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New Chiral Zwitterionic Phosphorus Heterocycles: Synthesis, Structure, Properties and Application as Chiral Solvating Agents

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In memory of Ilya M. Lyapkalo

Abstract: A family of new chiral zwitterionic phosphorus-containing heterocycles (zPHC) have been derived from methylene-bridged bis(imidazolines). These structures were unambiguously determined, including single-crystal XRD analysis for two compounds. The stability, acid/base and electronic properties of these dipolar phosphorus heterocycles were subsequently investigated. zPHCs can be successfully employed as a new class of chiral solvating agents for the enantiodifferentiation of chiral carboxylic and sulfonic acids by NMR spectroscopy. The stoichiometry and binding constants for the donor–acceptor complexes formed were established by NMR titration methods.

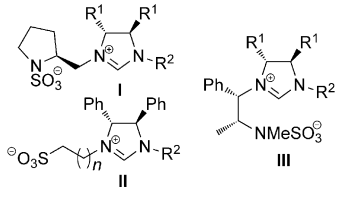
Keywords: binding constants · chirality · enantioselectivity · NMR spectroscopy · phosphorus heterocycles · zwitterions

Introduction

Significant advances in asymmetric chemistry have expedited demand for faster methods of analysis for enantiomeric mixtures.[1,2] Although chiral chromatography (LC or GC) is the accepted industrial standard for quantifying enantiomeric purity, these methods typically require several minutes, if not hours, and the assignment of the absolute stereochemistry can only be achieved by correlation with known compounds. In contrast, the use of a chiral derivatising agent (CDA) or chiral solvating agent (CSA) allows the enantiomeric ratio to be determined in a few minutes by NMR spectroscopy,[3] which is an available, automated and high-throughput technique available in modern laboratories. As an added advantage, the absolute stereochemistry of a particular enantiomer can also be established by further NMR experiments.[4]

CSAs form diastereomeric complexes with chiral analytes through weak intermolecular interactions, which lead to chemical-shift inequivalence in analogous nuclei. Because the technique is non-destructive, they are inherently more desirable than CDAs, which require the formation of a covalent bond. In general, there are two main types of interactions between a CSA and the analyte: 1) Host–guest interactions that involve the intercalation of the enantiomer within a supramolecular architecture, such as cyclodextrins, crown ethers, or peptides; and/or 2) Donor–acceptor interactions, mostly through H bonding with certain functional groups, for example, amines, alcohols, acids and sulfoxides.

To date, there has only been one report of zwitterionic CSAs, comprising of a chiral imidazolinium moiety with a sulfonate or sulfamate counteranion (Figure 1).[5] These molecules could provide multiple points of ionic contact for greater chiral recognition. However, because the charges are well separated, this can limit their solubility in organic solvents, for example, the best-performing compound **III** (R^1 = Ph, R^2 = 2-MeC_6H_4) is not soluble in toluene.



R^1 = H, Ph; R^2 = 2-MeC_6H_4, CH_2Mes; n = 1, 2

Figure 1. Chiral zwitterionic imidazolinium sulfonates/sulfamates.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300062. It includes data for new compounds, experimental procedures, crystallographic details, copies of ^1H and ^{13}C NMR spectra. X-ray crystallographic structures are provided as .cif files, as well as the checkpoint file for the calculated structure of compound **4a**.

Herein, we disclose the preparation, characterisation and properties of a structurally new class of chiral zwitterionic phosphorus heterocycles and their potential applications as CSAs for enantiodiscrimination of chiral carboxylic and sulfonic acids.

Results and Discussion

Design of zwitterionic phosphorus heterocycles: Prior to this work, examples of zwitterionic phosphorus compounds, containing a PO_2^- fragment with a positively charged sp^2 nitrogen atom, are limited to pyridinium or imidazolium adducts of metaphosphates (Figure 2).[6–8] These were reported as stable, crystalline compounds that can be isolated and fully characterised.

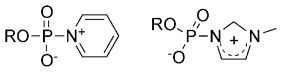


Figure 2. Known zwitterionic P^V compounds.

Chiral C_2-symmetric bisoxazolines **1** (BOX, Figure 3) are a unique class of privileged ligands for many metal-catalysed asymmetric reactions.[9–13] Of these, the class of zwitterionic boron-BOXates **2** were derived in 2006 by Bandini et al., and were shown to be moderately successful catalysts for the asymmetric reduction of prochiral ketones.[14]

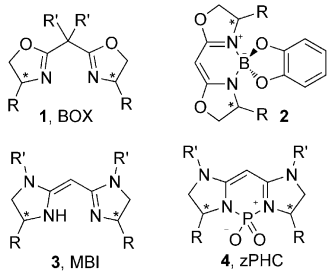


Figure 3. Zwitterionic structures derived from BOX (**1**) and MBI (**3**).

In 2007, methylene-bridged bis(imidazoline) ligands **3** (MBI) were reported as more flexible analogues of BOX.[15,16] Herein, the MBI scaffold was employed as a means of providing a rigid, chiral framework to construct zwitterionic P^V heterocycles **4**, which we abbreviated herein as zPHC (Figure 3).

By embedding a negatively charged PO_2^- fragment within a bisamidinium six-membered ring chelate, the resultant product may be stabilised by resonance structures **IV** and **V** (Figure 4); further, fine tuning of the steric and electronic properties can be achieved by modifying N-substituents of the parent MBI.

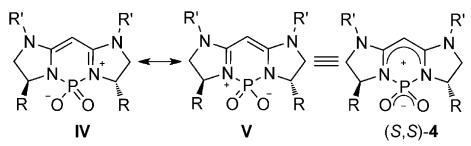
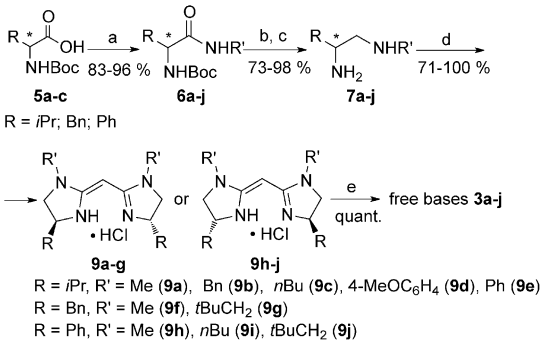


Figure 4. Resonance structures of **4**.

Improved synthesis of MBIs: MBI compounds **3** were prepared from the commercially available *N*-Boc protected amino acids, *N*-Boc-*S*-valine (**5a**), *N*-Boc-*S*-phenylalanine (**5b**) and *N*-Boc-*R*-phenylglycine (**5c**), by modifying a four-step procedure previously described by Pfaltz and co-workers (Scheme 1).[15] The *N*-Boc moiety in **6** was first unmasked by using AcCl/MeOH. The resultant hydrochloride salts were then directly employed in a reduction step with $LiAlH_4$, leading to an improved yield of 1,2-diamines **7**. Subsequently, the transformation of **7** into the desired MBIs **3** was achieved in two steps: the condensation of diamines **7** with diethyl malonimidate dihydrochloride **8** gave MBI derivatives **9** as HCl salts, isolated in good-to-excellent yields as easy-to-handle crystalline compounds. From these, the corresponding free MBI bases **3** can be released quantitatively, by treatment with 10% aqueous NaOH, immediately before their deployment in the subsequent reactions.

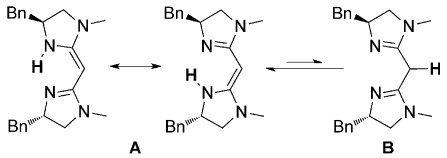


Scheme 1. Synthesis of MBI scaffolds **3**. a) NMM, $ClCO_2iBu$, $R'NH_2$; b) AcCl/MeOH, 0 °C to RT, 24 h; c) $LiAlH_4$, THF, reflux, 24–48 h; d) $CH_2(C(=NH)OEt)_2 \cdot 2HCl$ (**8**), CH_2Cl_2, RT to reflux, 24–96 h; e) $NaOH/CH_2Cl_2/H_2O$.

Compound **9f** was transformed into its tetrafluoroborate salt by ion exchange with aqueous $NaBF_4$ (3 M) to give single crystals suitable for X-ray crystallographic analysis (Figure 5). The molecular structure of (*S,S*)-**3f**·HBF_4 is largely similar to its unsubstituted analogue of 2,2′-methylene-bis(4,5-dihydro-1*H*-imidazole) hydrochloride (*H*-MBI).[16] The only significant difference was the dihedral angle, τ, between least-square planes of two five-membered rings, being 20.09(8)° for the **3f**·HBF_4, compared to 15.69(9)° for *H*-MBI. However, this angle is rather flexible and can be strongly affected by N−H···X hydrogen bonds.

Free MBI bases **3** exist as either one of two possible tautomeric forms in solution, which are strongly dependent upon the solvent. This was demonstrated by recording a series of ^1H NMR spectra of **3f** in seven different solvents at 23 °C (Table 1). In all cases, the conjugated tautomer (**A**) was thermodynamically more favourable than the unconjugated tautomer (**B**). The greatest stabilisation was provided by polar aprotic media, such as $[D_6]$DMSO and $[D_6]$acetone,

Table 1. Solvent-dependent tautomerisation of **3f** at 23 °C.



Solvent	$(CD_3)_2CO$	$(CD_3)_2SO$	$C_6D_5CD_3$	C_6D_6	CD_2Cl_2	CD_3OD	$CDCl_3$
A/B[a]	14:1	13:1	12:1	9:1	6:1	3:1	3:2

[a] Determined by comparison of ^{1}H NMR spectra integrals of N-CH_3 or BnC*H*N signals.

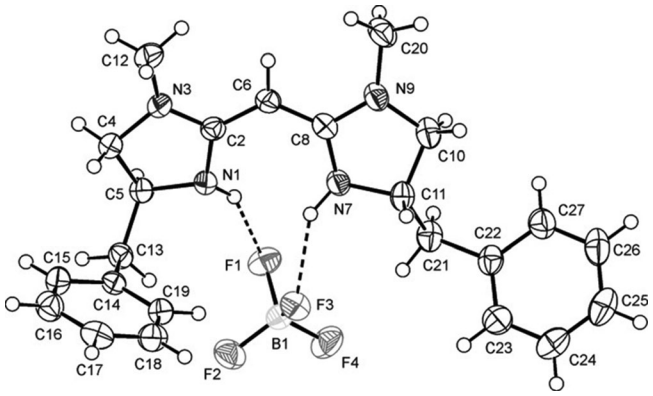
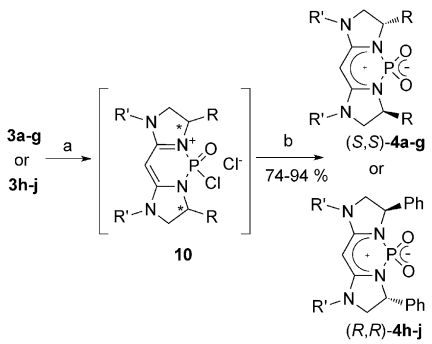


Figure 5. ORTEP representation of the molecular structure of (*S*,*S*)-**3f**·HBF_4. The displacement parameters are drawn at 50% probability level. The selected bond lengths [Å] and angles [°]: N1–C2 1.3607(17), N1–C5 1.4797(17), C2–N3 1.3348(17), N3–C4 1.4617(17), C4–C5 1.537(2), C2–C6 1.4012(18), C6–C8 1.3928(19), N7–C8 1.3562(18), C8–N9 1.3450(16), N9–C10 1.4562(19), N7–C11 1.4754(17), C10–C11 1.522(2); C8-C6-C2 125.97(12). Hydrogen-bond parameters for N1–H1···F1/N1···F1 2.9537(14) Å, angle at H1 151°; for N7–H7···F3: N7···F3 2.9309(14) Å, angle at H7 145°.

in which ratios of 13:1 and 14:1 were observed, corresponding to a relative stabilisation energy of approximately 6.5 kJ mol^{-1}. On the other hand, the lowest ratio of 3:2 was observed in $CDCl_3$ (ca. 1 kJ mol^{-1}).

Synthesis of zPHCs: The phosphorus heterocycle was formed by the reaction between MBI and phosphorus oxychloride ($POCl_3$), performed at room temperature in dry CH_2Cl_2 or THF, in the presence of NEt_3 (Scheme 2). The reaction proceeded smoothly to give the target zPHCs **4a–j** within 24 h. Monitoring the progress of the reaction by ^{31}P NMR spectroscopy, the formation of the ionic intermediate **10** can be detected in the crude reaction mixture, indicated by a distinct singlet resonance between −1 to −3 ppm. Upon treatment with a basic solution, the hydrolysis of **10** to the inner salt **4** was denoted by an upfield shift to between −13 to −15 ppm.



Scheme 2. Synthesis of zPHC **4**. a) $POCl_3$, NEt_3, CH_2Cl_2, 0 °C to RT, 24 h; b) aqueous NaOH (10%), RT.

The method was applied to the synthesis of a family of ten zPHCs (**4a–j**), which were isolated in good-to-excellent yields (74–94%). The zwitterionic products were fully characterised (see the Supporting Information), and further confirmation was provided by single-crystal X-ray analysis of compounds **4a** and **4f** (Figures 6 and 7). Both molecules have two-fold symmetry, with the C_2 axis dissecting the central methine carbon and phosphorus atom. It is interesting to note that the central six-membered rings are not quite planar. Comparing the structure of these zPHC molecules with the parent MBI (Figure 5), the incorporation of PO_2 moiety does not appear

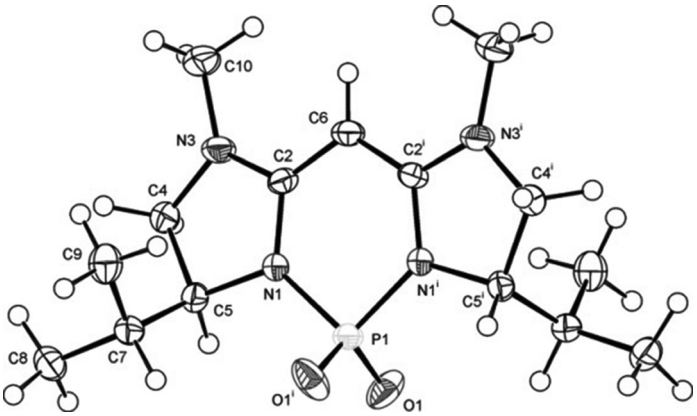


Figure 6. ORTEP representation of the molecular structure of (*S*,*S*)-**4a**. The displacement parameters are drawn at 50% probability level. The selected bond lengths [Å] and angles [°]: P1–O1 1.4761(14), P1–N1 1.7116(16), N1–C2 1.359(2), N1–C5 1.492(2), C2–N3 1.345(2), N3–C4 1.453(3), C4–C5 1.536(3), C2–C6 1.387(2); C2-C6-C2^{i} 118.8(2). Symmetry codes: i) $-x+2$, $-y$, z.

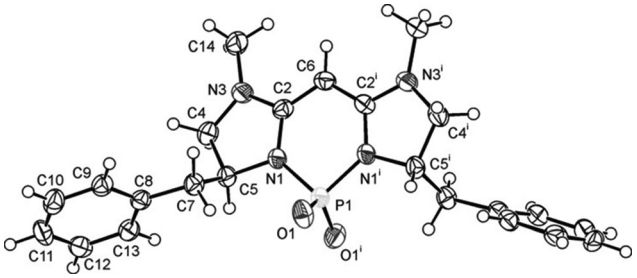


Figure 7. ORTEP representation of the molecular structure of (*S*,*S*)-**4f**. The displacement parameters are drawn at 50% probability level. The selected bond lengths [Å] and angles [°]: P1–O1 1.4737(19), P1–N1 1.711(2), N1–C2 1.359(3), N1–C5 1.483(3), C2–N3 1.347(3), N3–C4 1.454(3), C4–C5 1.536(4), C2–C6 1.391(3); C2-C6-C2^{i} 118.6(3). Symmetry codes: i) $-x+2$, $-y+2$, z.

to affect the conjugation within imidazolines rings, because the bond lengths found in **4a** and **4f** are almost identical with respective lengths of (*S,S*)-**3f**·HBF_4, with the exception of a more acute angle at the central methine carbon, being 118.8 and 118.6° for **4a** and **4f**, respectively, compared to 125.6° in **3f**.

The electronic properties of the zPHC compounds were investigated by performing DFT calculation of the distribution of charges in **4a**, which showed that the molecule possesses a sizeable dipole moment of 12 D along the C_2 axis (Figure 8). Interestingly, although the negative charge is localised on the oxygen atoms, the positive charge is distributed extensively over the MBI framework.

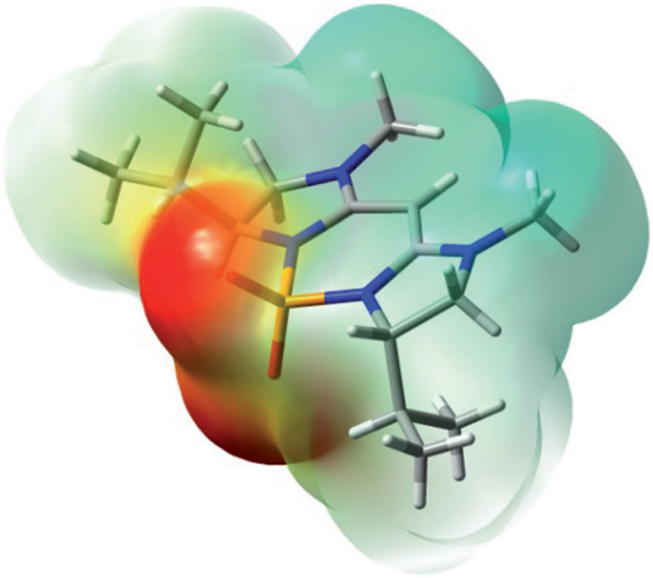


Figure 8. Electrostatic potential map of compound **4a**, as was determined by DFT calculations. Negative, neutral and positive potentials are represented in red, green and blue, respectively.

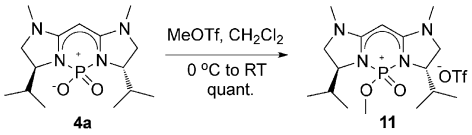
Properties of the phosphorus heterocycles 4: The zPHC compounds **4** are stable as solids, which can be kept at ambient temperature for at least a year without decomposition. They are soluble in common organic solvents and, in the case of R′=Me, in water. The stability of three zPHC compounds **4a**, **4f** and **4h** was also evaluated under neutral or basic conditions in DMSO, at ambient and elevated temperatures (Table 2). All three compounds were hydrolytically stable in a mixture of H_2O/DMSO at neutral pH up to 100 °C. However, upon addition of a hydroxide base, slow decomposition of the phenyl-substituted zPHC **4h** was detected at room temperature, which was accelerated at 100 °C to form an intractable mixture of compounds. In contrast, zPHC analogues **4a** and **4f**, containing isopropyl and benzyl substituents, respectively, were stable in the alkaline media at 100 °C for up to 24 h, that is, the substituents at the stereogenic C-3 and C-7 have a major effect on the stability of these molecules.

Table 2. Stability of compounds **4a**, **f**, **h** (R′=Me) in neutral and basic solutions of [D_6]DMSO/H_2O (10:1 v/v).[a]

zPHC	pH	*t* [h]	*T* [°C]	Decomposition [%]
4a, **f**, **h**	neutral	24	RT	–[c]
		1	100	–[c]
		24	100	–[c]
4a, **f**	basic[b]	24	RT	–[c]
		1	100	–[c]
		24	100	–[c]
4h	basic[b]	24	RT	5
		1	100	15
		24	100	50

[a] Monitored by ^{1}H NMR spectroscopy. The amount of decomposition was measured by integrating the Me (R′) signal against an internal standard (anisole). [b] [D_6]DMSO/H_2O/50 % aqueous KOH (10:1:1, v/v/v). [c] No decomposition was observed within the detection limit.

The inherent nucleophilicity of the P–O^- bond was examined by the reaction of **4a** with a number of alkylating agents: BnBr, MeI, TBSOTf and MeOTf. The formation of the phosphoric acid ester **11** was only successful by using MeOTf, showing the molecule to be weakly nucleophilic (Scheme 3). Conversely, compound **11** is prone to hydrolysis, reverting to the zPHC **4a** upon exposure to aqueous NaOH or KOH (10 %) under ambient conditions. Thus, the cation–anion interaction between the ion pair of **11** is weaker than that found in the inner salt **4a**.



Scheme 3. Methylation of zPHC **4a**.

Applications of zPHC 4 as CSAs: Chiral carboxylic acids can be found in many biologically active natural products, in which they constitute a class of important chiral building blocks in the development of agrochemical and pharmaceutical products. For chiral HPLC and GC to be deployed for enantiomeric excess (*ee*, %) determination, the presence of a CO_2H moiety in the analyte often requires derivatization into the ester or amide to alter its polarity and/or volatility for analysis. This can be potentially problematic, particularly if the carboxylic acid has an intrinsically low reactivity due to steric or electronic effects, as incomplete derivatization can lead to errors in analysis. Consequently, the development of CSAs for the analysis of chiral carboxylic acids is a highly topical research area. Commercially available chiral amines, such as phenethylamine and (pseudo)ephedrines, are generally not effective for acids due to the formation of ammonium carboxylate salts, which may not be soluble in the NMR solvent.[17] Apart from macrocyclic receptors,[18,19] recent development of small-molecule CSAs are dominated by diamine and/or amide derivatives.[20–29]

Potentially, the zPHC scaffold could provide multiple sites for dipole–dipole, hydrogen-bonding and π–π interactions,

as was suggested by the electron distribution shown in Figure 8. In a previous study,[30] we have shown that heterocycles of type **4** possess certain basic character. Keeping this in mind, the application of these compounds as CSAs for chiral acids was examined in this work. The initial study was carried out by recording ^{1}H NMR spectra (400 MHz) of equimolar mixtures of racemic mandelic acid (MA) as a model analyte with **4a**, **4f**, **4h** or **4j** at 23 °C. The addition of a solution of receptor **4h** (26.3 mM) to a solution of racemic MA (26.3 mM) in $CDCl_3$ caused the stereogenic C–H signal of the α-chiral acid to shift upfield and split into two equally intense singlets. Variation of the *N*-Me substituent in **4h** to a bulky *N*-neopentyl in **4j** did not induce significant changes in the enantiodiscrimination (Figure S1 in the Supporting Information). Conversely, the isopropyl- and benzyl-substituted derivatives, **4a** and **4f**, respectively, were ineffective CSAs.

To define the binding interactions, NMR titration experiments were performed by using compounds **4h** and **4j**.[31,32] The effect of concentration on the chemical shift differences ($\Delta\Delta\delta$) was examined by the addition of **4h** to a solution of (*rac*)-MA (Figure 9). Baseline resolution was achieved over a considerably wide concentration ratio of [**4**]/[(*rac*)-MA] (ca. 0.25–9.0), with (*S*)-MA undergoing the larger upfield shift.

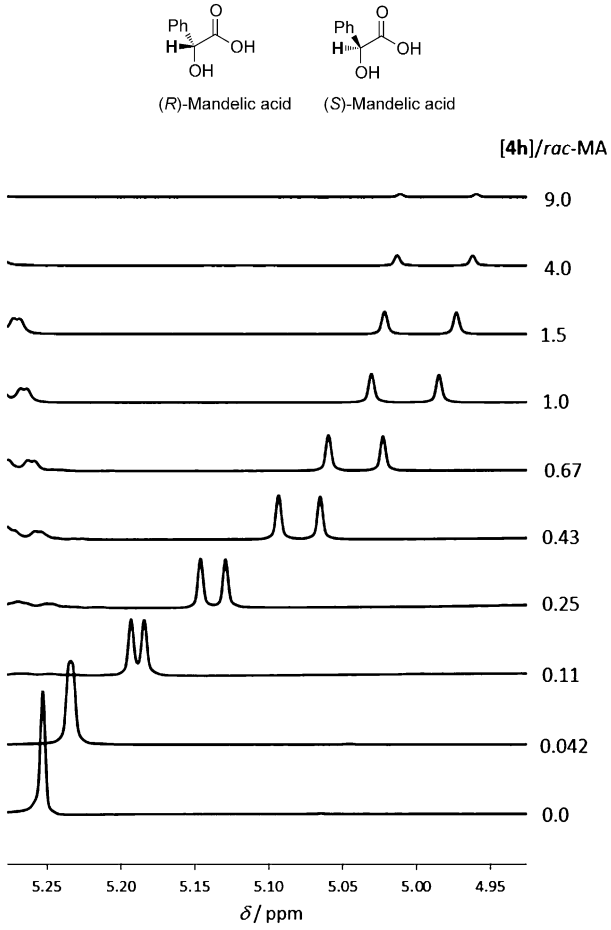


Figure 9. Variation with concentration of $\Delta\Delta\delta$ for (*rac*)-MA (26.3 mM) in the presence of **4h** ($CDCl_3$, 400 MHz, 23 °C).

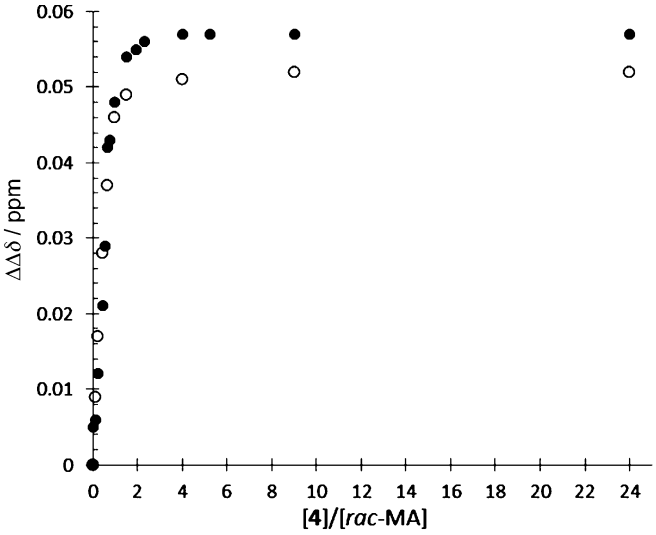


Figure 10. Chemical shift non-equivalencies ($\Delta\Delta\delta$) of the enantiomeric α-H signals of (*rac*)-MA (26.3 mM in $CDCl_3$; spectra were recorded at 23 °C) as a function of molar ratio for the receptors **4h** (●) and **4j** (○).

Figure 10 represents changes in the chemical shift non-equivalence ($\Delta\Delta\delta$) observed for the interaction of (*rac*)-MA in the presence of increasing amounts of **4h** and **4j**. In both cases, the enantiomeric separation increased sharply and maximum $\Delta\Delta\delta$ values of 0.052 ppm (21 Hz) and 0.057 ppm (23 Hz) were observed for **4h** and **4j**, respectively, near [**4**]/[(*rac*)-MA] = 2.

The stoichiometry of the donor–acceptor complex was established by using Job's plots (see Figure S3 in the Supporting Information). Keeping the total concentration of [**4h**] + [MA] constant at 20.3 mM, the plot of $\Delta\delta$ versus the mole fraction of (*R*)- or (*S*)-MAs (*X*) showed a maximum at $X = 0.67$, providing the evidence that both enantiomers of MA form 2:1 complexes with zPHC. The binding constants of **4h** for MA were subsequently determined quantitatively, by varying the concentration of single enantiomers of MA in the presence of a constant concentration of **4h** (Figure 11). By using the established 1:2 complex stoichiometry, non-linear least-squares fitting[33] revealed $K(S) = (341 \pm 11)\,\text{M}^{-1}$ and $K(R) = (176 \pm 5)\,\text{M}^{-1}$, corresponding to a chiral recognition energy ($\Delta\Delta G°$) of -0.39 kcal mol^{-1}.[34]

Last but not least, excellent correlation between expected and observed *ee* values was established by integration of the α-proton signal of mandelic acid (*ee* between −85 to 85 %) in the presence of two equivalents of **4h** (Figures 12 and S6 in the Supporting Information). The excellent linearity fit showed that the method can be used to determine the enantiopurity of MA with a high level of accuracy.

In a preliminary study, **4h** was also employed for the enantiodiscrimination of other types of chiral acids. We were particularly interested in dibenzoyltartaric (or tartaric acid dibenzoate, $pK_a = 1.85$) and camphorsulfonic ($pK_a = 1.2$) acids, which are substantially more acidic than MA

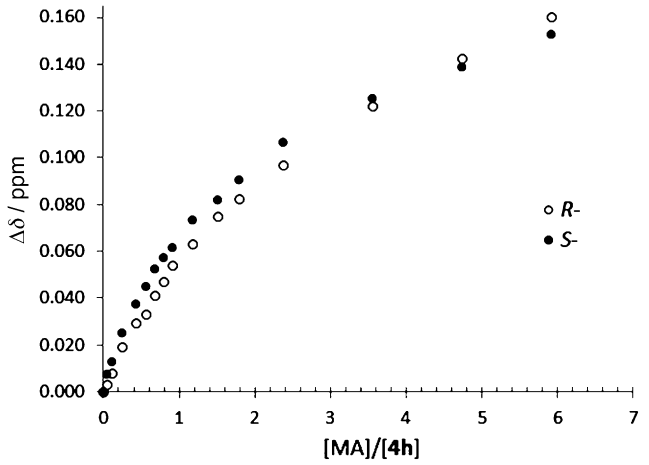


Figure 11. Plots of $\Delta\delta$ for the N-*Me* signal of **4h** (5.07 mM) as a function of [MA]/[**4h**] ratio ($CDCl_3$, 400 MHz, 23 °C). ● = binding with *S*-MA and ○ = binding with *R*-MA.

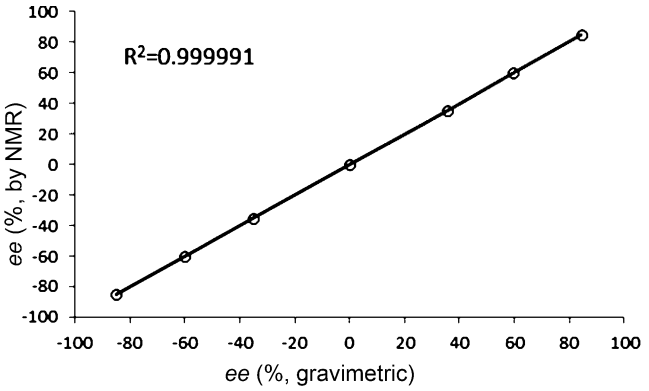


Figure 12. Correlation between the prepared and observed % *ee* values.

($pK_a = 3.41$). Consequently, they present a considerable challenge for CSAs that contain Brønsted basic sites (e.g., chiral-amine derivatives), which can form insoluble salts with these analytes.

Addition of an equimolar of **4h** to dibenzoyltartaric acid induced an upfield shift of the methine protons (Figure 13). In this case, the protons remained chemically equivalent in each complex, that is, the C_2 symmetry appeared to be retained, at least on the NMR timescale. A chemical-shift difference of $\Delta\Delta\delta = 0.12$ ppm (48 Hz) was subsequently recorded, which is significantly larger than that reported with other CSAs derived from chiral amines.[22,23,25] To date, there is only one CSA reported for the enantiodiscrimination of a chiral sulfonic acid.[21] Thus, we were delighted to find that **4h** can induce splitting in the C8 and C9 methyl resonances of 10-camphorsulfonic acid (Figure 14). In this case, $\Delta\Delta\delta$ of 0.0195 (7.8 Hz) and 0.0215 ppm (8.6 Hz) were recorded when [acid/**4h**] = 1:1, whereas 0.0214 (8.5 Hz) and 0.0223 ppm (8.9 Hz) were observed when the ratio was changed to 2:1.

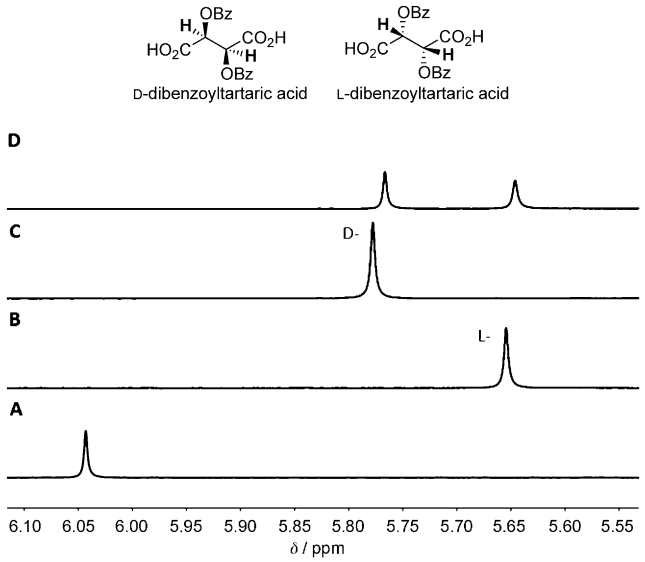


Figure 13. Resolution of dibenzoyltartaric acid by the addition of **4h** (20 mM in $CDCl_3$, 400 MHz, 23 °C). Signals corresponding to the methine protons are presented. a) Racemic acid; b) **4h** + L-acid (100 % *ee*); c) **4h** + D-acid (100 % *ee*); and d) **4h** + racemic acid.

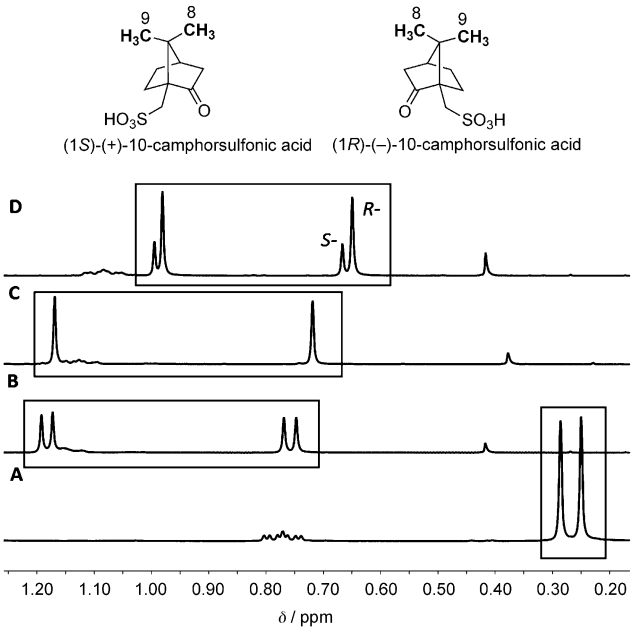


Figure 14. Resolution of camphor-10-sulfonic acid (17.2 mM in C_6D_6; 400 MHz; 23 °C). Resonances corresponding to C8 and C9 methyl groups are presented. a) Racemic acid; b) **4h** + racemic acid; c) **4h** + *R*-acid (100 % *ee*); d) **4h** + *R*-acid (35 % *ee*). The signals at approximately 0.4 ppm belongs to residual water; other signals belong to the analyte.

Conclusion

A family of chiral zwitterionic phosphorus-containing heterocycles (zPHC) have been designed, synthesised and characterised. X-ray structural analysis and DFT calculations suggest that these zPHCs are highly polar molecules, combining a concentration of electron density on the PO_2^-

moiety, with a highly diffused cation within the bisimidazoline framework. These special qualities were exploited in their application as structurally new chiral-solvating agents, in resolving a wider range of analytes. Our preliminary studies showed that they can be used to resolve an α-hydroxyl acid, a diacid and a sulfonic acid. Examples of such broad applicability of a CSA across different types of chiral acids are rare. The nature of the binding will be examined in our future work, including potential applications in asymmetric synthesis.

Experimental Section

General: Solvents were dried by passing through columns of molecular sieves in a solvent-purification system (Innovative Technology Inc.). Unless otherwise stated, materials obtained from commercial suppliers were used without further purification. Preparative separations were performed by silica-gel gravity-column chromatography. TLCs were visualized with molybdate dip or UV light. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{31}P NMR (162 MHz) and ^{19}F NMR (377 MHz) spectra were recorded at 25 °C on Bruker Avance 400 MHz spectrometers. Chemical shifts (δ) are reported in ppm relative to residual $CHCl_3$ ($\delta = 7.26$ ppm) or DMSO ($\delta = 2.50$ ppm) for ^{1}H NMR and $CDCl_3$ ($\delta = 77.00$ ppm) or $[D_6]$DMSO ($\delta = 39.52$ ppm) for ^{13}C NMR. $(MeO)_3P{=}O$ ($\delta = 3.0$ ppm in $CDCl_3$) was used as internal standard for ^{31}P NMR spectra. IR spectra were recorded on FTIR spectrometers Bruker Equinox 55 or Perkin–Elmer Spectrum 100 as neat samples or as solutions in $CHCl_3$. HR MS were recorded on GTC Premier, LTQ Orbitrap XL, Micromass Autospec Premier, Micromass LCT Premier, or VG Platform II spectrometers by using EI or ESI ionization methods in methanol, acetonitrile or chloroform. Optical rotation was measured on Autopol IV polarimeter. Elemental analysis was performed by using PE 2400 Series II CHNS/O elemental analyser. Melting points were determined by using an Electrothermal Gallenhamp apparatus fitted with a calibrated thermometer with an error of ±2 °C. HPLC analyses were performed on Hewlett Packard 1050 HPLC machines by using CHIRACEL OD and OD-H columns.

Mulliken partial charges and electrostatic potential surfaces for compound **4a** were calculated by DFT by using Gaussian 09[35] and GaussView 5.0 software (www.gaussian.com), by employing a B3LYP/6–311G-(d,p) basis set.

X-ray structure determination: CCDC-900435 (**3f**·HBF_4), CCDC-900436 (**4a**) and CCDC-900437 (**4f**) contain 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.

Synthesis of phosphorus zwitterionic heterocycles 4: *General procedure:* A mixture of the corresponding salt **9** (1 mol equiv) and aqueous NaOH (10%, 15 mol equiv) in CH_2Cl_2 (15 mL per 1 mmol of **9**) was vigorously shaken in a separatory funnel for 5 min. The organic phase was separated; the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic phases were washed with H_2O (20 mL), dried over $MgSO_4$ and concentrated to dryness under reduced pressure to provide the corresponding free base **3** quantitatively as a white solid. The free MBI base **3** was then dissolved in dry CH_2Cl_2 (5 mL per 1 mmol of salt **9**), the resulting solution was cooled to 0 °C followed by the dropwise addition of phosphorus oxychloride (1 mol equiv) and triethylamine (2 mol equiv) under the atmosphere of dry argon. The reaction mixture was stirred for 24 h at RT, concentrated to dryness under reduced pressure and quenched with aqueous NaOH (10%, 10 mol equiv). After 12 h of stirring at RT, the reaction mixture was extracted with CH_2Cl_2 (3×50 mL), the combined organic phases were washed with H_2O (20 mL), dried over $MgSO_4$ and concentrated to afford pure inner salts **4** as white or pale yellow solids. Analytical samples of **4** were prepared by recrystallization from a suitable solvent. For further details, see the Supporting Information.

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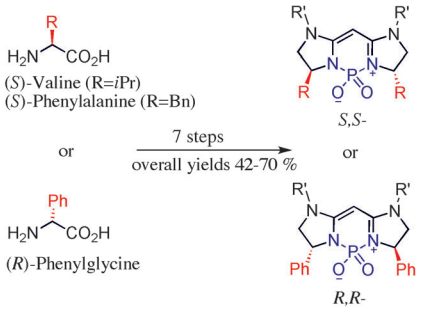
A convenient synthetic approach to a new class of chiral zwitterionic phosphorus-containing heterocycles starting from methylene-bridged bis(imidazolines) was designed and executed. Stability and properties of the synthesized compounds were investigated. The applicability of the designed compounds as chiral solvating agents for the determination of the enantiomeric excesses of chiral acids was demonstrated.



Synthetic Methods

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New Chiral Zwitterionic Phosphorus Heterocycles: Synthesis, Structure, Properties and Application as Chiral Solvating Agents