EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201301912

# Synthesis, Characterisation, and Organocatalytic Activity of Chiral Tetrathiahelicene Diphosphine Oxides

Silvia Cauteruccio,*[a] Davide Dova,[a] Maurizio Benaglia,*[a] Andrea Genoni,[a] Manuel Orlandi,[a] and Emanuela Licandro[a]

**Keywords:** Helical structures / Organocatalysis / Fused-ring systems / Diastereoselectivity / Phosphines

Two new chiral tetrathia[7]helicene (7-TH) based tertiary phosphine oxides (±)-**2b** and (±)-**2c**, bearing two substituents on the phosphorus atoms with different steric and electronic properties, have been synthesised and fully characterised by means of analytical and spectroscopic techniques. The resolution of (±)-**2a–c** into their antipodes was accomplished by HPLC separation on a chiral stationary phase, and their chiroptical properties were investigated by CD spectroscopy. The behaviour of **2a–c** as organocatalysts was assessed in representative reactions mediated by tri- or tetrachlorosilane. 7-TH-based phosphine oxides **2a** and **2b** promoted both ketoimine reduction and stereoselective carbon–carbon bond formation in good chemical yields and diastereoselectivity, albeit with low enantioselectivity, thus opening the way to the development of a novel class of enantiopure helical-based phosphorus organocatalysts.

## Introduction

Helicenes are *ortho*-annulated polycyclic aromatic or heteroaromatic compounds endowed with an inherently chiral π-conjugated system. Such compounds have attracted considerable attention due to their unique properties and potential applications,[1] mostly based on their chiral conformation. Remarkable examples of their application include chiroptical devices,[2] self-assembly,[3] supramolecular chemistry,[4] biomolecular recognition,[5] and asymmetric catalysis.[6–8] The unique stereochemical properties of these inherently chiral helical systems allow the chiral environment in the proximity of the catalytically active centre to be tuned by structural modification. It is therefore rather surprising that this area of research is still underdeveloped in terms of the number of compounds, the structural diversity, and applications. In fact, whereas the use of helicenes as building blocks for the design of phosphorus-based chiral ligands in homogeneous transition-metal catalysis has been explored,[7] helical structures have been considered much less as potential chiral ligands in organocatalysis, despite the impressive amount of work over the last decade in the design of chiral metal-free catalysts.[9] Only 1-azahelicenes have been successfully used as chiral Lewis base organocatalysts, including helical pyridine *N*-oxides,[8a,8b,8e] 2-aminopyridinium ions,[8d] and a helicenoidal 4-(dimethylamino)-pyridine (DMAP) catalyst,[8f,8g] whereas, to the best of our knowledge, no study on the use of phosphorus derivatives having helical scaffolds as chiral Lewis bases in organocatalysis has been reported.

In the course of our studies on thiahelicene derivatives, we have paid particular attention to the synthesis and functionalisation of tetrathia[7]helicenes (7-TH; Figure 1), which are a class of configurationally stable heterohelicenes[10] that are potentially very interesting for applications in optoelectronics[11] and in catalysis.[6c,7d,12] Moreover, these systems can be easily functionalised at the alpha positions of the two terminal thiophene rings, allowing modulation of the chemical and physical properties of the material by varying the substituents.[10b,10d,10e] In particular, we have recently reported the synthesis of 7-TH-based phosphine derivatives as ancillary ligands in the $Au^{I}$[12] and $Rh^{I}$[7d] complexes (Figure 1), by demonstrating the efficiency of

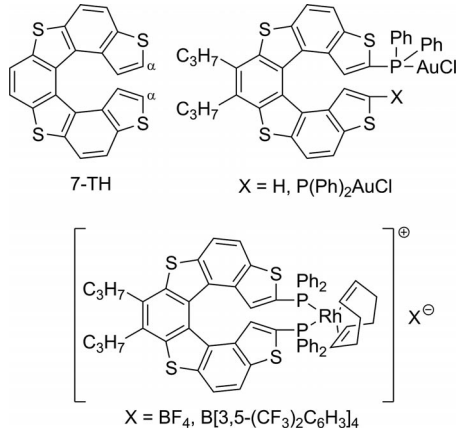



Figure 1. 7-TH-based phosphine derivatives.

[a] Dipartimento di Chimica, Università degli Studi di Milano, via Golgi 19, 20133 Milano, Italy
E-mail: maurizio.benaglia@unimi.it
silvia.cauteruccio@unimi.it
http://www.unimi.it

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301912.

this new class of organometallic complexes in homogeneous transition-metal catalysis.

To further investigate the potential applications of the 7-TH phosphorus derivatives as chiral ligands in asymmetric catalysis, we designed and realised the synthesis of novel 7-TH diphosphine oxides to test them, for the first time, as chiral Lewis bases in stereoselective organocatalytic reactions. Although a plethora of small organic Lewis bases,[13] including naturally-occurring alkaloids, amino acids, synthetic amine-based catalysts, *N*-oxides, and phosphines have been developed as organocatalysts to promote regio- and stereoselective bond-formation reactions, phosphine oxides have received little attention so far, despite their easy accessibility from the corresponding phosphines, and their promising results as organocatalysts in polyhalosilane-mediated reactions.[14,15]

In this article, we describe the synthesis, characterisation, and resolution of three tertiary diphosphine oxides (±)-**2a**–**c** based on the 7-TH skeleton; the target molecules were characterised by substituents on the phosphorus atoms featuring different electronic and steric properties. The first study on the use of **2a**–**c** as chiral Lewis base organocatalysts in $SiCl_4$- or $HSiCl_3$-mediated aldol-type reactions and ketoimine reduction is also reported.

## Results and Discussion

Based on our previous experience on the selective functionalisation of 7-TH systems,[7d,10b–10e] the introduction of dialkyl or diaryl-substituted phosphinic groups in both the 2- and 13-positions of the helicene (±)-**1**, to prepare phosphine oxides (±)-**2a**–**c**, was easily accomplished by deprotonation of the alpha positions of the terminal thiophene rings of **1** with BuLi, and reaction with a suitable electrophile. Following this general procedure, phosphine oxide (±)-**2a** was prepared by reacting the dianion, generated from **1** with 4 equiv. *t*BuLi, with 4 equiv. of the commercially available diphenylchlorophosphine oxide $Ph_2POCl$ in tetrahydrofuran (THF) at –78 °C (Scheme 1).

After 5 h at room temperature, the reaction mixture did not contain the starting helicene (±)-**1**, and the expected product (±)-**2a** was isolated in 70% yield after chromatographic purification.

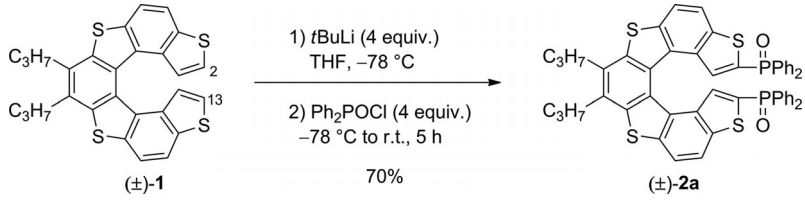
Because chlorophosphine oxides $[3,5\text{-}(Me)_2C_6H_3]_2POCl$ and $(C_6H_{11})_2POCl$, necessary to prepare (±)-**2b** and (±)-**2c**, respectively, are not commercially available, the first synthetic approach explored was the oxidation, with $H_2O_2$, of phosphines (±)-**3b** and (±)-**3c**. These were, in turn, obtained by reacting (±)-**1** with 4 equiv. *n*BuLi and 4 equiv. of the commercial chlorophosphines $[3,5\text{-}(Me)_2C_6H_3]_2PCl$ and $(C_6H_{11})_2PCl$ at –78 °C, respectively (Scheme 2).

The crude reaction mixtures so obtained were either directly treated with an aqueous solution of $H_2O_2$ (35%, 10 equiv.) or quickly purified by column chromatography and then treated with $H_2O_2$; however, in both cases, very complex mixtures were obtained, from which (±)-**2b** and (±)-**2c** were isolated in only 10 and 20% yield, respectively (Scheme 2). Thus, to prepare (±)-**2b** and (±)-**2c** we then considered an alternative two-step procedure involving the preparation of phosphines (±)-**3b** and (±)-**3c**, and their transformation in situ into the corresponding stable phosphine–borane complexes (±)-**4b** and (±)-**4c**, as reported for analogous substrates (Scheme 3).[7d]

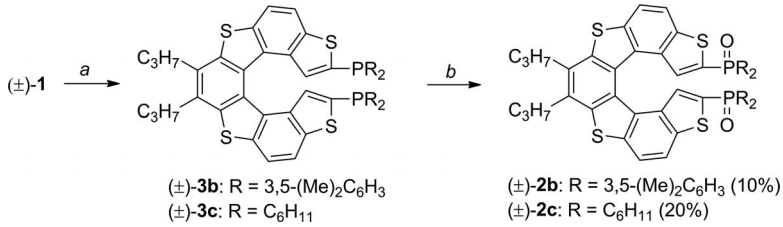
In particular, the reaction of helicene (±)-**1** with 4 equiv. *n*BuLi and 4 equiv. chlorophosphines $[3,5\text{-}(Me)_2C_6H_3]_2PCl$ or $(C_6H_{11})_2PCl$ at –78 °C, followed by the addition of an excess of $BH_3$·THF, provided diborane adducts (±)-**4b** and (±)-**4c** in 50 and 70% yield, respectively.

The borane adducts (±)-**4b** and (±)-**4c** were then converted into phosphine oxides (±)-**2b** and (±)-**2c** by a one-pot reaction involving the deprotection of (±)-**4b**,**c** by heating at reflux in a mixture of EtOH and THF under a nitrogen atmosphere, followed by oxidation in situ of the corresponding free phosphines (±)-**3b**,**c** with an aqueous solution of $H_2O_2$ (35%, 10 equiv.) in toluene at room temperature (Scheme 4).

The oxidation in situ of free phosphines (±)-**3b** and (±)-**3c**, derived from adducts (±)-**4b** and (±)-**4c**, respectively,

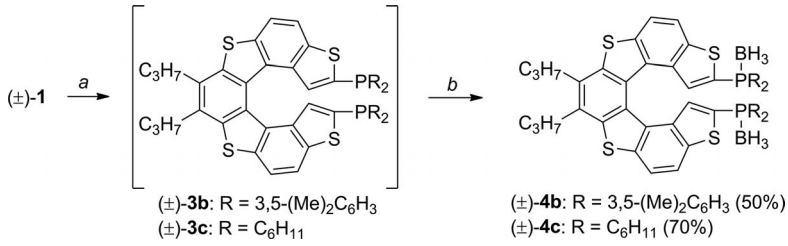



Scheme 1. Synthesis of phosphine oxide (±)-**2a**.

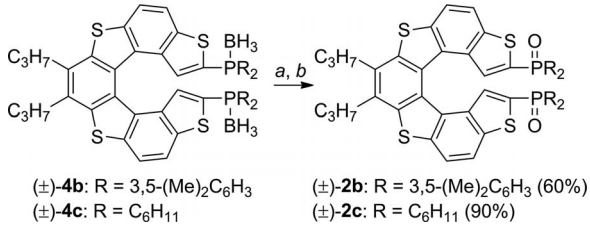



Scheme 2. *Reagents and conditions:* (a) *n*BuLi (4 equiv.), $R_2PCl$ (4 equiv.), THF, –78 °C to r.t., 5 h; (b) $H_2O_2$ (35%, 10 equiv.), toluene, 0 °C to r.t., overnight.




Scheme 3. Synthesis of phosphine–borane adducts (±)-**4b** and (±)-**4c**. *Reagents and conditions:* (a) *n*BuLi (4 equiv.), $R_2PCl$ (4 equiv.), THF, –78 °C to r.t., 5 h. (b) $BH_3$·THF (1 M in THF, 10 equiv.), 0 °C to r.t., 48 h.




Scheme 4. Synthesis of phosphine oxides (±)-**2b** and (±)-**2c**. *Reagents and conditions:* (a) EtOH, THF, reflux, 5–24 h. (b) $H_2O_2$ (35%, 10 equiv.), toluene, 0 °C to r.t., overnight.

provided phosphine oxides (±)-**2b** and (±)-**2c** in good yield (60–90%).

It should be noted that the two-step procedure described above, due to the formation of adducts (±)-**4b**,**c** followed by the removal of the borane moiety and oxidation of phosphines (±)-**3b**,**c** in situ, is much more efficient than the procedure described in Scheme 2. This useful protection-deprotection methodology is an example of the participation of a protective group in rendering the experimental procedure easier, and allows better results to be obtained.

Both phosphine oxides (±)-**2a**–**c** and phosphine–borane adducts (±)-**4b** and (±)-**4c** were isolated as yellow solids after chromatographic purification, and fully characterised by standard analytical and spectroscopic methods. The most relevant feature of adducts (±)-**4b**,**c** and phosphine oxides (±)-**2a**–**c** was observed in their $^{31}P\{^1H\}$ NMR spectra. Whereas the spectra of borane adducts (±)-**4b** and (±)-**4c** displayed one broad signal at +14 and +26 ppm, respectively, the $^{31}P\{^1H\}$ NMR spectra of phosphine oxides (±)-**2a**–**c** showed sharp singlets, ranging from +44 ppm for the dialkyl-substituted (±)-**2c** to +23 ppm for the diaryl-substituted (±)-**2a**,**b**, which are values consistent with those found in similar tertiary phosphine–borane adducts and tertiary phosphine oxides.

In view of the utilisation of enantiopure phosphine oxides **2a**–**c** in asymmetric organocatalysis, we then focused our attention on their resolution into the corresponding optically pure **2a**–**c** antipodes. To this end, we first investigated the resolution of diastereomeric salts obtained from the reaction with camphorsulfonic and tartaric acid derivatives, as chiral resolving agents, which were successfully applied to the resolution of BINAP and related $C_2$-symmetric diphosphine oxides.[16] Unfortunately, all attempts at fractional crystallisation of the diastereomeric salts obtained from (±)-**2a**–**c** with enantiopure dibenzoyl-tartaric acid (DBTA) and di-*p*-tolyl-tartaric acid (DPTTA) failed. However, an alternative resolution method involving HPLC separation on chiral stationary phase was successful. The direct resolution of (±)-**2a**–**c** using a chiral semipreparative column (Chiralpack IA) packed with amylose tris(3,5-dimethylphenylcarbamate) was achieved when an appropriate mixture of solvents was used as the mobile phase (Table 1).

For diaryl-substituted phosphine oxides **2a** and **2b**, the earlier eluting fractions consisted of the enantiomers exhibiting a positive optical rotation, which were isolated in 60–98% yield (up to 98% *ee*), whereas for dialkyl-substituted phosphine oxide **2c**, the earlier eluting fractions contained the enantiomer with negative optical rotation, which was isolated in 90% yield (98% *ee*). Later eluting fractions gave oxides (–)-**2a**, (–)-**2b** and (+)-**2c** in 40–97% yield (90–98% *ee*). The specific rotation values obtained for both enantiomers of **2a**–**c** were found to be very high (up to 1100), in agreement with the known feature of helical structures.

Because neither of the two enantiomers of (±)-**2a**–**c** afforded crystals that were suitable for the determination of

Table 1. Chiral HPLC resolution of phosphine oxides (±)-**2a**–**c**.

| | Eluent | $t_R$ [min] | $[\alpha]_D$[a] | Yield [%] | *ee* [%] |
|---|---|---|---|---|---|
| (+)-**2a** | hexane/*i*PrOH/EtOAc (45:40:15) | 16.5 | +1006[b] | 98 | 99 |
| (–)-**2a** | hexane/*i*PrOH/EtOAc (45:40:15) | 22.9 | –1001[b] | 97 | 98 |
| (+)-**2b** | hexane/*i*PrOH (80:20) | 11.2 | +1084[c] | 60 | 96 |
| (–)-**2b** | hexane/*i*PrOH (80:20) | 14.5 | –1024[c] | 40 | 90 |
| (–)-**2c** | hexane/*i*PrOH/EtOAc (70:15:15) | 10.8 | –1166[d] | 90 | 98 |
| (+)-**2c** | hexane/*i*PrOH/EtOAc (70:15:15) | 17.9 | +1077[d] | 80 | 92 |

[a] Recorded in $CHCl_3$ at 20 °C. [b] $c$ = 0.55 g/100 mL. [c] $c$ = 0.12 g/100 mL. [d] $c$ = 0.10 g/100 mL.

their structure by X-ray diffraction, we assigned the absolute configuration of both antipodes on the basis of their circular dichroism (CD) spectra. In particular, the chiroptical properties of phosphine oxide (±)-**2a**, which was selected as model 7-TH diphosphine oxide, have been investigated; the CD spectra of (+)-**2a** and (–)-**2a** are reported in Figure 2.

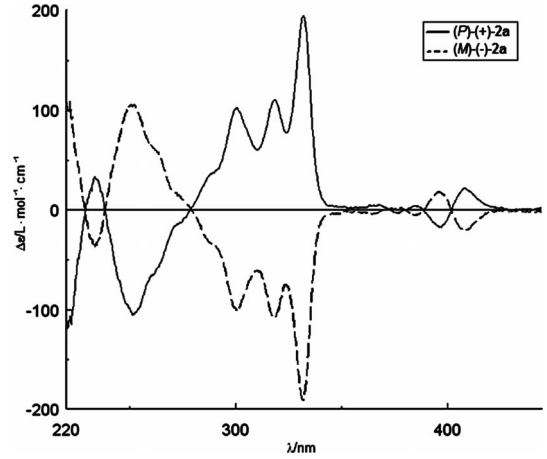



Figure 2. CD spectra of (—) (*P*)-(+)-**2a** ($CHCl_3$, $c = 10^{-5}$ M), and (- - -) (*M*)-(–)-**2a** ($CHCl_3$, $c = 10^{-5}$ M).

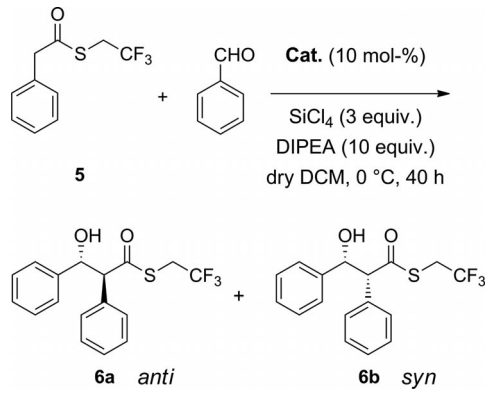
As expected, enantiomers (+)-**2a** and (–)-**2a** give mirror image spectra, and possess both spectral envelopes and absorbances analogous to typical conjugated helicenes, including the two intense bands at 250 and 335 nm, which are the fingerprint of helicene derivatives.[17] In particular, (+)-**2a**, with a positive value of $[\alpha]_D$, displayed two strong bisignate negative and positive Cotton effect (CE) peaks around 240–280 nm and 280–340 nm, respectively. These CD spectral characteristics are in good agreement with those of known (*P*)-helicenes, so the absolute configuration of (+)-**2a** is *P* (right-handed helix), then the absolute configuration of (–)-**2a** is *M* (left-handed helix). Likewise, the configuration of (+)-**2b** and (+)-**2c** is *P*, and the absolute configuration of (–)-**2b** and (–)-**2c** is *M*.

The catalytic behaviour of the helical chiral Lewis bases **2a**–**c** was next investigated in $SiCl_4$-mediated reactions, involving the formation of hypervalent cationic silicon species.[18] The direct addition of the activated thioester **5** to benzaldehyde, in the presence of a stoichiometric amount of tetrachlorosilane was first studied (Table 2).[15a]

The condensation of thioester **5** (2 equiv.) with benzaldehyde (1 equiv.) in the presence of silicon tetrachloride (3 equiv.), DIPEA (10 equiv.), and racemic phosphine oxide (±)-**2a** (10 mol-%) in $CH_2Cl_2$ at 0 °C afforded the corresponding β-hydroxytrifluoroethyl thioester **6** in 85% yield after 40 hours (Table 2, entry 1). The product was isolated almost entirely as a single diastereoisomer (*dr* 92:8).

When the enantiomerically pure catalyst (+)-**2a** was employed, product **6** was isolated in good yield (71%), comparable diastereoselectivity (*syn*/*anti* = 88:12), and low enantioselectivity (Table 2, entry 2). Unfortunately, at lower

Table 2. Stereoselective addition of thioester **5** to benzaldehyde.[a]




| Entry | Cat. | Yield [%][b] | *syn*/*anti* ratio[c] | *ee syn* (*ee anti*) [%][d] |
|---|---|---|---|---|
| 1 | (±)-**2a** | 85 | 92:8 | – |
| 2 | (+)-**2a** | 71 | 88:12 | 12 (n.d.) |
| 3[e] | (+)-**2a** | n.r. | – | – |
| 4 | (±)-**2b** | 75 | 87:13 | – |
| 5 | (+)-**2b** | 87 | 92:8 | 23 (n.d.) |
| 6 | (+)-**2c** | < 5 | – | – |
| 7[f] | (–)-BINAPO | 35 | 97:3 | 81 (n.d.) |

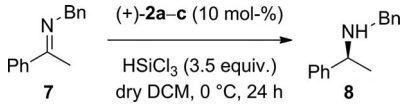
[a] Reaction conditions: benzaldehyde (0.5 mmol), **5** (1 mmol), anhydrous $CH_2Cl_2$, 0 °C, 40 h; n.r.: no reaction, n.d.: not determined. [b] Isolated yield. [c] Evaluated by $^1$H NMR analysis of the crude reaction mixture. [d] Evaluated by chiral HPLC analysis of the isolated product. [e] Reaction run at –40 °C. [f] Literature data,[15a] BINAPO [bis(diphenylphosphanyl)binaphthyl dioxide].

reaction temperature (–40 °C), the reaction did not proceed to a significant extent (Table 2, entry 3).[19] Whereas catalyst (+)-**2c** did not promote the transformation (Table 2, entry 6), probably because steric hindrance of the cyclohexyl moieties prevented $SiCl_4$ complexation (see theoretical studies below), racemic phosphine oxide (±)-**2b**, bearing 3,5-dimethylphenyl rings at the phosphorus atoms, provided product **6** in 75% yield and good diastereoselectivity (Table 2, entry 4). With enantiopure catalyst (+)-**2b**, although only a marginal improvement in the enantioselectivity was observed [Table 2, entries 2 and 5; 12% *ee* with catalyst (+)-**2a** vs. 23% *ee* with catalyst (+)-**2b**], **6** was obtained in high yield and excellent *syn* selectivity (Table 2, entry 5).[20] For comparison, with respect to phosphine oxides (+)-**2a** and (+)-**2b**, commonly used (–)-BINAPO catalysed the reaction under the same reaction conditions in a significantly lower chemical yield, comparable *syn*/*anti* diastereoselectivity, but higher enantioselectivity (compare Table 2, entries 2 and 5 with entry 7).[15a]

Chiral phosphine oxides (+)-**2a**–**c** were also tested in two other reactions in the presence of trichlorosilane.[22] The catalytic efficiency of these new organocatalysts were evaluated in the stereoselective reduction of *N*-benzyl imine **7**. By performing the reaction in anhydrous $CH_2Cl_2$ at 0 °C with catalyst (+)-**2a**, the corresponding chiral amine **8** was produced in 43% yield and 22% enantioselectivity (Scheme 5).

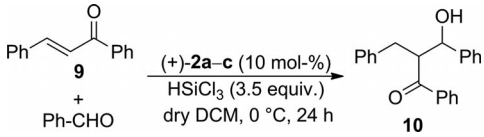
Finally, organocatalysts (+)-**2a**–**c** were also employed in the reductive aldol reaction between benzaldehyde and the




Scheme 5. $HSiCl_3$-mediated stereoselective reduction of imine **7**.

α,β-unsaturated ketone **9**, specifically the *trans* chalcone, in the presence of trichlorosilane (Scheme 6). In this case the best results were also obtained by using the catalyst (+)-**2a**, which gave the product **10** in 40% yield, excellent diastereoselectivity (*syn*/*anti*, 94:6), but low enantioselectivity.




Scheme 6. $HSiCl_3$-mediated stereoselective reductive aldol reaction.

Very preliminary theoretical studies were also performed to elucidate the complexation behaviour of the helical 7-TH phosphine oxides. A conformational analysis with Monte Carlo techniques was performed with the MMFF force field[21] on the two 7-TH phosphine oxides **2a** and **2c**, and on their silicon tetrachloride complexes $ASiCl_4$ and $BSiCl_4$, respectively.

The global minimum energy structures were, in a second stage, optimised with DFT methods at the B3LYP/6-31G(d,p) level of theory (Figure 3). More detailed energy values were obtained by performing single-point calculations on these structures at the B3LYP/6-311G(2df,2pd) level.[22] The complexation energy to form the silicon tetrachloride complex of the two chiral bases was calculated[23] to give values of 12.8 and 17.7 kcal/mol for **2a** and **2c**, respectively. Although **2c** is expected to be a stronger Lewis base than **2a**, calculations show a difference in the complexation energy of 4.9 kcal/mol in favour of **2a**. This is probably due to the steric hindrance of the four cyclohexyl groups, which frustrates $SiCl_4$ coordination to the ligand and prevents formation of the hypervalent silicon specie $BSiCl_4$. In this context, the theoretical calculation may explain the experimentally observed very poor catalytic activity of **2c** in the addition of thioester **5** to benzaldehyde (Table 1, entry 6). Although the high diastereoselectivity depends on the mechanism of the aldol reaction (for details see ref. [15a]), more studies are needed to investigate the mechanism further and to attempt a rationalisation of the observed enantioselectivity. As a working hypothesis, a close inspection of the $SiCl_4$ complexes with helical phosphine oxides seems to suggest that low *ee* values are probably due to large chiral cavities around silicon atom, with the phosphine aryl groups being too far from the catalytic centre to efficiently control the stereochemistry of the reaction.

## Conclusions

The synthesis of new chiral tetrathiahelicene-based tertiary diphosphine oxides **2b** and **2c** was accomplished by the introduction of appropriate phosphinic groups to both the 2- and 13-positions of helicene (±)-**1**. Phosphine oxides (±)-**2a**–**c** were characterised in detail, resolved into their optical antipodes by chiral HPLC, and the chiroptical properties of both enantiomers of **2a** were investigated by CD spectroscopy. The catalytic behaviour of the enantiopure diphosphine oxides **2a**–**c** as Lewis bases was preliminarily investigated, for the first time, in both $SiCl_4$-mediated reactions and stereoselective reductions with trichlorosilane. Although the reaction products were obtained with modest enantioselectivity, the 7-TH phosphine oxides **2a**–**c** were found to be chemically active organocatalysts, affording the products with good chemical yield, and in some cases excellent diastereoselectivity. Although further studies are necessary to understand the origins of the stereoselection and to optimise the catalyst performance, the preliminary data described in this work represent a useful starting point for further development of a new and unexplored class of chiral organocatalysts.

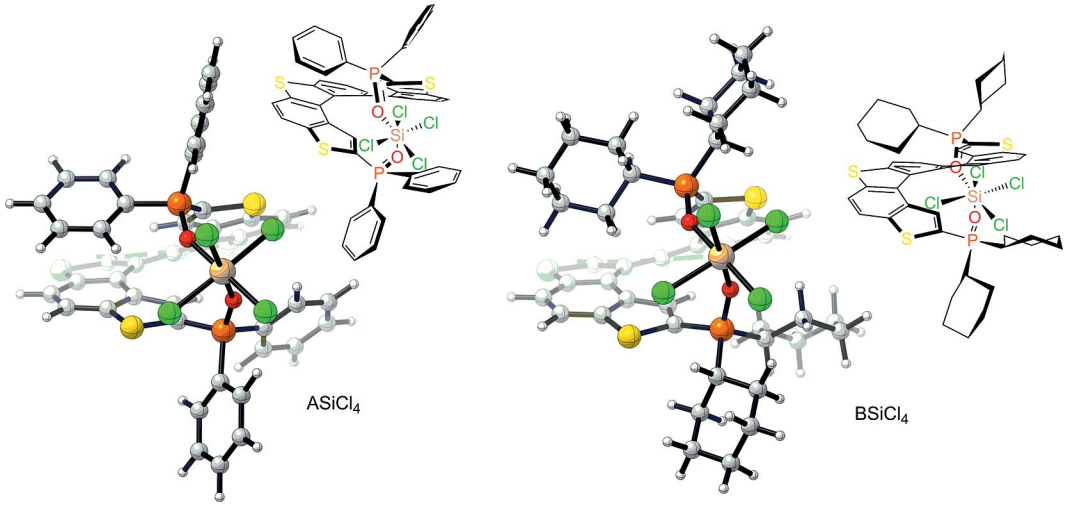



Figure 3. Calculated $SiCl_4$ complexes $ASiCl_4$ and $BSiCl_4$ of 7-TH phosphine oxides **2a** and **2c**, respectively.

## Experimental Section

**General:** Unless otherwise stated, all reactions were run under an inert atmosphere by means of standard Schlenk and vacuum-line techniques in flame-dried glassware. Commercial reagents and anhydrous solvents (DMSO, $CH_2Cl_2$, THF) were used as supplied. $Ph_2POCl$, $(C_6H_{11})_2PCl$ and $[3,5\text{-}(Me)_2C_6H_3]_2PCl$ were purchased from Aldrich. Solutions of *n*BuLi (1.6 M in hexane) were purchased and titrated prior to use. Tetrathiahelicene (±)-**1**,[10d] thioester **5**,[15a,15e] and *N*-benzyl-1-phenylethanimine (**7**)[15a,15e] were prepared as described in the literature. Reactions were monitored by thin-layer chromatography (TLC) on Merck precoated plates (silica gel 60 F254). Column chromatography was carried out on silica gel SI 60 (Merck, Germany), 0.063–0.200 mm (normal) or 0.040–0.063 mm (flash). Melting points were determined with a capillary melting-point apparatus (Büchi SMP-20) and are uncorrected. $^1H$ (300 MHz), $^{13}C$ (75 MHz), $^{19}F$ (282 MHz) and $^{31}P$ (121 MHz) NMR spectra were recorded with a Bruker AC 300 or a Bruker AMX 300 spectrometer (δ in ppm; *J* in Hz). Chemical shifts are reported relative to residual protonated solvent resonances ($^1H$ and $^{13}C$), external standards $CFCl_3$ ($^{19}F$), or $H_3PO_4$ ($^{31}P$). Infrared spectra (4000–400 $cm^{-1}$) were recorded with a Perkin–Elmer FTIR 1725X spectrophotometer. High-resolution electrospray ionisation (HR-ESI) mass spectra were recorded with a Bruker Daltonics ICR-FTMS APEX II. An Agilent 1100 series HPLC, equipped with DAD analyser and a chiral semipreparative column (Chiralpack IA; 250 × 10 mm) was used to resolve phosphine oxides (±)-**2a**–**c**.

**7-TH Diphosphine Oxide (±)-2a:** A solution of *t*BuLi (1.7 M in pentane, 1.40 mL, 0.820 mmol, 4 equiv.) was added dropwise to a stirring solution of helicene (±)-**1** (0.205 mmol, 0.100 g) in anhydrous THF (10 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred for 40 min at –78 °C, then the resulting yellow suspension was treated with $Ph_2POCl$ (0.156 mL, 0.820 mmol, 4 equiv.) at –78 °C, and the progress of the reaction was monitored by TLC (hexane/EtOAc, 90:10). After 5 h at –78 °C, the yellow solution was warmed to room temperature, and THF was removed under reduced pressure. The crude material was taken up with 5% aqueous $NaHCO_3$ (20 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were washed with water (2 × 20 mL), dried with $Na_2SO_4$, and the solvents were evaporated under vacuum. The crude product was purified by column chromatography on silica gel (EtOAc) to give (±)-**2a** (0.127 g, 70%) as a pale-yellow solid; m.p. 140–143 °C (hexane/$CH_2Cl_2$). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.86 (m, 4 H), 7.37 (m, 20 H), 6.98 (d, $J_{H,P}$ = 9.0 Hz, 2 H), 3.07 (m, 4 H), 1.83 (m, 4 H), 1.14 (t, *J* = 6.0 Hz, 6 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 141.6 (Cq), 140.3 (Cq), 136.6 (Cq), 134.9 (d, $J_{C,P}$ = 17 Hz, Cq), 133.8 (d, $J_{C,P}$ = 11.2 Hz, CH), 132.7 (2 Cq), 132.3 (CH), 131.9 (CH), 131.6 (d, $J_{C,P}$ = 10.5 Hz, 2 CH), 131.5 (Cq), 131.2 (d, $J_{C,P}$ = 10.5 Hz, 2 CH), 128.4 (d, $J_{C,P}$ = 12.0 Hz, 2 CH), 128.8 (d, $J_{C,P}$ = 13.0 Hz, 2 CH), 127.6 (Cq), 121.3 (CH), 120.9 (CH), 34.3 ($CH_2$), 23.2 ($CH_2$), 14.7 ($CH_3$) ppm. $^{31}P$ NMR (121 MHz, $CDCl_3$): $\delta$ = 23.5 (s) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{52}H_{46}P_2O_2S_4Na$ 909.1279; found 909.1264. The spectral properties of this compound were consistent with those previously reported.[7d]

Compounds (*P*)-(+)-**2a** and (*M*)-(–)-**2a** were obtained in 98 and 97% yield, respectively, by HPLC separation with a mixture of hexane/*i*PrOH/EtOAc (45:40:15) as eluent under isocratic conditions (3 mL/min flow rate): $t_R$ = 16.5 {$[\alpha]_D$ = +1006 (*c* = 0.55, $CHCl_3$), for (*P*)-(+)-**2a**}, 22.9 {$[\alpha]_D$ = –1001 (*c* = 0.55, $CHCl_3$), for (*M*)-(–)-**2a**} min.

**7-TH Diphosphine Oxide (±)-2b:** A solution of phosphine–borane adduct (±)-**4b** (100 mg, 0.1005 mmol) in a mixture of EtOH/THF (2:1, 70 mL) was stirred and heated to reflux under an argon atmosphere, and the progress of the reaction was monitored by $^{31}P$ NMR analysis. After 5 h, the yellow solution was cooled to room temperature, and the solvents together with triethyl borate as by-product were removed under reduced pressure at 50 °C for 2 h. The yellow solid was dissolved in degassed toluene (10 mL), and to the resulting solution was added dropwise an aqueous solution of $H_2O_2$ (35% w/w, 0.113 mL, 1.005 mmol, 10 equiv.) at 0 °C under an argon atmosphere. The mixture was stirred overnight at room temperature, then diluted with $H_2O$ (15 mL). The aqueous phase was extracted with toluene (3 × 20 mL), and the combined organic layers were dried with $Na_2SO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:9 to 0:10) to give (±)-**2b** (60.3 mg, 60%) as a yellow solid, m.p. 132–135 °C (hexane). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 7.85 (d, *J* = 8.6 Hz, 2 H), 7.68 (d, *J* = 8.6 Hz, 2 H), 6.98 (m, 14 H), 3.10 (m, 4 H), 2.27 (s, 12 H), 2.22 (s, 12 H), 1.86 (m, 4 H), 1.17 (t, *J* = 7.3 Hz, 6 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 141.6 (d, $J_{C,P}$ = 5.1 Hz, Cq), 140.2 (Cq), 138.1 (d, $J_{C,P}$ = 13.4 Hz, 2 Cq), 138.0 (d, $J_{C,P}$ = 13.3 Hz, 2 Cq), 136.3 (Cq), 134.9 (d, $J_{C,P}$ = 13.7 Hz, Cq), 134.2 (CH), 133.9 (CH), 133.7 (d, $J_{C,P}$ = 10.4 Hz, CH), 133.1 (d, $J_{C,P}$ = 53.2 Hz, Cq), 132.7 (Cq), 132.4 (d, $J_{C,P}$ = 52.5 Hz, Cq), 131.5 (Cq), 131.3 (d, $J_{C,P}$ = 104.2 Hz, Cq), 129.3 (d, $J_{C,P}$ = 10.4 Hz, 2 CH), 129.0 (d, $J_{C,P}$ = 10.4 Hz, 2 CH), 128.0 (Cq), 121.2 (CH), 120.1 (CH), 34.5 ($CH_2$), 23.4 ($CH_2$), 21.5 ($CH_3$), 21.4 ($CH_3$), 14.8 ($CH_3$) ppm. $^{31}P$ NMR (121 MHz, $CDCl_3$): $\delta$ = 23.3 (s) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{60}H_{56}S_4P_2O_2Na$ 1021.2531; found 1021.2530.

Compounds (*P*)-(+)-**2b** and (*M*)-(–)-**2b** were obtained in 60 and 40% yield, respectively, by HPLC separation with a mixture of hexane/*i*PrOH (80:20) as eluent under isocratic conditions (3 mL/min flow rate): $t_R$ = 11.2 {$[\alpha]_D$ = +1084 (*c* = 0.12, $CHCl_3$), for (*P*)-(+)-**2b**}, 14.5 {$[\alpha]_D$ = –1024 (*c* = 0.12, $CHCl_3$), for (*M*)-(–)-**2b**} ppm.

**7-TH Diphosphine Oxide (±)-2c:** A solution of phosphine–borane adduct (±)-**4c** (120 mg, 0.132 mmol) in a mixture of EtOH/THF (9:1, 70 mL) was stirred and heated to reflux under an argon atmosphere, and the progress of the reaction was monitored by $^{31}P$ NMR analysis. After 24 h, the yellow solution was cooled to room temperature, and the solvents together with triethyl borate as by-product were removed under reduced pressure at 50 °C for 2 h. The yellow solid was dissolved in degassed toluene (10 mL), and to the resulting solution was added dropwise an aqueous solution of $H_2O_2$ (35% w/w, 0.14 mL, 1.32 mmol, 10 equiv.) at 0 °C under an argon atmosphere. The mixture was stirred overnight at room temperature, then diluted with $H_2O$ (15 mL). The aqueous phase was extracted with toluene (3 × 20 mL), and the combined organic layers were dried with $Na_2SO_4$ and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:9 to 0:10) to give (±)-**2c** (110 mg, 90%) as a pale-yellow solid, m.p. 140–141 °C (hexane). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 8.01 (m, 4 H), 7.21 (d, $J_{H,P}$ = 6.6 Hz, 2 H), 3.11 (m, 4 H), 1.90 (m, 4 H), 1.59 (m, 20 H), 1.08 (m, 30 H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ = 141.2 (d, $J_{C,P}$ = 3.8 Hz, Cq), 140.4 (Cq), 137.0 (Cq), 136.0 (d, $J_{C,P}$ = 12.0 Hz, Cq), 132.8 (Cq), 132.1 (Cq), 132.0 (d, $J_{C,P}$ = 83.7 Hz, Cq), 131.6 (d, $J_{C,P}$ = 7.3 Hz, CH), 128.0 (Cq), 121.0 (CH), 120.8 (CH), 37.1 (d, $J_{C,P}$ = 31.6 Hz, CH), 36.2 (d, $J_{C,P}$ = 31.4 Hz, CH), 34.7 ($CH_2$), 26.7 ($CH_2$), 26.6 ($CH_2$), 26.5 ($CH_2$), 26.4 ($CH_2$), 26.3 ($CH_2$), 25.8 ($CH_2$), 25.3 ($CH_2$), 24.8 ($CH_2$), 24.73 ($CH_2$), 24.70 ($CH_2$), 24.6 ($CH_2$), 23.5 ($CH_2$), 14.8 ($CH_3$) ppm. $^{31}P$ NMR (121 MHz, $CDCl_3$): $\delta$ = 44.5 (s) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{52}H_{64}S_4P_2O_2Na$ 933.3156; found 933.3158.

Compounds (*P*)-(+)-**2c** and (*M*)-(–)-**2c** were obtained in 80 and 90% yield, respectively, by HPLC separation with a mixture of hexane/*i*PrOH/AcOEt (70:15:15) as eluent under isocratic conditions (3 mL/min flow rate): $t_R$ = 10.8 {$[\alpha]_D$ = –1166 (*c* = 0.10, $CHCl_3$), for (*M*)-(–)-**2c**}, 17.9 {$[\alpha]_D$ = +1077 (*c* = 0.10, $CHCl_3$), for (*P*)-(+)-**2c**} ppm.

**7-TH Phosphine–Borane Adduct (±)-4b:** A solution of *n*BuLi (1.6 M in hexane, 1.03 mL, 1.643 mmol, 4 equiv.) was added dropwise to a stirring solution of (±)-**1** (0.200 g, 0.411 mmol) in anhydrous THF (15 mL) at –78 °C under a nitrogen atmosphere. The solution was stirred for 30 min at –78 °C and 30 min at room temperature. The resulting yellow suspension was cooled to 0 °C, and treated with $[3,5\text{-}(Me)_2C_6H_3]_2PCl$ (0.412 mL, 1.643 mmol; 4 equiv.). After 10 min at 0 °C, the solution was warmed to room temperature and the progress of the reaction was monitored by TLC (hexane/$CH_2Cl_2$, 1:1). After 8 h, the yellow solution was cooled to 0 °C, and treated with a solution of $BH_3$·THF (1 M in THF, 16.4 mL, 16.4 mmol, 10 equiv.). The suspension was stirred for 30 min at 0 °C, then for 48 h at room temperature. A saturated aqueous solution of $NH_4Cl$ (20 mL) was then slowly added to the final reaction mixture at 0 °C, and the aqueous phase was extracted with $CH_2Cl_2$ (3× 15 mL). The organic layers were washed with water (2× 20 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/$CH_2Cl_2$, 7:3 to 1:1) to give (±)-**4b** (0.204 g, 50%) as a pale-yellow solid, m.p. 250 °C (dec.). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.90 (d, *J* = 8.6 Hz, 2 H), 7.79 (d, *J* = 8.6 Hz, 2 H), 7.18 (d, *J* = 7.8 Hz, 2 H), 6.95 (m, 12 H), 3.10 (m, 4 H), 2.23 (s, 12 H), 2.15 (s, 12 H), 1.86 (m, 4 H), 1.16 (t, *J* = 7.3 Hz, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 142.3 (d, $J_{C,P}$ = 3.3 Hz, Cq), 140.0 (Cq), 138.3 (d, $J_{C,P}$ = 11.1 Hz, 2 Cq), 137.9 (d, $J_{C,P}$ = 11.1 Hz, 2 Cq), 136.2 (Cq), 135.4 (d, $J_{C,P}$ = 11.4 Hz, Cq), 134.6 (d, $J_{C,P}$ = 9.7 Hz, CH), 133.3 (d, $J_{C,P}$ = 2.2 Hz, CH), 133.2 (d, $J_{C,P}$ = 2.2 Hz, CH), 132.5 (Cq), 131.4 (Cq), 130.5 (d, $J_{C,P}$ = 10.2 Hz, 2 CH), 130.15 (d, $J_{C,P}$ = 56.3 Hz, Cq), 130.13 (d, $J_{C,P}$ = 10.2 Hz, 2 CH), 129.5 (d, $J_{C,P}$ = 59.5 Hz, Cq), 128.6 (d, $J_{C,P}$ = 58.1 Hz, Cq), 128.1 (Cq), 121.3 (CH), 120.0 (CH), 34.5 ($CH_2$), 25.3 ($CH_2$), 21.5 (2 $CH_3$), 14.9 ($CH_3$) ppm. $^{31}$P NMR (121 MHz, $CDCl_3$): $\delta$ = 14.7 (br. s) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{60}H_{62}P_2B_2S_4Na$ 1017.3318; found 1017.3324.

**7-TH Phosphine–Borane Adduct (±)-4c:** A solution of *n*BuLi (1.45 M in hexane, 0.56 mL, 0.820 mmol, 4 equiv.) was added dropwise to a stirring solution of (±)-**1** (0.100 g, 0.205 mmol) in anhydrous THF (10 mL) at –78 °C under an argon atmosphere. The solution was stirred for 30 min at –78 °C and then treated with $(C_6H_{11})_2PCl$ (0.181 mL, 0.820 mmol; 4 equiv.). After 10 min at –78 °C, the solution was warmed to room temperature and the progress of the reaction was monitored by TLC (hexane/$CH_2Cl_2$, 1:1). After 5 h, the yellow solution was cooled to 0 °C and treated with a solution of $BH_3$·THF (1 M in THF, 2 mL, 2.05 mmol, 10 equiv.). The suspension was stirred for 30 min at 0 °C, then for 48 h at room temperature. A saturated aqueous solution of $NH_4Cl$ (20 mL) was then slowly added to the final reaction mixture at 0 °C, and the aqueous phase was extracted with $CH_2Cl_2$ (3× 10 mL). The organic layers were washed with water (2× 10 mL), dried with $Na_2SO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane/$CH_2Cl_2$, 7:3 to 1:1) to give (±)-**4c** (0.130 g, 70%) as a pale-yellow solid, m.p. 263 °C (dec.). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 8.02 (m, 4 H), 7.30 (d, $J_{H,P}$ = 7.1 Hz, 2 H), 3.12 (m, 4 H), 1.81 (m, 24 H), 1.10 (m, 30 H), 0.15 (m, 6 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 141.8 (Cq), 140.2 (Cq), 136.8 (Cq), 135.7 (d, $J_{C,P}$ = 10.5 Hz, Cq), 134.9 (d, $J_{C,P}$ = 8.1 Hz, CH), 132.7 (Cq), 131.7 (Cq), 128.0 (Cq), 126.6 (d, $J_{C,P}$ = 42.3 Hz, Cq), 121.2 (CH), 120.7 (CH), 34.5 ($CH_2$), 32.7 (d, $J_{C,P}$ = 35.0 Hz, CH), 32.3 (d, $J_{C,P}$ = 35.0 Hz, CH), 27.0 ($CH_2$), 26.8 ($CH_2$), 26.7 ($CH_2$), 26.5 ($CH_2$), 26.3 ($CH_2$), 26.2 ($CH_2$), 26.11 ($CH_2$), 26.09 ($CH_2$), 25.8 ($CH_2$), 23.5 ($CH_2$), 14.9 ($CH_3$) ppm. $^{31}$P NMR (121 MHz, $CDCl_3$): $\delta$ = 25.7 (br., s) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{52}H_{70}S_4P_2B_2Na$ 929.3914; found 929.3923.

**General Procedure of the Direct Aldol Condensation of Thioester 5 with Benzaldehyde:** To a stirred solution of catalyst **2a**–**c** (10 or 20 mol-%) in anhydrous $CH_2Cl_2$ (2 mL), thioester **5** (1 mmol, 2 equiv.) and diisopropylethylamine (5 mmol, 10 equiv.) were added. The mixture was then cooled to the chosen temperature and freshly distilled tetrachlorosilane (0.75 mmol, 1.5 equiv.) was added dropwise by using a syringe. After 15 min, freshly distilled benzaldehyde (0.50 mmol, 1 equiv.) was added and the mixture was stirred for 5 h, then the same amount of tetrachlorosilane (0.75 mmol, 1.5 equiv.) was added. After 40 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL). The mixture was warmed to room temperature and stirred for 30 min, then water (5 mL) and ethyl acetate (15 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (15 mL). The combined organic layers were washed with saturated aq. $NH_4Cl$ (20 mL) and brine (20 mL), dried with $Na_2SO_4$, filtered, and concentrated under vacuum at room temperature. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc, 8:2) to afford the pure aldol adduct **6** {$R_f$ = 0.62 (hexane/EtOAc,8:1; stained blue with phosphomolibdic acid for **6b**); $R_f$ = 0.58 (hexane/EtOAc, 8:2; stained blue with phosphomolibdic acid for **6a**)}, yields and *ee* for each reaction are indicated in Table 2. The *syn*/*anti* ratio was determined by $^1$H NMR spectroscopic analysis of the crude product; the enantiomeric excess was determined by HPLC analysis on a chiral stationary phase. The chiral phosphine oxide was quantitatively recovered by further elution with 10% MeOH in $CH_2Cl_2$.

***anti*-Aldol Adduct 6a:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.36 (s, 5 H), 7.30 (s, 5 H), 5.35 (d, *J* = 10.0 Hz, 1 H), 4.12 (d, *J* = 4.8 Hz, 1 H), 3.70–3.55 (m, 2 H), 2.20 (br. s, 1 H) ppm.

***syn*-Aldol Adduct 6b:** $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.37 (s, 5 H), 7.31 (s, 5 H), 5.40 (d, *J* = 9.0 Hz, 1 H), 4.10 (d, *J* = 7.5 Hz, 1 H), 3.38 (m, 2 H), 2.37 (br. s, 1 H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 195.4, 140.3, 133.6, 129.4, 128.9, 128.5, 128.4, 126.6, 126.9 (q, $J_{C,F}$ = 264.7 Hz), 75.0, 68.2, 30.7 (q, $J_{C,F}$ = 33.7 Hz) ppm. HRMS (ESI): *m*/*z* calcd. for $C_{17}H_{15}F_3O_2SNa^+$ 363.0637; found 363.0633. The enantiomeric excess of **6b** was determined by chiral HPLC with Daicel Chiralcel AD column [hexane/*i*PrOH, 9:1; 0.8 mL/min; detection: 230 nm; $t_R$ = 14.3, 16.5, 20.4, 24.7 min].

**General Procedure for the Reduction of Ketoimine 7:** To a stirred solution of catalyst (+)-**2a**–**c** (0.05 mmol, 10 mol-%) in $CH_2Cl_2$ (2 mL), imine **7** (0.50 mmol, 1 equiv.) was added. The mixture was then cooled to 0 °C and trichlorosilane (1.75 mmol, 3.5 equiv.) was added dropwise by using a syringe. After stirring at this temperature for 24 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (1 mL). The mixture was warmed to room temperature and water (2 mL) and $CH_2Cl_2$ (5 mL) were added. The organic phase was separated and the combined organic phases were dried with $Na_2SO_4$, filtered, and concentrated under vacuum at room temperature to afford the crude product, which was purified by column chromatography (hexane/EtOAc, 8:2) to afford pure *N*-benzyl-1-phenylethanamine **8**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.31 (m, 10 H), 3.82 (q, *J* = 6.6 Hz, 1 H), 3.67 (d, *J* = 13.1 Hz, 1 H), 3.60 (d, *J* = 13.1 Hz, 1 H), 1.57 (br. s, 1 H), 1.37 (d, *J* = 6.6 Hz, 3 H) ppm. The enantiomeric excess of **8** was determined by chiral

HPLC analysis with a Daicel Chiralcel OD-H column (hexane/*i*PrOH, 99:1; 0.8 mL/min; detection: 210 nm; $t_R$ = 7.1, 7.6 min).

**General Procedure for Reductive Aldol Reaction of Chalcone 9 with Benzaldehyde:** A stirred solution of catalyst (+)-**2a**–**c** (0.05 mmol, 10 mol-%) and *trans*-chalcone **9** (0.5 mmol, 1 equiv.) in $CH_2Cl_2$ (2 mL) was cooled to 0 °C and freshly distilled trichlorosilane (1.75 mmol, 3.5 equiv.) was added dropwise by using a syringe. After 15 min, freshly distilled benzaldehyde (0.60 mmol, 1.2 equiv.) was added. After 24 h, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL), then the mixture was warmed to room temperature and stirred for 30 min. After filtration through a Celite pad, the aqueous layer was extracted with EtOAc (2× 30 mL) and the combined organic layers were successively washed with 15% HCl (3× 20 mL), water (20 mL), saturated aq. $NaHCO_3$ (20 mL), brine (20 mL), and dried with $Na_2SO_4$. After filtration and evaporation, the obtained crude product was purified by column chromatography (hexane/ethyl acetate, 95:5) to furnish the aldol product **10** as a diastereomeric mixture. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7. 67–6.93 (m, 15 H, *syn* + *anti*), 5.12 (d, $J$ = 4.6 Hz, 1 H, *syn*), 4.97 (dd, $J$ = 6.4, 6.9 Hz, 1 H, *anti*), 4.13–4.00 (m, 1 H, *syn* + *anti*), 3.45 (d, $J$ = 6.9 Hz, 1 H, *anti*), 3.26 (br. s, 1 H, *syn*), 3.19 (dd, $J$ = 11.0, 13.7 Hz, 1 H, *syn*), 3.09–3.02 (m, 1 H, *syn* + *anti*), 2.91 (dd, $J$ = 6.4, 13.8 Hz, 1 H, *anti*) ppm. The enantiomeric excess was determined by chiral HPLC analysis with a Daicel Chiralcel OD-H column (hexane/*i*PrOH, 95:5; 1.0 mL/min flow rate; detection: 225 nm; $t_R$ = 14.5, 16.1, 20.0, 22.4 min).

**Supporting Information** (see footnote on the first page of this article): $^1$H, $^{13}$C and $^{31}$P NMR spectra of compounds **2b**, **2c**, **4b**, and **4c**. HPLC analysis for compounds **6**, **8** and **10**.

## Acknowledgments

M. B. and E. L. thank the Ministero dell'Università e della Ricerca (MIUR), Roma, and the University of Milan (UNIMI) within the national project "Nuovi metodi catalitici stereoselettivi e sintesi stereoselettiva di molecole funzionali" (PRIN 2009). M. B. also acknowledges the European COST Action ORCA – CM0905-Organocatalysis. S. C. acknowledges UNIMI for a postdoctoral fellowship. D. D., A. G., and M. O. acknowledge UNIMI for PhD fellowships.

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[20] The use of different stoichiometry in the reaction did not lead to any improvement. For example, with catalyst (+)-**2b**, the direct condensation of thioester **5** (1 or 0.5 equiv.) with benzaldehyde (1 equiv.) afforded product **6** in 60 and 50% yield, respectively, both with *ee* values lower than 15% for the major isomer.

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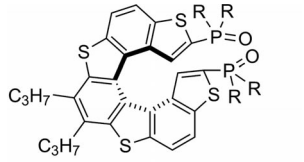
Received: December 23, 2013
Published Online: ■

A novel class of tetrathia[7]helicene-based diphosphine oxides has been synthesised, and their catalytic behaviour as chiral helical phosphorus Lewis bases has been preliminary investigated in organocatalytic reactions.




**Helical Organocatalysts**



**Keywords:** Helical structures / Organocatalysis / Fused-ring systems / Diastereoselectivity / Phosphines