Design and Synthesis of Helically Chiral Spirocyclic P3 Phosphazenes and Characterization of Their Onium Salts

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Abstract: Helically chiral spirocyclic P3 phosphazenes were designed as a novel family of chiral organosuperbases. The newly designed chiral P3 phosphazenes were synthesized from commercially available sources in several steps and characterized by X-ray crystallographic analysis of their onium salts. The optically pure P3 phosphazenium salt was obtained by using preparative chiral stationary phase HPLC and the absolute configuration of the helical chirality was determined.

Key words: chirality, enantiomeric resolution, helical structure, phosphazene, spirocycle

For more than three decades, the design and synthesis of uncharged strong organobases has attracted much attention[1] because their unique characteristics allow deprotonation of a wide range of weak acids and results in the generation of weakly coordinated 'naked-like', and hence highly reactive, anionic species. Schwesinger's phosphazenes[2] and Verkade's phosphatranes[3] are representative of phosphorus-based strong organobases. In efforts to enhance the basicity of uncharged organobases, inclusion of increasing numbers of iminophosphorane units has afforded a series of phosphazene organosuperbases such as P2, P3, and P4 phosphazenes.[4]

Another significant issue in the arena of strong organobases is the development of chiral variants that can be utilized for catalytic enantioselective transformations. In this regard, chiral guanidines and P1 phosphazenes have emerged as efficient enantioselective catalysts, and significant progress has been made in the development of a wide range of enantioselective transformations using these chiral strong organobases.[5–7] However further enhancement of the basicity of a chiral uncharged organobase, leading to a chiral organosuperbase, has remained largely unexploited so far.[8,9] The design and synthesis of chiral organosuperbases is still a challenging topic in synthetic organic chemistry because of the unique features of uncharged organobases. We, therefore, envisaged the design and synthesis of a novel chiral organosuperbase. In our approach to a chiral organosuperbase, we adopted a P3 phosphazene framework, not only to gain high basicity but also to construct a C_2-symmetrical structure around the central iminophosphorane core. The fundamental structure of such a chiral P3 phosphazene **1** is depicted in Figure 1 as the free base **1** and its conjugate acid form [**1**·H]$^+$. Herein, we report the synthesis of novel chiral P3 phosphazene organosuperbases **1** from commercially available sources in several steps and isolation as well as X-ray crystallographic analysis of their **1**·HX salts. In addition, the preparation of optically pure phosphazenium salts by using chiral stationary phase HPLC and the determination of the absolute configuration are also presented.

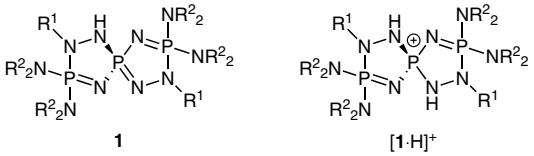

Figure 1 Fundamental structure of helically chiral spirocyclic P3 phosphazene **1** and its protonated form [**1**·H]$^+$

The prominent structural feature of the newly designed P3 phosphazenes **1** is their helical chirality around the five-membered spirocyclic system. In addition, we arranged hydrogen bond donor and acceptor sites around the central phosphorus atom, because the side-by-side arrangement of the donor and acceptor sites has proven to be fundamental to achieving highly efficient enantioselective chiral organobase catalysts such as chiral guanidines and P1 phosphazenes.[5] As shown in the free base **1** (Figure 1), the nitrogen atom of the central iminophosphorane moiety (N=P) functions as the hydrogen bond acceptor, whereas the N–H moiety adjacent to the central phosphorus atom functions as the hydrogen bond donor. In line with this molecular design, we synthesized two types of helically chiral P3 phosphazenium salts, **1a**·HI and **1b**·HCl, as shown in Figure 2.

Chiral P3 phosphazenium salt **1a**·HI possesses phenyl groups on the nitrogen atoms of the hydrazine moieties and ethylenediamine units on the terminal phosphorus atoms, giving four continuous spirocycles. The synthesis of **1a**·HI began with treatment of *N*-Boc-phenylhydrazine (**2**) with 2-chloro-1,3-dimethyl-1,3,2-diazaphosphorane (**3**) followed by Staudinger reaction with Cbz azide to provide P1 phosphazenium **4** in 95% yield over two steps (Scheme 1). After removal of the Cbz group under reductive conditions, the spirocyclic structure was constructed

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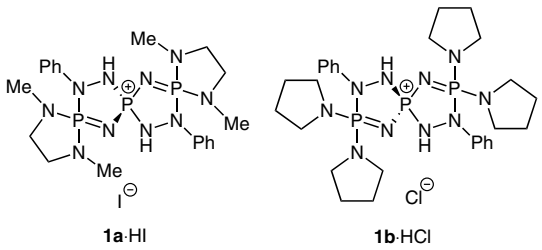
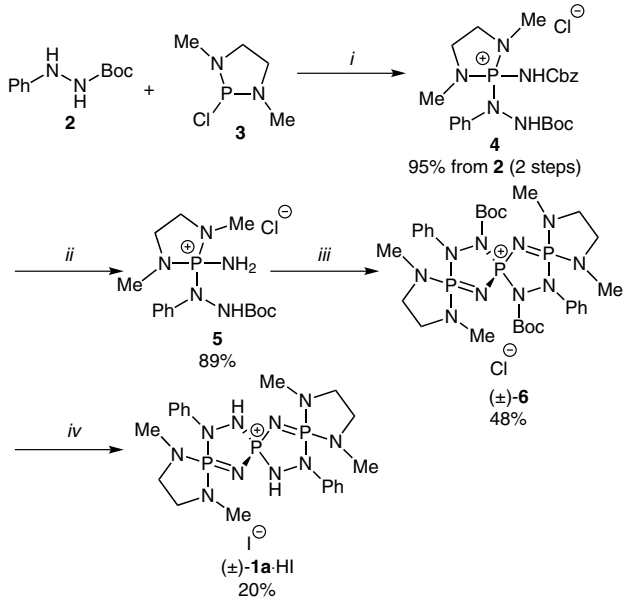


Figure 2 Molecular structure of helically chiral spirocyclic P3 phosphazenium salts **1a**·HI and **1b**·HCl

by treating **5** with pentachlorophosphorane in the presence of the Hünig's base. Finally, the synthesis of racemic **1a**·HI was accomplished by removing the Boc group with sodium iodide and chlorotrimethylsilane. After exchanging the counter anion from iodide to tetrafluoroborate, each enantiomer of (±)-**1a**·HBF_4 was resolved by using analytical HPLC equipped with a chiral stationary phase column.[10]



Scheme 1 Synthesis of (±)-**1a**·HI. *Reagents and conditions*: (*i*) (1) **3** (1.3 equiv), DIPEA (5.0 equiv), toluene, 0 °C to r.t., 2 h; (2) $CbzN_3$ (1.3 equiv), r.t., 12 h; (*ii*) $PdCl_2$ (15 mol%), Et_3SiH (4.0 equiv), Et_3N (70 mol%), CH_2Cl_2, reflux, 2 h; (*iii*) PCl_5 (0.48 equiv), DIPEA (4.8 equiv), CH_2Cl_2, 0 °C to r.t. (containing small amount of impurities); (*iv*) NaI (6.0 equiv), TMSCl (6.0 equiv), MeCN, 50 °C, 48 h.

As illustrated in Figure 3, the structure of **1a**·HI was verified by single-crystal X-ray diffraction analysis of the racemic P3 phosphazenium salt.[11] Importantly, the iodide anion is located in close proximity to the two N-H protons, which strongly suggests the formation of hydrogen bonds between the iodide anion and the two N-H protons.

We then synthesized spirocyclic **1b**·HCl, having pyrrolidine moieties at the terminal phosphorus atoms. As shown in Scheme 2, the synthesis of **1b**·HCl was initiated by the preparation of P1 phosphazenium salt **7**. Trichlorophosphine was treated with two equivalents of pyrrolidine

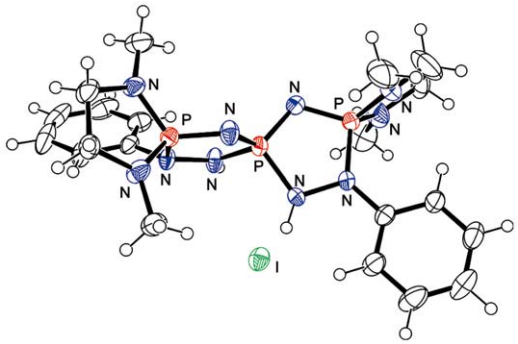
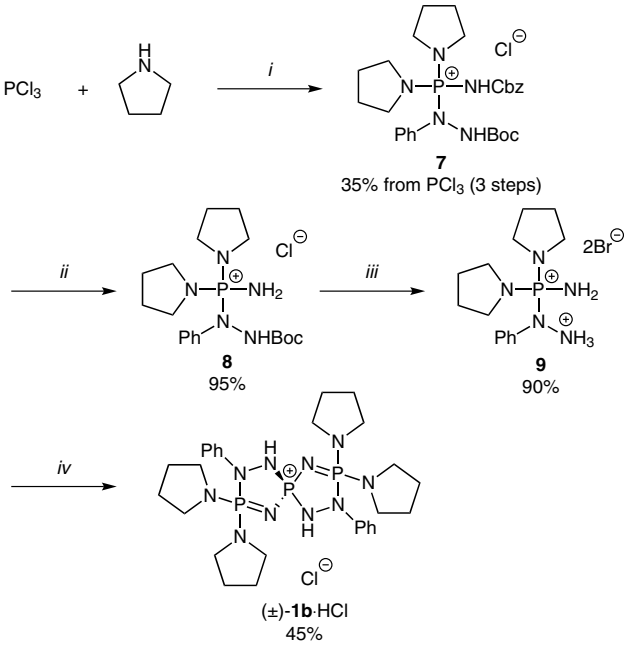


Figure 3 ORTEP drawing of **1a**·HI with probability ellipsoids drawn at the 50% level. Although the absolute structure is depicted as the (*M*)-form, the X-ray grade crystal was obtained from a racemic mixture of **1a**·HI.

to afford the diaminochlorophosphine intermediate. Subsequently, addition of *N*-Boc-phenylhydrazine (**2**) followed by Staudinger reaction with Cbz azide furnished P1 phosphazenium salt **7** in 35% yield over three steps. After removal of the Cbz and Boc groups by sequential reduction and acid hydrolysis, respectively, the synthesis of racemic P3 phosphazenium salt **1b**·HCl was accomplished by the reaction of **9** with pentachlorophosphorane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). It is noteworthy that during the synthesis of **1b**·HCl from **7**, no silica gel column purification was required. In each step, washing the crude mixture with an appropriate solvent, such as hexane (for **8**), acetonitrile (for **9**), or acetone (for **1b**·HCl), provided effectively pure compounds.



Scheme 2 Synthesis of (±)-**1b**·HCl. *Reagents and conditions*: (*i*) (1) Et_3N (2.1 equiv), pyrrolidine (2.0 equiv), toluene, 0 °C, 2 h; (2) *N*-Boc-phenylhydrazine (**2**; 1.0 equiv), Et_3N (4.0 equiv), 0 °C to r.t., 2 h; (3) $CbzN_3$ (1.2 equiv), r.t., 12 h; (*ii*) $PdCl_2$ (15 mol%), Et_3SiH (4.0 equiv), Et_3N (70 mol%), CH_2Cl_2, reflux, 5 h; (*iii*) 47% HBr (5.0 equiv), MeOH, 50 °C, 7 h; (*iv*) PCl_5 (0.55 equiv), DBU (4.5 equiv), CH_2Cl_2, –60 °C, 18 h.

The optical resolution of racemic P3 phosphazenium salt (±)-**1b**·HCl was attempted by using preparative chiral stationary phase HPLC. After thorough screening of separation conditions by using analytical chiral stationary phase HPLC, Daicel CHIRALPAK IB was found to be effective (Figure 4).[12] The enantiomer of the first peak was successfully isolated by using preparative chiral stationary phase HPLC under the optimized conditions.[13] The first peak of **1b**·HCl was found to be the (+)-form on the basis of its specific rotation.[14]

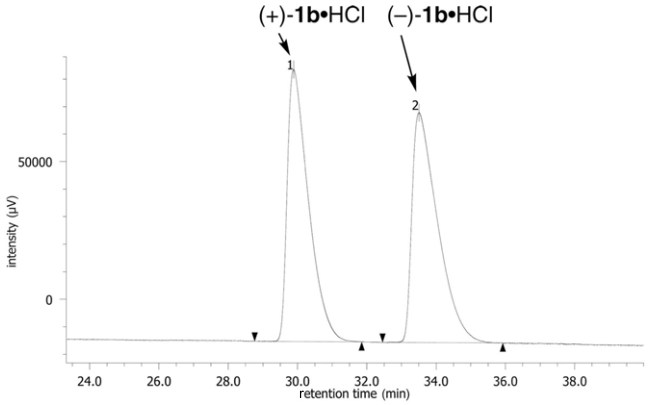


Figure 4 Chiral stationary phase HPLC analysis of (±)-**1b**·HCl

To determine the absolute configuration of optically pure (+)-**1b**·HCl, we attempted single-crystal X-ray diffraction analysis, however, an X-ray grade single crystal of (+)-**1b**·HCl could not be obtained. We therefore exchanged the counter anion from chloride to bromide. To our satisfaction, an X-ray grade single crystal of optically pure **1b**·HBr could be obtained from a mixture of acetone/hexane/chloroform, and the helical chirality of **1b**·HBr, derived from (+)-**1b**·HCl, was determined to be the (*P*)-form (Figure 5).[15]

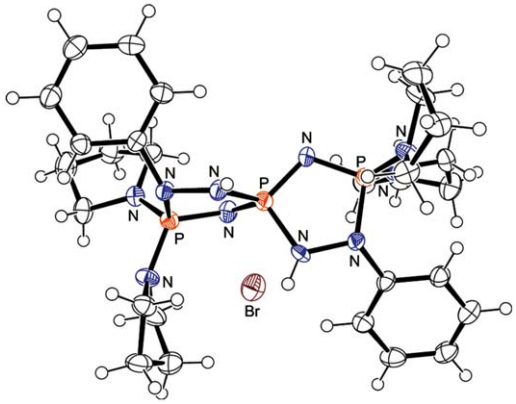


Figure 5 ORTEP drawing of (*P*)-**1b**·HBr with probability ellipsoids drawn at the 50% level. The solvent molecule ($CHCl_3$) is omitted for clarity. The X-ray grade crystal was obtained from optically pure **1b**·HBr, which was prepared from (+)-**1b**·HCl through counterion exchange.

In conclusion, we have designed and synthesized helically chiral spirocyclic P3 phosphazenes as a new family of chiral organosuperbases. The structure of these novel P3 phosphazenes was successfully verified by X-ray single crystal analysis of their halide salts. The optical resolution of a racemic helically chiral P3 phosphazenium salt was achieved by using preparative chiral stationary phase HPLC to afford the optically pure P3 phosphazene in its onium salt form. The present structural motif is potentially useful as a fundamental structural class of chiral organosuperbase catalysts. Further studies are in progress to apply the helically chiral P3 phosphazene derivatives to catalytic enantioselective transformations.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) The enantiomers of (±)-**1a**·HBF_4 were resolved by using analytical HPLC equipped with a Daicel CHIRALPAK IB (MeOH–Et_2NH = 100:0.1, 1.0 mL/min, 240 nm, 40 °C): t_R = 23.3, 26.0 min. See Supporting Information (page S14).
(11) CCDC-964338 [(±)-**1a**·HI] 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.
(12) The enantiomers of (±)-**1b**·HCl were resolved by using analytical HPLC equipped with a Daicel CHIRALPAK IB (MeOH–Et_2NH = 100:0.1, 1.0 mL/min, 240 nm, 40 °C): t_R = 29.9 (isolated), 33.5 min. See Supporting Information (page S18).
(13) The second peak could not be isolated in an optically pure form because of overlap with the first peak under the preparative chiral stationary phase HPLC conditions.
(14) Specific rotation of the first eluting enantiomer, (+)-**1b**·HCl: $[\alpha]_D^{27}$ +91.7 (*c* 0.90, $CHCl_3$).
(15) CCDC-964339 [(±)-**1b**·HBr] 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.

