Phosphorus Heterocycles

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# 1*H*-Phosphindoles as Structural Units in the Synthesis of Chiral Helicenes**

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Helical arrangements and the associated chirality have well-known implications in a variety of areas ranging from natural biological systems to materials science. In particular *ortho*-fused polyaromatic systems with π-conjugated helical structures display unique physicochemical properties which have stimulated countless studies[1] oriented towards self-assembly and chiral recognition,[2] chiroptical devices,[3] molecular machines,[4] material chemistry,[5] organometallic and organocatalysis,[6,7] as well as asymmetric synthesis.[8,9]

In the general context of the growing interest in helical derivatives, helicenes displaying phosphorus functions represent promising scaffolds. Trivalent phosphorus functions and the related metal complexes are easily designed to tune the electronic and physicochemical properties of helicenes,[10] as well as to offer a wide range of potential uses in organometallic chemistry and catalysis. It is therefore rather surprising to note that the field today is still in its infancy, first of all in terms of number of compounds as well as structural diversity. So far, most phosphorus derivatives having helical chirality display polyaromatic (or heteroaromatic) helical scaffolds with pendant phosphorus functions (phosphites,[2a,6b,11] trivalent phosphines and phosphine oxides,[6a,12] phospholes,[10a,b] etc.). Very little is known about their properties and behaviors.

The aim of this work is to expand the range of heterohelicenes to chiral helicenes where phosphorus is embedded within the helical framework itself, at the external edge of the fused ring sequence (Figure 1). Helical phosphines of this class would not only display peculiar electronic features resulting from extended π conjugation, but also take full advantage of the dissymmetric steric environment generated by the helical chirality at the external edge. Helicenes of this class are unknown to date, whereas phosphahelicenes, wherein phosphorus is embedded in the internal section of the helical framework, have been reported only recently by Tanaka and co-workers and Nozaki and co-workers.[13]

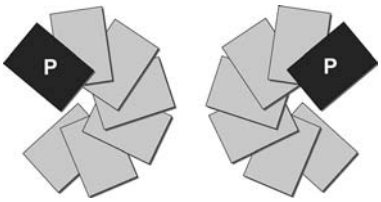
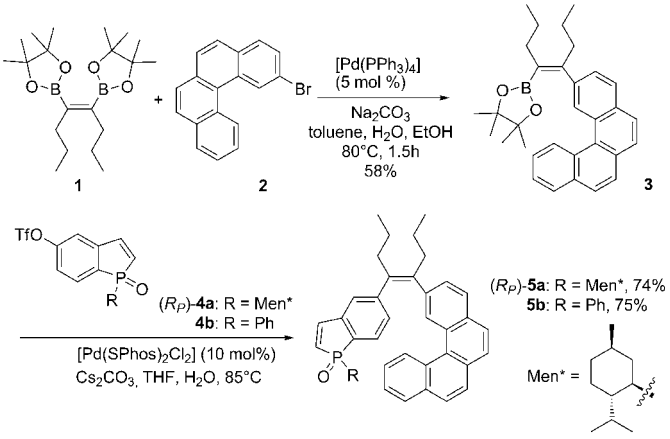



***Figure 1.*** Targeted helical structures: phosphorus heterocycles at the external edge of *ortho*-fused aromatic sequences.

We intend to disclose here: a) the first diastereo- and enantioselective access to [6]- and [7]helicenes in which the fused ring sequence ends with a phosphole unit; b) the structural and chiroptical properties of enantiomerically pure derivatives of this class; c) the enantiospecific self-assembly of columnar arrangements in the solid state; and d) the photochemical [2+2] annulations of phosphole-fused [6]helicenes into dimeric helical structures.

When targeting helicenes where phosphorus is embedded within the helical framework itself, we envisioned 1*H*-phosphindole oxides as suitable building blocks and have adapted the classical helicene synthesis, based on the photochemical cyclization/dehydrogenation of diarylolefins, to these substrates.[14] Our starting materials are the olefins **5** which combine a 1*H*-phosphindole unit and a benzo[*c*]phenanthrene fragment. They have been prepared according to a known procedure,[15] by using two consecutive palladium-promoted Suzuki couplings. First the alkene **1** is coupled with 2-bromobenzo[*c*]phenanthrene (**2**)[16] and the resulting product **3** is then coupled with either the 1*H*-phosphindol-5-yl tosylate **4a** or **4b**[17] (Scheme 1).




***Scheme 1.*** Synthesis of the olefinic substrates **5** by palladium-promoted Suzuki couplings. Men* = (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

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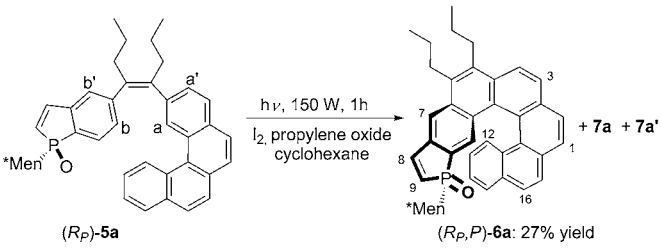
Of the two 1*H*-phosphindole oxides used in this work, **4b** displays a phenyl substituent on phosphorus, and **4a** displays a chiral L-menthyl group. The P-menthyl-substituted phosphindole oxide ($R_P$)-**4a** was obtained in diastereomerically pure form by chromatographic separation of a mixture of epimers with opposite configurations at the stereogenic phosphorus center. The $R_P$ configuration of **4a** has been assigned by X-ray crystal studies.

The olefins **5** have been converted into helical derivatives by the oxidative photocyclization method illustrated in Scheme 2. A priori, photocyclization of **5** might afford four different isomers of the polyaromatic structures depending on

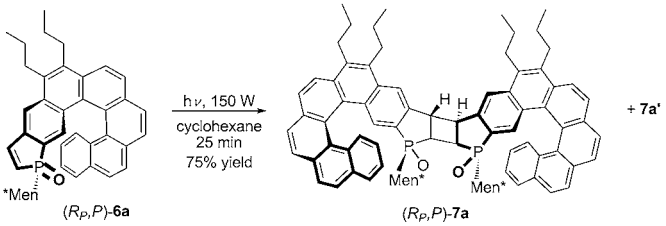



***Scheme 2.*** Diastereoselective synthesis of a phosphindole-based [6]helicene.

the carbon atoms that are involved in the ring closure, that is, either carbon atoms b or b′ for the phosphindole fragment, and either a or a′ for the benzo[*c*]phenanthrene unit. Moreover, starting from ($R_P$)-**5a**, the resulting helical structures might be produced as mixtures of two diastereomers with opposite relative configurations of the stereogenic phosphorus center and the helical scaffold. Gratifyingly, the photocyclization of olefins **5** proved to be regio- and stereochemically controlled in such a way that only one or two, out of six possible isomers, were typically obtained. For instance, UV irradiation of a solution of the L-menthyl-substituted substrate ($R_P$)-**5a** in cyclohexane for 1 hour afforded ($R_PP$)-**6a** as the major product [27% yield upon isolation; $^{31}$P NMR: $\delta =$ 61 ppm; $[\alpha]_D = +1860$, ($c = 1$, $CHCl_3$)].[18]

The phosphine oxide ($R_PP$)-**6a** results from C–C bond formation between the carbon atoms a and b of the starting olefin. In the $^1$H NMR spectrum the phosphole moiety shows peaks at $\delta = 6.27$ ppm (dd, $J_{H\text{-}P} = 24.5$ Hz, $J_{H\text{-}H} = 8.5$ Hz, H-9) and $\delta = 7.32$ ppm (dd, $J_{H\text{-}P} = 35.5$ Hz, $J_{H\text{-}H} = 8.5$ Hz, H-8). These signals are not significantly shifted with respect to the starting material. The terminal phenyl ring shows peaks at $\delta =$ 6.77 ppm (t, $J_{H\text{-}H} = 7.0$ Hz) and $\delta = 7.18$ ppm (t, $J_{H\text{-}H} = 7.5$ Hz), which are significantly shifted to high-field values with respect to the starting material [($R_P$)-**5a**: $\delta = 7.47$ ppm (t, $J_{H\text{-}H} =$ 7.5 Hz) and $\delta = 7.57$ ppm (t, $J_{H\text{-}H} = 7.2$ Hz)].

NMR analysis of the crude reaction mixture of the photocyclization experiment in Scheme 2, showed the presence of two minor products, **7a**,**a′**, whose amounts increased after prolonged UV irradiation of the mixture. Based on the well-known behavior of phospholes, benzothiophenes, and analogous heterocycles under photochemical conditions,[19] we postulated that such minor products might result from an intermolecular photochemical [2+2] cyclization of the initially formed [6]helicene ($R_PP$)-**6a**. According to this hypothesis, compounds **7a**,**a′** could be conveniently prepared by photolysis of the pure helicene ($R_PP$)-**6a**, as shown in Scheme 3 (25 min, 75% total yield, 1:1 ratio).




***Scheme 3.*** Photochemical dimerization of the helical phosphindole oxide ($R_P$,$P$)-**6a**.

The solid-state structure of compound **7a** was unambiguously established by the X-ray crystal structure shown in Figure 2. X-ray data demonstrate a head-to-head dimerization of ($R_PP$)-**6a** through a [2+2] cyclization of the olefinic functions. The two homochiral helical units, which have *P* configurations, are connected by a cyclobutane moiety with a (*R*,*S*,*S*,*R*) configuration, while the stereogenic phosphorus center displays an *R* configuration ($[\alpha]_D = +1505$, ($c = 1$, $CHCl_3$)).

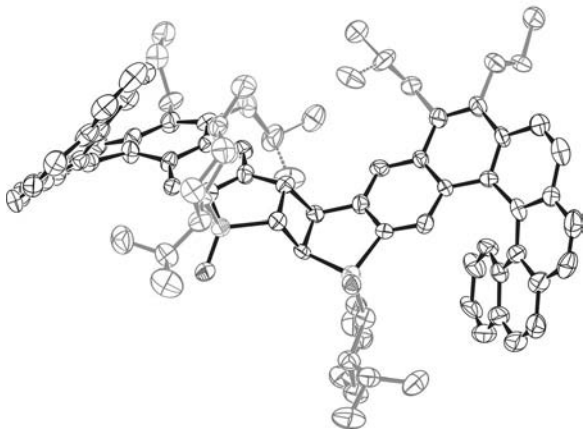


***Figure 2.*** X-ray crystal structure of the dimeric phosphahelicene ($R_P$,$P$)-**7a**. For reasons of clarity the pendant alkyl groups are in gray. Thermal ellipsoids are shown at 30% probability.

The second compound **7a′** ($[\alpha]_D = +1150$, ($c = 1$, $CHCl_3$)) is assumed to be the epimer of the head-to-head dimer, with (*S*,*R*,*R*,*S*) configuration of the cyclobutane ring. This assignment is based on NMR data and mass spectrometry since crystals suitable for X-ray studies could not be obtained.

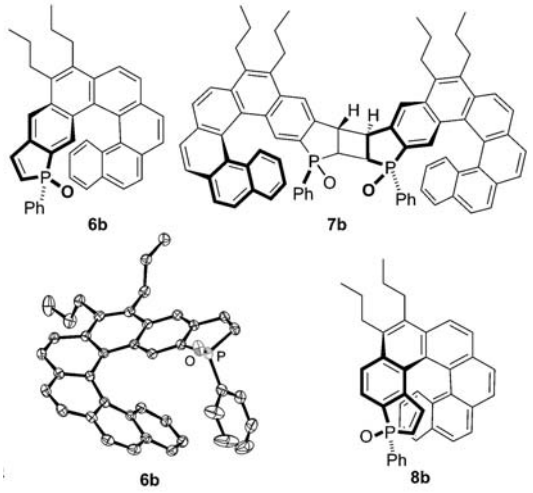
The dimerization reaction in Scheme 3 demonstrates that the presence of a phosphole unit at the end of helical sequences opens the way to unprecedented extended helical structures. To the best of our knowledge, [2+2] dimerizations of analogous heterohelicenes have never been mentioned in the literature, although they are easily anticipated to take

place from a variety of five-membered heterocycles under photochemical conditions.

In the crude reaction mixture of the photochemical cyclization in Scheme 2, compounds ($R_P$,$P$)-**6a**, **7a**, and **7a′**, and the residual starting material represent a total of 75% of the molar amount. A nonhelical side product is also observed (15%). This mass balance demonstrates that the photocyclization reaction takes place with a high level of diastereoselectivity with the screw sense of the helical chirality being efficiently controlled by the chiral substrate. We will see hereafter that this stereochemical control does not relate to the presence of the chiral menthyl group on phosphorus, since the same control operates in the case of P-phenyl-substituted phosphindoles. It is the *R*-configured stereogenic phosphorus center of ($R_P$)-**5a** that induces a *P* helical configuration in the final products.

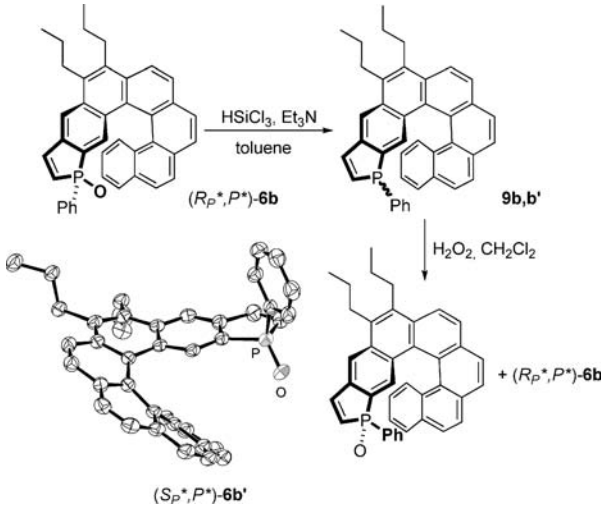
In additional experiments, the racemic P-phenylphosphindole oxide **5b** was subjected to the photochemical cyclization reaction under standard reaction conditions. This substrate undergoes the expected cyclization at a lower rate compared to that of the P-menthyl-substituted derivative ($R_P$)-**5a**. As a consequence, the photochemical [2+2] dimerization starts well before total consumption of the substrate and the reaction affords mixtures of products, with product ratios depending upon the reaction time. From these mixtures we have isolated the three compounds shown in Scheme 4. The X-ray crystal structures for the three compounds are given in the Supporting Information.




***Scheme 4.*** Helical phosphindole derivatives obtained from *rac*-**5b** under oxidative photocyclization ($I_2$, cyclohexane, propylene oxide, $h\nu$ 150 Watt). X-ray crystal structure of ($R_P$,$P$)-**6b**. Thermal ellipsoids are shown at 30% probability.

Compounds **6b** and **7b** are the analogues of the P-menthyl-substituted compounds ($R_P$,$P$)-**6a** and **7a**, respectively. The new compound **8b** is a phospha[7]helicene obtained through C–C bond formation between the carbon atoms a and b' of the olefinic precursor (Scheme 2). The helical pitch of **8b** (3.33 Å) is slightly larger than that of **6b** (3.12 Å), thus suggesting an increased strain of the [7]helicene-type structure **8b**. Similar to the packing of the *rac*-helicene described by Nozaki and co-workers,[13b] crystals of *rac*-**8b** display a columnar arrangement, aligned with the helical axis, in which each column is made of a single enantiomer (see the Supporting Information). Both phosphahelicenes **6b** and **8b** have been obtained in enantiomerically pure form by SFC on columns having a chiral stationary phase (see the Supporting Information).

An intriguing feature of the photochemical cyclization/dehydrogenation reactions is that they always afford the corresponding helical compounds with relative $R_P$*,P*-helical configurations as the unique (or largely predominant) diastereomer. Unexpectedly, in these diastereisomers the phosphorus substituents are oriented toward the polyaromatic scaffold, that is, in the most hindered space region. This sense of stereochemical control is not well understood thus far. It seems to have, however, a kinetic origin, as suggested by the experiments shown in Scheme 5.




***Scheme 5.*** Reduction of the phosphindole oxide ($R_P$*,$P$*)-**6b** and subsequent oxidation leading to an epimeric mixture. Thermal ellipsoids are shown at 30% probability.

Phosphindole oxide ($R_P$,$P$)-**6b** ($\delta$ $^{31}$P NMR = 42 ppm) was reduced with a $HSiCl_3$/$Et_3N$ mixture to give the corresponding trivalent phosphine as a mixture of two isomers, **9b**,**b′** ($\delta$ $^{31}$P NMR = 0.2 and −2.4 ppm), in a 1:0.8 ratio. These epimeric phosphines are assumed to equilibrate slowly, because of the comparatively low pyramidal inversion barriers of benzophospholes with respect to other phosphines.[20] The subsequent oxidation of the mixture with $H_2O_2$ produced the two diastereomers of the phosphahelicene oxide with opposite phosphorus configurations, (($R_P$,$P$)-**6b** and ($S_P$,$P$)-**6b′**; $\delta$ $^{31}$P NMR = 42 and 40 ppm, respectively) in a 1:1 ratio. X-ray diffraction studies afforded direct evidence for the molecular structure of the ($S_P$*,$P$*)-configured oxide **6b′** (Scheme 5).[21]

This experiment demonstrates that both epimers of the phosphine oxide can be formed and seems to be equally favored. Thus, the preferential formation of ($R_P$*,$P$*)-**6b** under photochemical conditions does not correlate with

a possible stabilization of the final product. An alternative rational to the observed diastereoselectivity might be a preferential helical folding of the substrate, driven by intramolecular π stacking or steric repulsions, which would be locked then in the photocyclization process.[22]

In summary, we have used 1*H*-phosphindole as a new platform to access polyaromatic helicene scaffolds terminating with a heterocyclic moiety. We have shown that, in the photochemical synthesis of these new systems, helicity can be controlled by taking advantage of the stereogenic phosphorus atom. Moreover, the reactive olefinic function of the phosphole unit allows unprecedented dimeric helicene derivatives to be accessed. Further studies will be oriented toward uses of these new phosphahelicenes in organometallic chemistry and catalysis.

## Experimental Section

Typical photocyclization procedure: Iodine (0.4 mmol, 157 mg), propylene oxide (20 mmol, 1.4 mL), and cyclohexane (350 mL) were added to (*Z*)-5-(5-(benzo[c]-phenanthren-2-yl)oct-4-en-4-yl)-1-phenyl-1H-phosphindole 1-oxide [($R_P$)-**5a**] (0.2 mmol, 125 mg) dissolved in 5 mL of THF. The mixture was irradiated for 1 h (Heraeus TQ, 150 Watt), after which the lamp was switched off and the mixture was stirred at RT for 30 min. After removal of the solvent, the crude reaction mixture was monitored by $^1$H NMR spectroscopy and purified by column chromatography on silica gel with a heptane/ethyl acetate gradient. Three fractions were collected and contain **7a** ($R_f$ = 0.4 in 50% EtOAc/Heptanes), ($R_PP$)-**6a** ($R_f$ = 0.2), and **7a′** ($R_f$ = 0.1) as the major components, respectively. Compound ($R_PP$)-**6a** was purified again by preparative HPLC (Waters Sunfire C18 OBD, 5 μm, 19 × 150 mm (12 min gradient: 10 to 0% $H_2O$/90 to 100% MeOH/0.1% formic acid; retention time: 10.4 min) (35 mg, 27% yield).[23]

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[17] For the synthesis of the phosphindole oxides **4a**,**b**, see the Supporting Information.

[18] The molecular structure of ($R_P$*P*)-**6a** has been unambiguously ascertained from the X-ray crystal structure of its derivative **7a** (Figure 2).

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[23] CCDC 870526 [($R_P$*P*)-**6b**], 870530 [($S_P$*P*)-**6b′**], 870528 (**7a**), 870529 (**7b**), and 870527 (**8b**) contains 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.