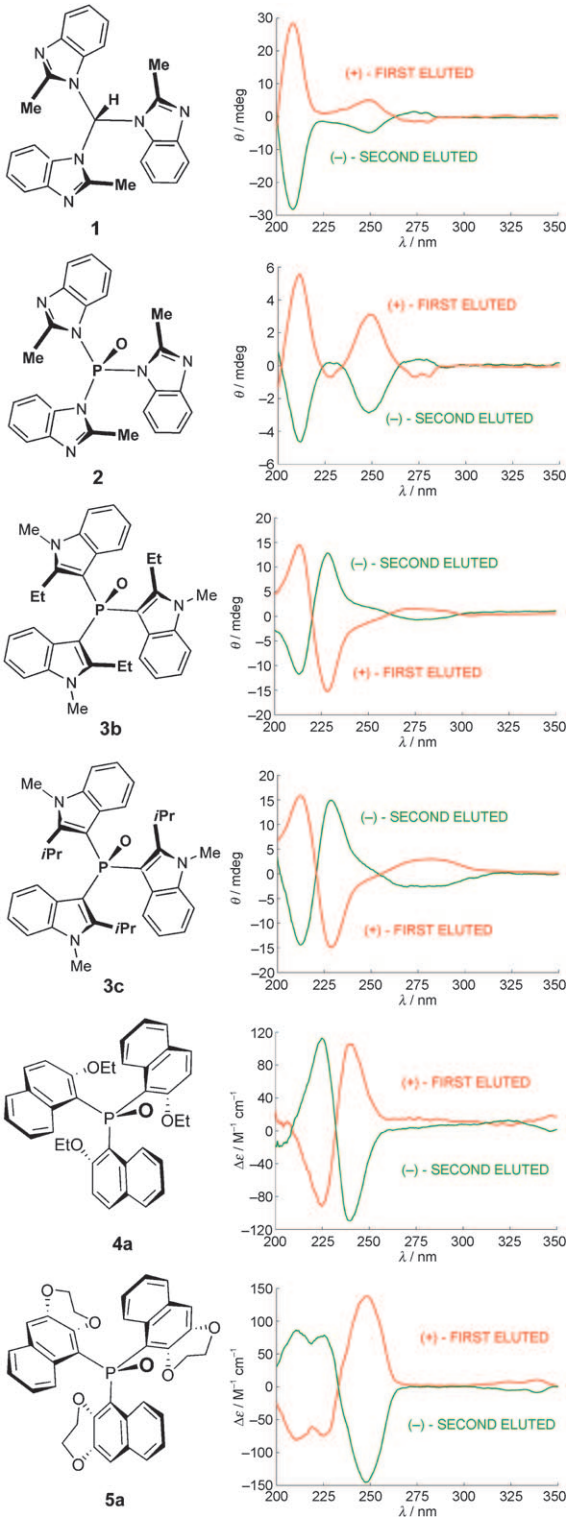

Figure 4. CD spectra of all known resolvable three-bladed propeller-shaped molecules, with the corresponding elution order under similar CSP HPLC conditions [column: ChromTech CHIRAL-AGP; eluant: acetonitrile:water 15:85 for **1**, **2**; 28:72 for **3b**; 30:70 for **3c**; 35:65 for **4a**; acetonitrile for **5a**] and the optical rotation sign at 589 nm.

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tially influence the CD behaviour, since carbon- and phosphorus-centred propellers display very similar spectra, both showing maxima at 210 and 250 nm, with a lower intensity peak at 275 nm.

The main difference between the spectra of **1** and **2** is a low intensity peak, flanked by Cotton effects at both sides, at 230 nm, visible in the spectra of the phosphane oxide **2** only. This peak is present in the spectra of all the other phosphane oxides, even though characterised by a much higher intensity.

There is agreement between the elution order of the antipodes, the optical rotation sign and the sign of their CD curves, in the sense that both the first eluted enantiomers display positive sign of the ellipticity at 210 and 250 nm and negative sign at 275. Taking into account that the preferred conformation for both **1** and **2** is *sss*, just as for **3b** and **3c**, we assign to both first-eluted (+)-**1** and (+)-**2** antipodes the absolute configuration P_{res}.

On the basis of the arguments discussed before, all first eluted isomers, all dextrorotatory, should have P_{res} absolute configuration, even if the preferred blade conformation is not constant.

Conclusion

The possibility of producing C_3-symmetric phosphorus-centred propellers existing as configurationally stable residual enantiomers was investigated. Two new phosphanes **4b** and **5b** and the corresponding phosphane oxides **4a** and **5a**, were synthesised and fully characterised by XRD analysis.

Racemic phosphane oxides were resolved by semipreparative HPLC on a chiral stationary phase and the antipodes were found quite stable at room temperature with an enantiomerisation barrier of 27–28 kcal mol^{-1}, evaluated by CD decay kinetics.

The racemisation barrier for phosphanes was found about 18–20 kcal mol^{-1}, at the lower limit for configurational stability at room temperature, and about 10 kcal mol^{-1} lower than that exhibited by the corresponding oxides. Previous theoretical calculations showed that the M_0 mechanism racemisation barrier is significantly lowered on passing from phosphane oxide **3b** to the corresponding phosphane.[4] However, since the XRD data show that blade gearing is very similar in phosphanes and phosphane oxides, we cannot exclude that phosphorus inversion, a racemisation mechanism only possible in the case of phosphanes, could contribute to such a fast racemisation. We found that there is a relationship between the electronic availability at the phosphorus atom of phosphanes, measured by CV experiments, and their configurational stability, that is, the more electron-poor the phosphorus atom, the higher the racemisation barrier.

The residual racemate of **5a** was found to crystallise as a conglomerate from dichloromethane. In this case the resolution could be efficiently performed at a preparative scale level by seed-induced crystallisation and, for the first time, we were able to assign the absolute configuration to the residual antipodes by anomalous X-ray scattering.

This assignment allowed us to perform the correlative, CD- and CSP HPLC-based configurational assignment to all C_3-symmetric carbon- and phosphorus-centred propellers known so far and displaying a configurational stability high enough to allow their survival during the CSP HPLC resolution process.

The last problem faced in this work was coining configurational descriptors for the residual enantiomers of three-bladed propellers. The matter is not trivial since residual enantiomers are devoid of rigid stereogenic elements and a single antipode is constituted by groups of stereoisomers displaying both *P* and *M* helicity. The general rule we suggest is to assign to a residual enantiomer the configurational descriptor P_{res} or M_{res} (in which the subscript *res* means residual) according to the helix exhibited by the *sss* stereoisomer, displaying all the priority edges above the reference plane.

Current research is directed toward the modification of phosphanes **4b** and **5b** that display a very efficient blade gearing, but are not stable enough at room temperature to guarantee a successful resolution. According to the results of the electrochemical experiments, a possible strategy is to regioselectively introduce tailored electron-withdrawing substituents on the blades, in order to increase the enantiomerisation barrier of the few kcal mol^{-1} necessary to accede to configurationally stable residual C_3-tris(aryl)phosphanes to test in stereoselective synthesis.

Experimental Section

Organic Synthesis: $[\alpha]_D$ were determined with a Jasco P-1030 polarimeter. CD spectra and dichroism decay experiments were recorded with a Jasco P-810 spectropolarimeter provided with a temperature-controlled probe Peltier Jasco PFD 425S. HPLC analyses and semipreparative separations were performed on a Waters 600E instrument equipped with a UV detector Waters 486 and recorded at 220 nm. Analytical column: ChromTech CHIRAL-AGP column (α_1-acid glycoprotein immobilised on silica, 100×4.0 mm, 5 μm); loop: 20 μL; substrate concentration: 1 mg mL^{-1}. Semipreparative column: CromTech CHIRAL-AGP column (150×10.0 mm, 5 μm); loop: 500 μL. NMR spectra were recorded on Bruker AV400 and Bruker AC300 spectrometers. Chemical shifts are given in ppm and the coupling constants in Hz. Mass spectra were recorded on Bruker Daltonics high-resolution FT-ICR (Fourier Transform ion cyclotron resonance) model APEXTM II (4.7 Tesla Magnex cryomagnet supplied with ESI source) and Thermofiningan LCQ Advance (APCI). Purifications by column chromatography were performed using Merck silica gel 60 (230–400 mesh for flash-chromatography and 70–230 mesh for gravimetric chromatography).

1-Bromo-2,3-ethylenedioxynaphthalene: A solution of 2,3-ethylenedioxy naphthalene[7] (4.03 g, 21.7 mmol) in DMF (25 mL) was added dropwise to a solution of NBS (3.87 g, 23.6 mmol) in DMF (25 mL) over a period of 1 h; the reaction mixture was stirred at room temperature for 48 h. The solvent was removed under reduced pressure, and the residue dissolved in CH_2Cl_2 and washed with a NaCl saturated solution. The organic layer was separated and dried (Na_2SO_4) and the solvent removed under reduced pressure to give a residue which was subjected to chromatography (silica gel, *n*-hexane/AcOEt 95:5). The first fractions eluted provided some unreacted material; the intermediate fractions were collected, concentrated under reduced pressure to give a mixture of 1-bromo-2,3-ethylenedioxynaphthalene and 1,4-dibromo-2,3-ethylenedioxynaphthalene

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(4.30 g). The solid was triturated with warm *n*-hexane (2×20 mL) and the insoluble dibromoderivative was removed by filtration (0.67 g). M.p. 195–198 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (dd, ^3J(H,H) = 6.51 Hz, ^4J(H,H) = 3.30 Hz, 2H), 7.47 (dd, ^3J(H,H) = 6.51 Hz, ^4J(H,H) = 2.74 Hz, 2H), 4.48 ppm (s, 4H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 141.79 (s), 128.63 (s), 126.64 (s), 126.59 (s), 108.07 (s), 65.35 ppm (s). 1-Bromo-2,3-ethylenedioxynaphthalene crystallised from the filtrate in a pure state as a white solid (3.63 g, 63%). M.p. 44–45 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, ^3J(H,H) = 8.52 Hz, 1H), 7.64 (d, ^3J(H,H) = 8.03 Hz, 1H), 7.42 (td, ^3J(H,H) = 6.95 Hz, ^4J(H,H) = 2.68 Hz, 1H), 7.34 (td, ^3J(H,H) = 8.2 Hz, ^4J(H,H) = 1.36 Hz, 1H), 7.26 (s, 1H), 4.46 (m, 2H), 4.34 ppm (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 141.87 (s), 141.79 (s), 127.24 (s), 126.13 (s), 125.86 (s), 125.32 (s), 112.71 (s), 108.09 (s), 65.62 (s), 64.56 ppm (s); elemental analysis calcd (%) for $C_{12}H_9O_2Br$: C 54.37, H 3.42; found: C 54.31, H 3.31.

Tris[1-(2-ethoxynaphthyl)]phosphane (4b): All the manipulations were carried out under inert atmosphere and the solvents were previously degassed. A solution of 1-bromo-2-ethoxynaphthalene (7.26 g, 28.8 mmol)[18] in dry THF (16 mL) was added dropwise under nitrogen to a suspension of magnesium (735 mg) in THF (5 mL), previously activated with iodine. The addition was completed over a period of 30 min and the mixture was heated to reflux for 6 h; a solution of PCl_3 (0.42 mL, 4.8 mmol) in dry THF (5 mL) was added at room temperature. The reaction mixture was heated to refluxed under nitrogen for 1 h and stirred at room temperature for further 12 h. The solvent was removed under reduced pressure and the residue treated with water (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The organic layer was dried and the solvent evaporated under reduced pressure to give a residue that was triturated with CH_2Cl_2 (16 mL). The solid was recovered by filtration to give a first amount of **4b** (1.06 g); the filtrate was concentrated to give a solid which was triturated with ethyl acetate to give a second sample of **4b** (0.74 g). The combined crops (1.8 g, 72.4%) were crystallised from CH_2Cl_2/AcOEt 1:1 (100 mL). M.p. 225–228 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.49 (dd, ^3J(H,H) = 6.31 Hz, ^4J(H,H) = 4.4 Hz, 1H), 7.78 (d, ^3J(H,H) = 8.81 Hz, 1H), 7.74 (d, ^3J(H,H) = 8.81 Hz, 1H), 7.23 (m, 2H,), 7.12 (dd, ^3J(H,H) = 8.8 Hz, ^4J(H,H) = 2.35 Hz, 1H), 3.74 (m, 1H), 3.61 (m, 1H), 0.53 ppm (t, ^3J(H,H) = 7.05 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 158.98 (d, ^2J(C,P) = 4.69 Hz), 137.53 (d, ^2J(C,P) = 21.13 Hz), 130.55 (s), 129.62 (d, ^3J(C,P) = 4.69 Hz), 128.40 (s), 127.18 (d, ^3J(C,P) = 25.82 Hz), 126.01 (s), 123.30 (s), 120.11 (d, ^1J(C,P) = 21.13 Hz), 115.15 (s), 64.70 (s), 14.21 ppm (s); ^{31}P NMR (300 MHz, $CDCl_3$): δ = −57.67 ppm (s); HR-MS (APCI): *m/z* calcd for $C_{36}H_{33}PO_3$: 544.6; found: 545.3 [M^+].

Tris[1-(2,3-ethylenedioxynaphthyl)]phosphane (5b): All the manipulations were carried out under inert atmosphere and the solvents were previously degassed. A solution of 1-bromo-2,3-ethylenedioxynaphthalene (1.91 g, 7.2 mmol) in dry THF (10 mL) was added dropwise under nitrogen into a suspension of magnesium turnings (175 mg) previously activated with iodine in THF (2 mL). The addition was completed over a period of 30 min and the reaction mixture was heated to reflux until the magnesium completely reacted. A solution of PCl_3 (0.14 mL, 1.6 mmol) in dry THF (5 mL) was added at room temperature to the Grignard solution and the reaction mixture was heated to reflux under nitrogen for a further 16 h. The solvent was removed under reduced pressure and the residue dissolved into CH_2Cl_2 (15 mL) and washed with water (15 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil which, triturated with AcOEt, provided **5b** as a whitish solid (0.51 g, 55%). M.p. 247 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (dd, ^3J(H,H) = 8.52 Hz, ^4J(H,H) = 3.88 Hz, 1H), 7.60 (d, ^3J(H,H) = 8.07 Hz, 1H), 7.22 (d, ^3J(H,H) = 7.52 Hz, 1H), 7.20 (s, 1H), 7.10 (td, ^3J(H,H) = 6.84 Hz, ^4J(H,H) = 1.19 Hz, 1H), 4.17 (m, 1H,), 4.01 (m, 1H), 3.63 (m, 1H), 3.44 ppm (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 145.99 (d, ^2J(C,P) = 3.70 Hz), 143.00 (s), 131.71 (d, ^2J(C,P) = 20.35 Hz), 129.53 (d, ^3J(C,P) = 5.55 Hz), 126.83 (s), 126.05 (s), 125.70 (s), 123.64 (s), 118.58 (d, ^1J(C,P) = 20.35 Hz), 113.42 (s), 63.84 (s), 63.40 ppm (s); ^{31}P NMR (300 MHz, $CDCl_3$): δ = −55.24 ppm (s); HR-MS (EI): *m/z* calcd for $C_{36}H_{27}O_6P$: 586.54; found: 586.3 [M^+].

Tris[1-(2-ethoxynaphthyl)]phosphane oxide (4a): A solution of phosphane **4b** (2.55 g, 4.7 mmol) in CH_2Cl_2 (30 mL) and a 30% aqueous solution of H_2O_2 (3 mL) were stirred for 12 h at room temperature. The organic layer was separated, dried and concentrated under reduced pressure to give a solid which was subjected to chromatography (silica gel, CH_2Cl_2/AcOEt 7:3) to give **4a** as a white solid (2.28 g, 89%). M.p. 330–333 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.99 (m, 1H), 7.84 (d, ^3J(H,H) = 9.05 Hz, 1H), 7.72 (m, 1H), 7.26 (m, 2H), 7.01 (m, 1H), 3.68 (m, 1H), 3.28 (m, 1H), 0.35 ppm (t, ^3J(H,H) = 7.03 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$): δ = 157.80 (s), 136.02 (d, ^2J(C,P) = 6.79 Hz), 133.18 (s), 129.44 (d, ^3J(C,P) = 9.06 Hz), 127.96 (s), 127.34 (d, ^3J(C,P) = 5.28 Hz), 126. 60 (s), 123.34 (s), 119.10 (d, ^1J(C,P) = 107.93 Hz), 113.66 (d, ^4J(C,P) = 7.55 Hz), 63.86 (s), 13.38 ppm (s); ^{31}P NMR (300 MHz, $CDCl_3$): δ = 21.55 ppm (s); HR-MS (APCI): *m/z* calcd for $C_{36}H_{33}O_4P$: 560; found: 561.2 [M^++1]; analytical CSP HPLC: (+)-**4a**, 99% *ee*, retention time 3.1 min; (−)-**4a**, 98% *ee*, retention time 5.8 min; eluent MeCN/H_2O 35:65; flow rate 0.7 mL min^{-1}; Semi-preparative CSP HPLC: (+)-**4a**, retention time 4.0 min; (−)-**4a**, retention time 8.2 min; eluant MeCN/H_2O 35:65; flow rate 4.0 mL min^{-1}.

Tris[1-(2,3-ethylenedioxynaphthyl)]phosphane oxide (5a): A solution of phosphane **5b** (3.37 g, 5.7 mmol) in CH_2Cl_2 (50 mL) and a 30% aqueous H_2O_2 solution (10 mL) were stirred for 12 h at room temperature. The organic layer was dried and concentrated under reduced pressure to give a solid that was triturated with AcOEt and subjected to chromatography (silica gel, CH_2Cl_2/AcOEt 7:3) to give **5a** as a white solid (2.80 g, 81%). M.p. >370 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (d, ^3J(H,H) = 8.52 Hz, 1H), 7.63 (d, ^3J(H,H) = 8.01 Hz, 1H), 7.25 (m, 3H), 4.12 (m, 1H), 3.94 (m, 1H), 3.51 (m, 1H), 3.12 ppm (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 146.01 (d, ^2J(C,P) = 3.82 Hz), 142.85 (d, ^3J(C,P) = 10.87 Hz), 131.13 (d, ^2J(C,P) = 6.14 Hz), 130.40 (d, ^3J(C,P) = 11.27 Hz), 127.39 (s), 126.86 (d, ^3J(C,P) = 5.43 Hz), 125.33 (s), 124.79 (s), 118.97 (d, ^1J(C,P) = 106.77 Hz), 116.59 (d, ^4J(C,P) = 2.51 Hz), 64.11 (s), 63.78 ppm (s); ^{31}P NMR (300 MHz, $CDCl_3$): δ = 19.52 ppm (s); HR-MS (APCI): *m/z* calcd for $C_{36}H_{27}O_7P$: 602.53; found: 603.3 [M^++1]; elemental analysis (%) calcd for $C_{36}H_{27}O_7P$: C 71.76, H 4.52; found: C 71.64, H 4.42.

Resolution of the tris[1-(2,3-ethylenedioxynaphthyl)]phosphane oxide (5a): A solution of (±)-**5a** (2.05 g) in CH_2Cl_2 (31 mL) was allowed to stand at 4 °C overnight in the presence of a ground optically active quartz fragment. The needle-shaped crystals $[\alpha]_D^{25}$ = +3.68 (*c* = 1% in CH_2Cl_2) were collected by filtration and the filtrate evaporated to dryness to give a residue $[\alpha]_D$ = −1.22 (*c* = 1% in CH_2Cl_2). The two solids enantiomerically enriched were resolved according to the following procedure. The solid was dissolved at room temperature into a suitable amount of CH_2Cl_2 (solubility of (±)-**5a** in CH_2Cl_2: 1 g in 15.5 mL) and the solution, after seeding with small crystals of optically enriched **5a**, was stirred vigorously at 0 °C overnight. The solid precipitate was collected by filtration and submitted to the same procedure until 90% enantiomeric excess was reached: $[\alpha]_D$ > 400 (*c* = 1% in CH_2Cl_2). Final enantiomeric enrichment was obtained by a treatment at room temperature with AcOEt (50 mL g^{-1}). (+)-**5a** and (−)-**5a** were obtained in 98.0 and 96.5% *ee* $[\alpha]_D^{25}$ = +444 and −432, respectively (*c* = 1% in CH_2Cl_2); analytical CSP HPLC: (+)-**5a**, 98% *ee*, retention time 3.1 min; (−)-**5a**, 96% *ee*, retention time 6.9 min; eluant MeCN/H_2O 28:72; flow rate 0.8 mL min^{-1}.

Electrochemical measurements: The cyclovoltammetric study was performed at scan rates typically ranging 0.05 to 5 V s^{-1}, in HPLC-grade acetonitrile at a concentration of 0.00025–0.00075 M for each substrate, deaerated by N_2 bubbling, with 0.1 M tetrabutylammonium perchlorate (TBAP, Fluka) as the supporting electrolyte, at 298 K. The ohmic drop was compensated by the positive feedback technique.[19] The experiments were carried out by using an AUTOLAB PGSTAT 12 potentiostat (Eco-Chemie, The Netherlands), run by a PC with GPES software. The working electrode was a glassy carbon one (AMEL, diameter = 1.5 mm) cleaned by diamond powder (Aldrich, diameter = 1 micron) on a wet cloth (STRUERS DP-NAP); the counter electrode was a platinum wire; the reference electrode was an aqueous saturated calomel electrode, with a difference of −0.385 V vs. the Fc^+/Fc couple (the intersolvental redox potential reference currently recommended by IUPAC)[20] in our working medium.

X-ray crystallography: CCDC-654561 ((±)-**4a**), CCDC-654562 ((±)-**4b**), CCDC-654563 ((±)-**5a**), CCDC-654564 ((−)-**5a**) and CCDC-654561

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((±)-**5a**), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] B. Laleu, G. Bernardinelli, R. Chauvin, J. Lacour, *J. Org. Chem.* **2006**, *71*, 7412, and references therein; M. Ciclosi, J. Lloret, F. Estevan, P. Lahuerta, M. Sanaû, J. Pérez-Prieto, *Angew. Chem.* **2006**, *118*, 6893; *Angew. Chem. Int. Ed.* **2006**, *45*, 6741; R. Romeo, S. Carnabuci, L. Fenech, M. R. Plutino, A. Albinati, *Angew. Chem.* **2006**, *118*, 4606; *Angew. Chem. Int. Ed.* **2006**, *45*, 4494; M. T. Powell, A. M. Porte, K. Burgess, *Chem. Commun.* **1998**, 2161; M. R. Whitnall, K. K. Hii, M. Thornton-Pett, T. P. Kee, *J. Organomet. Chem.* **1997**, *529*, 35; C. Bolm, W. D. Davis, R. L. Haltermann, K. B. Sharpless, *Angew. Chem.* **1988**, *100*, 882; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 835; C. Bolm, K. B. Sharpless, *Tetrahedron Lett.* **1988**, *29*, 5101.

[2] K. Mislow, *Acc. Chem. Res.* **1976**, *9*, 26; R. J. Boettcher, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1973**, *95*, 7157; P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 2165; P. Finocchiaro, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 2176; J. P. Hummel, D. Gust, K. Mislow, *J. Am. Chem. Soc.* **1974**, *96*, 3679.

[3] C. Foces-Foces, F. H. Cano, M. Martinez-Ripoll, R. Faure, C. Roussel, R. M. Claramunt, C. Lopez, D. Sanz, J. Elguero, *Tetrahedron: Asymmetry* **1990**, *1*, 61.

[4] T. Benincori, A. Marchesi, T. Pilati, S. Rizzo F. Sannicolò, *Chem. Eur. J.* DOI:10.1002/chem.200801505.

[5] H. Ohta, M. Tokunaga, Y. Obora, T. Iwai, T. Iwasawa, T. Fujihara, Y. Tsuji, *Org. Lett.* **2007**, *9*, 89; C. Qin, H. Wu, J. Cheng, X. Chen, M. Liu, W. Zhang, W. Su, J. Ding, *J. Org. Chem.* **2007**, *72*, 4102.

[6] T. Benincori, G. Celentano, T. Pilati, A. Ponti, S. Rizzo, F. Sannicolò, *Angew. Chem.* **2006**, *118*, 6339; *Angew. Chem. Int. Ed.* **2006**, *45*, 6193.

[7] S. Clavier, M. Khouili, P. Bouyssou, G. Coudert, *Tetrahedron* **2002**, *58*, 1533.

[8] Symbol *a* indicates that the priority edge (CIP rules) of a ring is *anti* to the P–O bond (or to the lone pair) and located below the reference plane (the plane defined by the three carbon atoms connected to the P centre); *s* would indicate a *syn* relationship. Alternative descriptors for propellers have been suggested, which, however, require the introduction of symbols not familiar to the stereochemical language; R. A. Baber, A. G. Orpen, P. G. Pringle, M. J. Wilkinson, R. L. Wingad, *Dalton Trans.* **2005**, 659 and reference therein.

[9] D. M. P. Mingos, T. E. Müller, *J. Organomet. Chem.* **1995**, *500*, 251; T. E. Müller, J. C. Green, D. M. P. Mingos, C. M. Mc Partlin, C. Whittingham, D. J. Williams, T. M. Woodroffe, *J. Organomet. Chem.* **1998**, *551*, 313; S. Sasaki, K. Sutoh, F. Murakami, M. Yoshifuji, *J. Am. Chem. Soc.* **2002**, *124*, 14830; S. Sasaki, R. Chowdhury, M. Yoshifuji, *Tetrahedron Lett.* **2004**, *45*, 9193.

[10] H. D. Flack, *Acta Crystallogr. Sect. A* **1983**, *39*, 876.

[11] A. D. Bain, *Prog. Nucl. Magn. Reson. Spectrosc.* **2003**, *43*, 63.

[12] R. D. Baechler, K. Mislow, *J. Am. Chem. Soc.* **1970**, *92*, 7012.

[13] M. Culcasi, Y. Berchadski, G. Gronchi, P. Tordo, *J. Org. Chem.* **1991**, *56*, 537.

[14] H. A. Bent, *Chem. Rev.* **1961**, *61*, 275; R. D. Baechler, W. B. Farnham, K. Mislow, *J. Am. Chem. Soc.* **1969**, *91*, 5686; R. D. Baechler, K. Mislow, *J. Am. Chem. Soc.* **1970**, *92*, 3290; A. Rauk, L. C. Allen, K. Mislow, *Angew. Chem.* **1970**, *82*, 453; *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 400; R. D. Baechler, K. Mislow, *J. Am. Chem. Soc.* **1971**, *93*, 773; R. D. Baechler, J. D. Andose, J. Stackhouse, K. Mislow, *J. Am. Chem. Soc.* **1972**, *94*, 8060; E. Magnusson, *Aust. J. Chem.* **1985**, *38*, 23; O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry* **1998**, *9*, 1279.

[15] T. Benincori, O. Piccolo, S. Rizzo, F. Sannicolò, *J. Org. Chem.* **2000**, *65*, 8340; T. Benincori, T. Pilati, S. Rizzo, F. Sannicolò, M. J. Burk, L. de Ferra, E. Ullucci, *J. Org. Chem.* **2005**, *70*, 5436.

[16] V. Prelog, G. Helmchen, *Angew. Chem.* **1982**, *94*, 614; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567.

[17] C. Djerassi, *Optical Rotatory Dispersion, Applications to Organic Chemistry*, McGraw-Hill, New York, **1960**; E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, **1994**, p. 115 and references therein; D. A. Lightner, J. E. Gurst, *Organic Conformational Analysis and Stereochemistry from Circular Dichroism Spectroscopy*, Wiley-VCH, New York, **2000**; *Circular Dichroism, Principles and Applications*, 2nd ed. (Eds.: N. Berova, K. Nakanishi, R. W. Woody), Wiley-VCH, New York, **2000**.

[18] V. Paul, A. Sudalai, T. Daniel, K. V. Srinivasan, *Tetrahedron Lett.* **1994**, *35*, 7055.

[19] A. J. Bard, L. R. Faulkner *Electrochemical Methods. Fundamentals and Applications*, Wiley, New York, **2002**, p. 648.

[20] G. Gritzner, J. Kuta, *Pure Appl. Chem.* **1984**, *56*, 461; G. Gritzner, *Pure Appl. Chem.* **1990**, *62*, 1839.

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