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A [2+2+2] cyclization strategy for the synthesis of phosphorus embedding [6]helicene-like structures†

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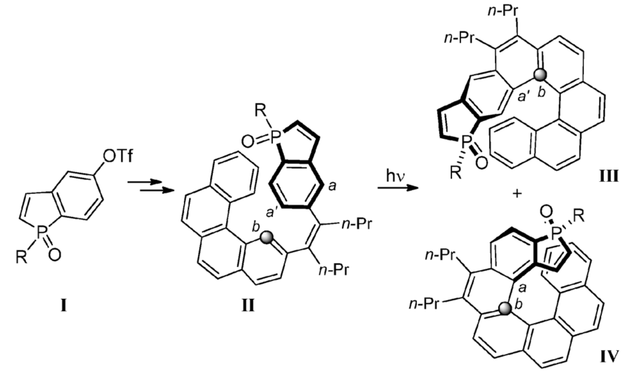
A Ni(0) promoted intramolecular [2+2+2] cyclotrimerization of triynes provides suitable access to a new series of phosphorus embedding helicenes. [6]Oxahelicenes in which the helical sequence terminates with a phosphole oxide unit have been prepared in both racemic and enantiopure forms and characterized by X-ray diffraction studies.

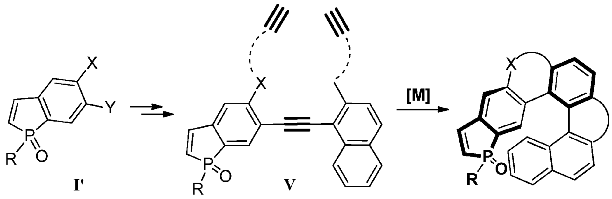
Helical structures with embedded phosphorus functions have been largely neglected so far in spite of the recognized importance of analogous carbo- and heterohelicenes, or helicene-like molecules, in extremely diverse fields and applications.[1] This is especially surprising when considering that the peculiar features of phosphorus functions have the potential of extensively modulating the properties of helical structures and consequently expanding the scope of such applications. Notably, the various oxidation states and coordination degrees existing for phosphorus, combined with its coordinating ability toward transition metals, would offer almost infinite opportunities for tuning the physicochemical properties and reactivity of helical derivatives.[2] So, it can be reasonably postulated that the underdevelopment of this area results from the lack of suitably diverse and general synthetic approaches, since only a very few synthetic strategies have been described in the pioneering work of Tanaka *et al.*[3] and Nozaki *et al.*[4] Thus, with the aim of filling this gap we have recently started extensive systematic studies on synthetic approaches to phosphorus containing helicenes.[5]



Scheme 1 Photochemical synthesis of phosphorus embedding helicenes.[5]

Our strategy involves the use of phosphindoles or dibenzophospholes as the key structural units, since, in principle, these fragments can be easily integrated into helical scaffolds through their condensed aromatic rings. So far, these synthons have been adapted successfully to the synthesis of phosphahelicenes[6] *via* one of the oldest and most classical method for the synthesis of carbohelicenes, *i.e.* the oxidative photocyclization of diarylolefins.[7] This strategy is presented in Scheme 1.

A well-known alternative for the synthesis of helical derivatives is the metal mediated [2+2+2] cyclotrimerization of alkynes.[8] The method has been introduced in helicene chemistry by Stará and co-workers[9a] and applied extensively by the same authors and others.[9b–p] Especially, intermolecular rhodium-promoted cyclotrimerizations have been used recently by Tanaka *et al.* to access the first series of phosphahelicenes.[3] We believe that this cyclotrimerization method, when combined with our strategy of using phosphindoles as starting materials, as shown in Scheme 2, has the potential of widely expanding the range of phosphorus embedding helical structures.



Scheme 2 Phosphorus embedding helicenes through metal promoted [2+2+2] cyclotrimerization (this work).

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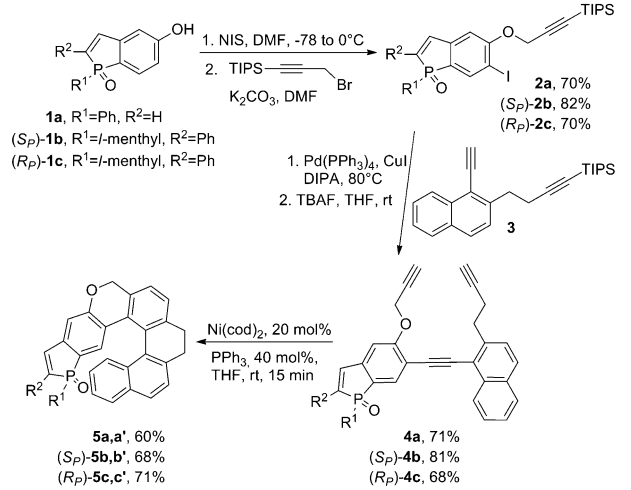


Scheme 3 Synthesis of the phosphorus embedding [6]-helicene-like derivatives **5**.

Thus, inspired by the work of Stará *et al.*,[9a,b,d,e] we have devised phosphindoles, with the general formula **I′**, as the key substrates and triynes **V** as the helicene precursors to test the feasibility of a [2+2+2] strategy. In these initial studies, the 5-hydroxy-substituted phosphindole oxides **1a–c**.[5a,c] have been selected as starting materials (Scheme 3). In compound **1a** the phosphorus substituent is a phenyl group, while **1b** and **1c** are the two epimers of the P-*l*-menthyl-substituted phosphindole displaying opposite configurations of the chirogenic phosphorus atom. The hydroxyl function of **1** enables the selective iodination of the 6-position by reaction with *N*-iodosuccinimide in DMF, then alkylation of the phenol with a TIPS-protected propargylic bromide affords phosphindole **2** which displays the desired alkyne unit. The second step of the reaction sequence shown in Scheme 3 takes advantage of the iodine function of **2** to link the phosphorus fragment to diyne **3**[9d] *via* a palladium catalysed Sonogashira coupling.

After *in situ* removal of the TIPS protecting groups, the desired triynes **4a–c** have been isolated in good yields at a 300–500 mg scale.

For the final [2+2+2] cyclization step, several catalysts can be envisioned, including Co(I),[9a,g,h,l,m,10] Rh(I),[3,9f,i,k,o] Ir(I)[9n] and Ni(0)[9b,p,11] derivatives. In this work, only Rh(I) and Ni(0) catalysts have been tested: a 1 : 2 mixture of Ni(cod)$_2$/PPh$_3$ proved to be the best catalyst, which afforded the desired helicenes **5** after reaction for only 15 min at room temperature, at a 20 mol% catalyst loading. The final phosphine oxides **5a–c** have been obtained as diastereomeric mixtures, due to the presence of both a stereogenic phosphorus centre and a helically chiral scaffold. The isomer pairs have been separated easily by flash chromatography on silica gel columns.

The diastereoselectivity of the cycloisomerization step depends on the nature of the phosphorus substituent R^1, and also, for the epimeric triynes (S_P)-**4b** and (R_P)-**4c**, on the stereochemistry of phosphorus. Thus, starting from **4a**, in which R^1 = Ph, a 40 : 60 ratio of the diastereomeric (R_P*,M*)-**5a** and (S_P*,M*)-**5a′** has been obtained. The structure of the major isomer (S_P*,M*)-**5a′** has been assigned by X-ray diffraction studies (Fig. 1).

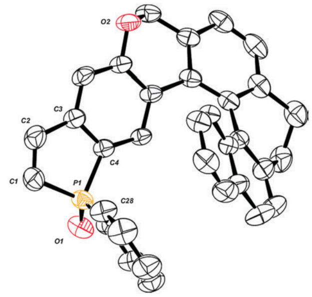
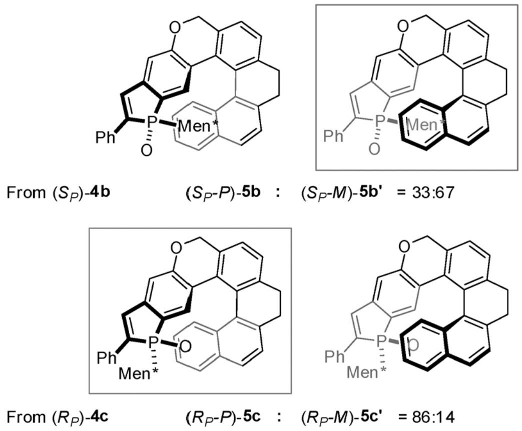


Fig. 1 X-ray crystal structure of (S_P*-M*)-**5a′** (major isomer), CCDC 960385.

Starting from the epimeric P-*l*-menthyl-substituted triynes (S_P)-**4b** and (R_P)-**4c**, the [2+2+2] cyclizations afford the product distributions as shown in Scheme 4: the (S_P)-**4b** epimer affords the M-configured helical compound (S_P,M)-**5b′** ($[\alpha]_\mathrm{D}^{25} = -902$ (c = 1, CHCl$_3$)) as the major isomer, in a 67 : 33 ratio to the minor P-configured helicene.[12] Fig. 2 displays the X-ray crystal structure of the minor isomer (S_P,P)-**5b**. On the other hand, the (R_P)-**4c** epimer affords the P-configured helical compound (R_P,P)-**5c** ($[\alpha]_\mathrm{D}^{25} = +844$ (c = 0.3, CHCl$_3$)) as the major isomer, in a 86 : 14 ratio to the minor M-configured helicene **5c′**.[13]

All the structural and stereochemical assignments mentioned above are based on the crystal structure of the (S_P,P)-**5b** isomer shown in Fig. 2, combined with the observed $[\alpha]_\mathrm{D}$ values which



Scheme 4 Product distribution in the nickel(0)-catalysed [2+2+2] cyclotrimerization of the P-menthyl substituted phosphindole oxides (S_P)-**4b** and (R_P)-**4c**.

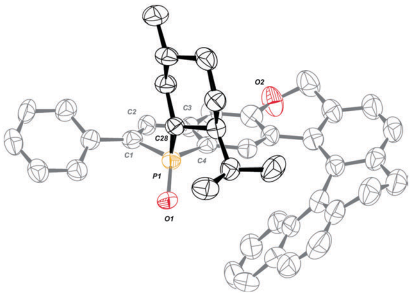


Fig. 2 X-ray crystal structure of (S_P-P)-**5b** (minor isomer), CCDC 960386.

are diagnostic of the helical configurations (positive $[\alpha]_D$ values for *P*-configured helicenes).

From the above results it appears that the $Ni(cod)_2/PPh_3$ promoted cycloisomerization of triynes **4a–c** always favors isomers in which the P=O functions occupy the external faces of the helical scaffolds (''*exo*''-isomers) while the phenyl or menthyl groups are oriented toward the internal faces. The same trend was observed in our previous work on the photochemical synthesis of phosphahelicenes: the photochemical reactions resulted in almost exclusive formation of the ''*exo*''-isomers, in spite of the significant steric hindrance of the phosphorus substituents.

Compared to our previous photochemical method,[5] the cyclotrimerization based approach to phosphahelicenes disclosed here displays lower stereocontrol in the formation of the helical structure. It involves however total chemoselectivity, as far as a single phosphahelicene scaffold is formed from the designed precursors **4**. This was not the case for the oxidative photocyclization of diarylolefins which usually afforded mixtures of the two isomeric helical compounds **III** and **IV** (Scheme 1). In the end, the [2+2+2] cyclotrimerization strategy proves to be at least as efficient as the previous photochemical approach. It provides access to a different series of phosphahelicene like derivatives and therefore suitably complements the previous method.

In summary, we have established a convenient, high yielding reaction sequence based on the nickel(0)-promoted [2+2+2] cyclotrimerization of alkynes leading to partially saturated phosphahelicenes displaying an ether function in their helical scaffolds. Among others, enantiomerically pure helical derivatives have been accessed easily. This method expands the range of phosphahelicenes, and complements the previously disclosed photochemical approach to which it compares favourably in terms of synthetic efficiency. It also complements the Tanaka's and Nozaki's series of phosphahelicenes, as far as it affords helicenes in which the phosphole function is located at the external edge of the helical structure.

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12 An almost identical isomer ratio (7 : 3 ratio) has been observed when $Rh(cod)_2BF_4/(\pm)$-BINAP/H_2 is used to promote the cyclotrimerization of **4b**.

13 The configurational stability of these [6]helicene-like phosphine oxides has been ascertained: no epimerization of the helical structure was observed after heating (S_P-*P*)-**5b** overnight at 100 °C in toluene.