Atropisomeric phosphinines: design and synthesis†‡

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Received 2nd October 2007, Accepted 3rd October 2007
First published as an Advance Article on the web 10th October 2007
DOI: 10.1039/b715197g

The first atropisomeric phosphinine was designed and prepared by introducing substituents into specific positions of the heterocyclic framework; the presence of axial chirality was predicted by means of DFT calculations and experimentally verified by chiral HPLC analysis, derivatization experiments as well as temperature dependent $^{31}P\{^{1}H\}$ NMR spectroscopy.

λ^3-Phosphinines (phosphabenzenes, phosphorins), the higher homologues of pyridines, have been known for many decades, due to the pioneering work of Märkl and Ashe III in the late 1960s.[1] These heterocycles are planar, aromatic systems in which one –CH– group of the aryl moiety is substituted by a low-coordinated, trivalent phosphorus atom.

While atropisomeric pyridines have recently been prepared by Heller *et al. via* enantioselective Co-catalyzed cyclotrimerization of bulky acetylenes and nitriles, their phosphorus containing analogues still remain elusive because the introduction of chirality into these flat systems is intrinsically difficult to achieve.[2] Only a few examples of chiral phosphinines exist in the literature, but they are based on chiral auxilliaries, such as oxazoline or binaphthol groups, which are attached to the heterocyclic framework.[3,4]

On the other hand, chiral phosphinines could be highly interesting ligands for asymmetric homogeneous catalysis. Monodentate triarylphosphinines, for example, have shown to be efficient ligands for the Rh-catalyzed hydroformylation of internal and less reactive alkenes, due to their special steric and electronic properties.[3,5] Moreover, phosphinines are precursors for the preparation of phosphabarrelenes.[6,7] These bicyclic systems have also been successfully applied as ligands in the Rh-catalyzed hydroformylation of internal alkenes, showing basically no isomerization activity towards 1-alkenes.[7] The preparation of chiral phosphinines and phosphabarrelenes could therefore lead to ligand systems, which are suitable for the efficient enantioselective functionalization of internal alkenes with relevance for both intermediates and the fine-chemicals industry.

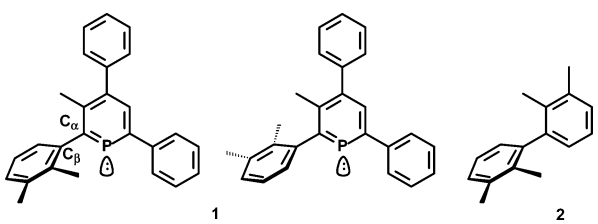
During the course of our investigations on functionalized phosphinines, we started to investigate the possibility of generating axial chirality within the heterocyclic framework and close to the phosphorus center, without changing the properties of these ligands by additional chiral auxilliaries.[4,8] We anticipated that the original phosphinine-synthesis described by Märkl would provide the opportunity to introduce substituents into specific positions of the heterocycle, due to their modular synthesis and the necessity to maintain the axial chirality. Thus, as a first approach we aimed for the preparation of the axially chiral phosphinine **1**. This compound resembles the molecular structure of 2,2′-3,3′-tetramethyl biphenyl **2** (Fig. 1; only one isomer is shown) and is at the same time expected to be synthetically accessible. The enantiopure biphenyl **2** has indeed a considerable optical stability due to the Buttressing-effect as well as the relatively large negative racemization entropy as reported previously in the literature.[9,10] In order to estimate the barriers for rotation around the C_α–C_β-bond in compounds **1** and **2**, we performed DFT calculations.[11] In fact, it has recently been shown that the rotational barriers of various biphenyls can be reliably predicted by theoretical calculations and are in good agreement with the experimentally determined values.[13] As anticipated for compounds with structural analogy, the calculated values§ for **1** and **2** are thus very similar and in the order of $\Delta G^{\ddagger}_{298} = 110 \pm 5$ kJ mol^{-1} (Table 1, entry 1 and 2).

Motivated by these findings, we continued with the experimental procedure for the synthesis of phosphinine **1**, having a barrier for internal rotation, which is expected to be high enough for further separation of the enantiomers at ambient conditions.

The key-intermediate for the preparation of triaryl-substituted phosphinines with the substitution pattern as depicted in Fig. 1 is 2,3-dimethylpropiophenone **3** (Scheme 1). The use of a propiophenone rather than an acetophenone ultimately results in locating a methyl-group in the 3-position of the heterocycle, necessary for maintaining the axial chirality.[14] Compound **3** was

Table 1 Calculated rotational barriers for **1**, **2** and **9**

Entry	Compound	$\Delta E^{\ddagger}$/kJ mol^{-1}	$\Delta G^{\ddagger}_{298}$/kJ mol^{-1}
1	**1**	106	116
2	**2**	101	109
3	**9**	92	100



1 2

Fig. 1 Axial chirality in **1** and **2**.

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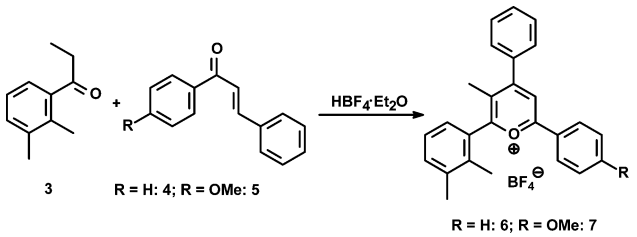
† CCDC reference number 659766. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b715197g

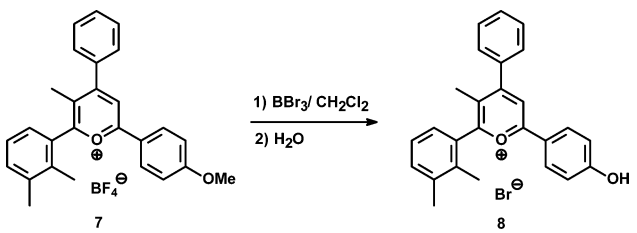
‡ Electronic supplementary information (ESI) available: A detailed list of all experimental procedures, cif file and crystallographic data for compound **8**. See DOI: 10.1039/b715197g



Scheme 1 Synthesis of substituted pyrylium salts.

synthesized in high yield, starting from commercially available bromoxylene, according to a literature procedure.[15] Reaction of **3** with two equivalents of the benzylidene-acetophenones **4** or **5**, respectively, and in the presence of $HBF_4{\cdot}Et_2O$ yields a racemic mixture of the corresponding pyrylium salts **6** (R = H) and **7** (R = OMe) as yellow–orange solids in moderate yields. **6** and **7** were fully characterized by means of ^1H, $^{13}C\{^1H\}$ and $^{19}F\{^1H\}$ NMR spectroscopy as well as elemental analysis.

In order to gain structural information on the pyrylium salts as well, we anticipated that hydroxy-functionalized compounds would be ideal candidates for obtaining single-crystals as demonstrated before by us.[4] Consequently, compound **7** was quantitatively converted into the yellow pyrylium salt **8** by reaction with excess BBr_3 in CH_2Cl_2 and subsequent aqueous workup (see Scheme 2).



Scheme 2 Preparation of pyrylium salt **8**.

The complete removal of the $-CH_3$ group was confirmed by ^1H NMR spectroscopy. At the same time, the reaction with H_2O produced substantial amounts of HBr which led to the anion exchange of BF_4^- for Br^- during aqueous workup as indicated by the lack of any resonance in the $^{19}F\{^1H\}$ NMR spectrum.

Red crystals of **8**, suitable for X-ray crystallography, were indeed obtained by slow crystallization from methanol and the molecular structure is illustrated in Fig. 2, along with selected bond lengths and angles. It confirms not only the expected substitution pattern and the formation of the hydroxy-functionalized pyrylium salt, but also the presence of a Br^-, rather than a BF_4^- anion with additional hydrogen bonding. **8** crystallizes as a racemate in the centrosymmetric space group $P2_1/c$. The torsion angle of +73.0(3)° shows that the xylyl-substituent in the 2-position is situated almost perpendicular to the plane, which is formed by the oxygen-containing heterocycle, due to the expected restricted rotation around the C_1–C_6 bond. In contrast, the planes of the hydroxy-functionalized aryl-moiety in the 6-position and of the heterocycle are almost parallel to one another as observed before for several pyrylium salts.[4,8]

Pyrylium salt **6** was further converted into the corresponding phosphinine **1** by reaction with excess $P(SiMe_3)_3$[16] in acetonitrile, or alternatively by reaction with $P(CH_2OH)_3$[17] in refluxing pyridine. Compound **1** was obtained as a yellow powder after column chromatography in 34% yield and fully characterized by means of ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectroscopy and elemental analysis. In the $^{31}P\{^1H\}$ NMR spectrum of **1** the single resonance at δ = 190.5 ppm (C_6D_6) is characteristic for the aromatic phosphinine.

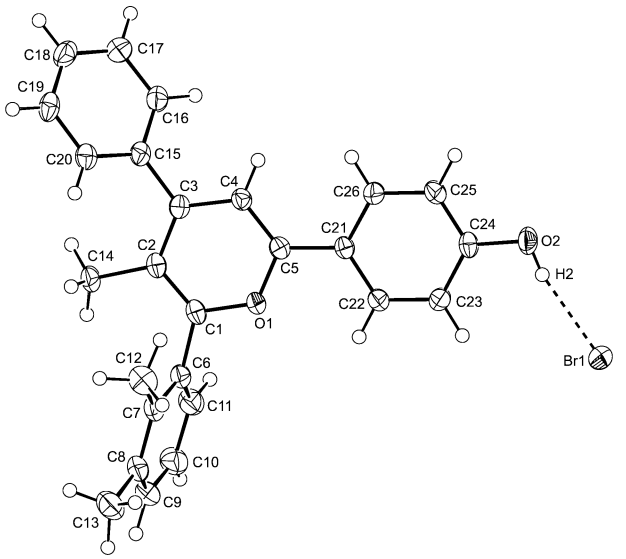


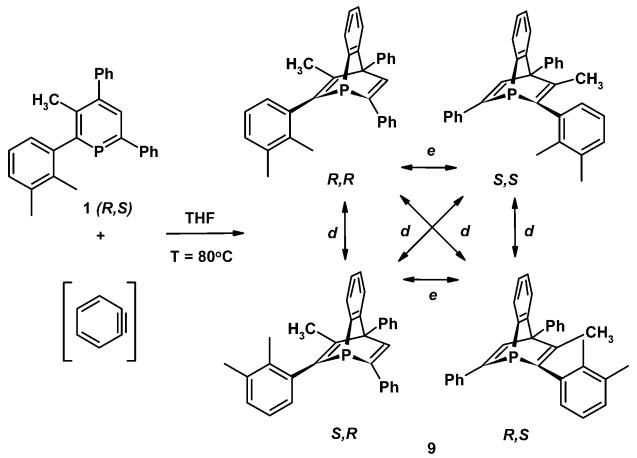
Fig. 2 Molecular structure of **8** in the crystal. Displacement ellipsoids are shown at the 50% probability level. The O–H · · · Br hydrogen bond is drawn with dashed lines. Selected bond lengths (Å): C1–O1: 1.358(2), O1–C5: 1.346(3), C5–C21: 1.452(3), C1–C6: 1.484(3), O2 · · · Br1: 3.1438(18). Torsion angle (°): C7–C6–C1–C2: +73.0(3).

A very good separation to a 1 : 1 mixture of enantiomers was achieved by analytical HPLC on a chiral stationary phase, using *n*-hexane as eluent (Chiralcel® OD–H, t_1 = 19.31 min, t_2 = 23.81 min, T = 25 °C, flow-rate 1 mL min^{-1}, see ESI‡), which confirms that the barrier of internal rotation is indeed reasonably high as expected.

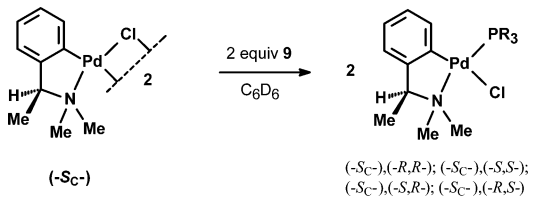
In order to additionally verify that phosphinine **1** is a racemate we transformed **1** into the corresponding phosphabarrelene **9** by reaction with *in-situ* generated benzyne, according to a procedure described by Märkl and Breit *et al.* (Scheme 3).[6,7] Compound **9** was obtained as a yellow solid in 35% yield after flash chromatography and was fully characterized. The reaction of a racemic mixture of a phosphinine with benzyne should lead to four stereoisomers, because a stereogenic phosphorus center is additionally established upon formation of the phosphabarrelene (Scheme 3).

The two enantiomeric pairs should consequently give rise to two different signals in the $^{31}P\{^1H\}$ NMR spectrum, if axial chirality is maintained in the molecule. Indeed, we could observe two resonances for **9** by $^{31}P\{^1H\}$ NMR spectroscopy at $\delta = -65.0$ ppm and $\delta = -66.4$ ppm (C_6D_6), respectively, in a diastereomeric ratio of 2 : 3 (see ESI‡).

The presence of four stereoisomers was further confirmed *in situ* by reaction of **9** with the enantiomerically pure chiral Pd complex (*S*)-$[PdCl\{C_6H_4CH(Me)NMe_2\}]_2$[18] in C_6D_6 (Scheme 4). Four resonances at δ = 6.0, 4.9, 2.2 and 0.0 ppm were observed by



Scheme 3 Synthesis of phosphabarrelene **9** from **1**. *e*: enantiomeric pair, *d*: diastereomeric pair.



Scheme 4 Reaction of **9** with a chiral Pd-complex.

$^{31}P\{^{1}H\}$ NMR spectroscopy and in the expected ratio of 3 : 2 : 2 : 3 (see ESI‡).

DFT calculations additionally revealed, that the calculated rotational barrier $\Delta G^{\ddagger}_{298}$ around the C_{α}–C_{β}-bond in compound **9** equals 100 kJ mol^{-1} and is therefore comparable to that in phosphinine **1** (Table 1, entry 3). Unlike for compound **1**, the mixture of stereoisomeric phosphabarrelenes also now provides the opportunity of determining experimentally the rotational barrier in compound **9**. Upon heating, rotation around the C_{α}–C_{β} is anticipated, leading to fast exchange on the NMR-time scale and consequently to the formation of enantiomers with a single resonance in the $^{31}P\{^{1}H\}$ NMR spectrum.

We therefore performed temperature dependent $^{31}P\{^{1}H\}$ NMR spectroscopy of compound **9** in xylene. At $T = 150\,^{\circ}C$, coalescence of the two signals starts to occur. Due to the experimental conditions, measurements at even higher temperatures could not be performed. Nevertheless, an experimental rotational barrier of at least $\Delta G^{\ddagger}_{A(rot)} \geq 85 \pm 5$ kJ mol^{-1} was estimated from the obtained data,[19] which agrees well with the above theoretical results. Due to the similar structure of phosphabarrelene **9** and phosphinine **1** as well as due to the slightly higher calculated rotational barrier for the latter compound, we believe that the experimental value determined for **9** can be adequately extrapolated to phosphinine **1**.

In summary, we demonstrated the design and the synthesis of the first atropisomeric monodentate phosphinine by introducing methyl-substituents into specific positions of the heterocyclic moiety. The phosphinine was obtained as a racemate and the presence of axial chirality was verified by chiral HPLC analysis and derivatization experiments towards atropisomeric phosphabarrelenes. The rotational barrier for racemization was estimated both theoretically by DFT calculations and experimentally by temperature dependent $^{31}P\{^{1}H\}$ NMR spectroscopy. Future investigations, which are out of the scope of this communication, will focus on the isolation of the enantiomers as well as their application in asymmetric homogeneous catalysis.

Notes and references

§ The activation energies reported correspond to the low-energy clockwise rotation path of the isomers shown in Fig. 1.

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