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Mannose derived hexacoordinated phosphate–a generally efficient chiral anion for asymmetric applications†

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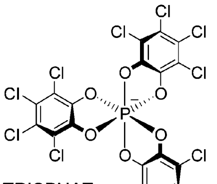
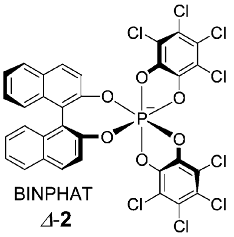
Mannose derived hexacoordinated phosphate—prepared in two steps from methyl-α-D-mannopyranoside—is a chiral anionic auxiliary with broad asymmetric efficiency.

Many chemical reactions and processes involve cationic prostereogenic or racemic reagents, intermediates or products. To afford non-racemic or enantiopure adducts, an asymmetric ion pairing of the cations with chiral anions can be considered, the counterions behaving as asymmetric auxiliaries, ligands or reagents.[1] Lately, the chemistry of hexacoordinated phosphate anions has been rejuvenated for exactly this purpose as chiral TRISPHAT **1** and BINPHAT **2** anions (Λ or Δ enantiomers) were shown to be valuable NMR chiral shift, resolving and asymmetry-inducing reagents.[1,2] Recently, results have indicated that **1** is essentially efficient with metallo-organic and organo-metallic complexes,[1,3] while **2** is primarily effective with organic compounds.[4] Anion **2**, which contains a strained 7-membered ring, is however sensitive to acid conditions and decomposes over time when associated with Brønsted or Lewis acidic cations.[2b,‡] An enantiopure hexacoordinated phosphorus anion, which would be (i) highly chemically stable, (ii) rapidly and stereoselectively synthesized and (iii) asymmetrically efficient with both organic and metallo-organic cations was thus looked for. Herein, we report that mannose derived hexacoordinated phosphate anion **3** [eqn. (1), Λ diastereomer], prepared in two steps from commercially available materials, is such a derivative.

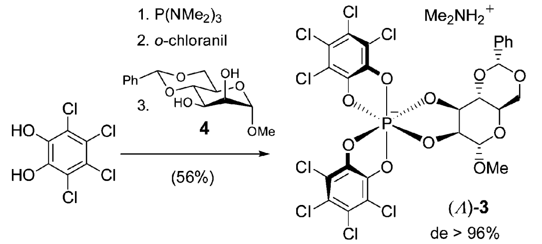


TRISPHAT
Δ-**1**



BINPHAT
Δ-**2**

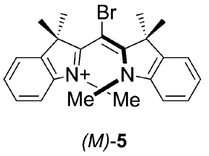
Carbohydrates are probably the class of natural compounds with the most asymmetric centers and potential ligand atoms per molecule. As such, they have often been used in asymmetric synthesis and catalysis.[5] From inexpensive commercially available sugars, interesting 1,2-, 1,3- and 1,4-diols can be synthesized in a few steps. Their use as chiral ligands for the stereoselective synthesis of hexacoordinated phosphate anions was therefore tempting. Of all possible compounds, methyl 4,6-*O*-benzylidene-α-D-mannopyranoside **4** [eqn. (1)] was selected for (i) its one-step preparation from commercially available methyl-α-D-mannopyranoside,[6] (ii) the rigidity of its skeleton, and (iii) the sterically-demanding *cis*-1,2-relationship of the free hydroxyl groups.§



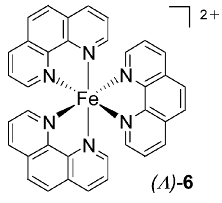
(1)

Anion **3** was then synthesized in a three-steps one-pot protocol: anhydrous tetrachlorocatechol and P(NMe$_2$)$_3$ were reacted in toluene at reflux. After concentration *in vacuo*, successive additions in CH$_2$Cl$_2$ of *o*-chloranil (3,4,5,6-tetrachloro-3,5-cyclohexadiene-1,2-dione) and diol **4** yielded the desired dimethylammonium salt of phosphate **3**, which precipitated upon addition of Et$_2$O (56%). Unlike [Me$_2$NH$_2$][**2**] which decomposes in solution over time, salt [Me$_2$NH$_2$][**3**] was found to be stable as no evidence for decomposition of the phosphate moiety was found in spectroscopic studies. Initial data further suggested the presence of only one diastereomer in the precipitate as a single set of signals was detected in ^{1}H, ^{13}C and ^{31}P NMR. Crystals of (+)-[Me$_2$NH$_2$][**3**] were obtained by diffusion of hexane to an acetone–EtOAc solution. X-Ray diffraction analysis confirmed the presence of a single diastereomer (Λ configuration, ESI†).¶ The configurational assignment was further established in solution by circular dichroism (CD) analysis of salt (+)-[Me$_2$NH$_2$][**3**] (MeOH, 1.67×10^{-5} M) which revealed strong exciton coupling in the π–π* region ($\Delta\varepsilon_{213} = -77$, $\Delta\varepsilon_{222} = +97$ M^{-1}cm^{-1}).[7]

To test the asymmetric efficiency of anion Λ-**3**, and compare it with that of anions **1** and **2**, chiral cationic substrates **5** (organic, helical, charge 1+, *P* or *M* enantiomers)[8] and **6** (metallo-organic, octahedral, charge 2+, Δ or Λ enantiomers) were selected for their different nature and geometry. Compounds **5** and **6** are configurationally labile in solution and their association with a chiral anion can be stereoselective if one diastereomeric ion pair is thermodynamically favored over the other (*e.g.* [*M*-**5**][Λ-**3**] over [*P*-**5**][Λ-**3**]).[9] The characterization and quantification of the asymmetry-induction (Pfeiffer Effect) is performed by CD and by NMR spectroscopy if the anionic auxiliary is—in addition—a good chiral shift agent.[2b,3d]



(M)-**5**



(*Λ*)-**6**

The association of monomethinium cation **5** with enantiopure anions **1**, **2** and **3** was realized following previously reported guidelines. Solutions of salt [**5**][BF$_4$] and of [cinchonidinium][Δ-**1**], [Me$_2$NH$_2$][Δ-**2**] or [Me$_2$NH$_2$][Λ-**3**] in CH$_2$Cl$_2$–acetone were prepared, mixed, concentrated and purified by

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† Electronic supplementary information (ESI) available: spectroscopic and crystallographic data on [Me$_2$NH$_2$][**3**]. See http://www.rsc.org/suppdata/cc/b3/b305169b/

Table 1

Anion		Λ-**3**			Δ-**1**			Δ-**2**		
Cation	Solvent	de (%)	Δδ (ppm)	Config[a]	de (%)	Δδ(ppm)	Config[a]	de (%)	Δδ(ppm)	Config[a]
5	$CHCl_3$	34	0.086[b]	*P*	0	0.007[b]	[c]	27	0.083[b]	*M*
6	2.5% DMSO –$CHCl_3$	89	0.445[d]	Λ	97	[c]	Δ	[c]	[c]	[c]
6	5.0% DMSO –$CHCl_3$	87	0.420[d]	Λ	95	[c]	Δ	[c]	[c]	[c]
6	10.0% DMSO –$CHCl_3$	81	0.332[d]	Λ	82	0.605[d]	Δ	[c]	[c]	[c]
6	15.0% DMSO –$CHCl_3$	70	0.231[d]	Λ	66	0.480[d]	Δ	[c]	[c]	[c]
6	20.0% DMSO –$CHCl_3$	57	0.220[d]	Λ	45	0.308[d]	Δ	[c]	[c]	[c]
6	30.0% DMSO –$CHCl_3$	30	0.107[d]	Λ	13	[c]	Δ	[c]	[c]	[c]

[a] Induced configuration of the cation. [b] NMe signal. [c] Not applicable. [d] H(2,9).

chromatography (SiO_2 or Al_2O_3, CH_2Cl_2) to afford the desired ion pairs [**5**][Δ-**1**], [**5**][Δ-**2**] or [**5**][Λ-**3**] as the most eluted compounds.[2b,||] After diastereomeric equilibration (> 5 hours), ^1H NMR analysis of the salts containing anions **2** and **3** revealed two distinctive sets of signals for **5** with rather large differences in chemical shifts between the *M* and *P* enantiomers (NMe signal, $\Delta\delta$ 0.083–0.086 ppm, Table 1). A moderate but definite stereoselective induction was measured by integration of the respective signals (Fig. 1, spectra c and d, de 27 and 34%), and confirmed by CD analysis of [**5**][Δ-**2**] and [**5**][Λ-**3**] ($\Delta\varepsilon_{519}$ = +5 and $\Delta\varepsilon_{511} = -13$ $M^{-1}cm^{-1}$, $CHCl_3$, 4.40×10^{-5} M); The positive and negative Cotton effects being indicative of a *M* and *P* configuration for **5** respectively.[2b,10] Overall, a slightly better asymmetric efficiency was observed for anion **3**. As expected, TRISPHAT **1** showed little effect (Fig. 1, spectrum b).

Association of iron(II) tris(1,10-phenanthroline) complex **6** with counterions **1**, **2** and **3** was attempted using the above-described method. Only salts [**6**][Δ-**1**]$_2$ and [**6**][Λ-**3**]$_2$ could be isolated (62 and 51%); anion Δ-**2** decomposing upon the ion pairing. Solutions of [**6**][Δ-**1**]$_2$ and [**6**][Λ-**3**]$_2$ were prepared in mixtures of $CDCl_3$ and DMSO-d_6 (2.5% to 30%). After diastereomeric equilibration (< 30 minutes), ^1H NMR analyses revealed an enantiodifferentiation of cation **6**. In low polar media (lower % DMSO), large differences in chemical shifts were observed between analogous protons of the diastereomers ($\Delta\delta$, Table 1) and a high diastereoselectivity was measured by integration of the respective signals (de up to 89 and 97%, Λ-**3** and Δ-**1** respectively, Table 1). The increase in $\Delta\delta$ values and of the diastereoselectivity as the solvent polarity is reduced is interpreted as the result of stronger interactions between the ions. CD spectra analyses revealed positive and negative signals at the longer wavelengths ([**6**][Δ-**1**]$_2$: $\Delta\varepsilon_{557}$ = +13; [**6**][Λ-**3**]$_2$: $\Delta\varepsilon_{549} = -17$ $M^{-1}cm^{-1}$, $CHCl_3$, 1.0×10^{-5} M) indicating induced absolute Δ and Λ configurations for **6**.[11] An efficient homochiral [Δ-**6**][Δ-**1**]$_2$ and [Λ-**6**][Λ-**3**]$_2$ ion pairing is therefore preferred regardless of the lower C_1 symmetry of **3**.[3c–d] Interestingly, anion **3** is more selective than **1** in more polar solvent conditions (DMSO / $CHCl_3$ > 15%). Further studies are performed to better characterize the association between **3** and **6** as discriminating interactions between carbohydrates and coordination complexes have recently been observed.[12]

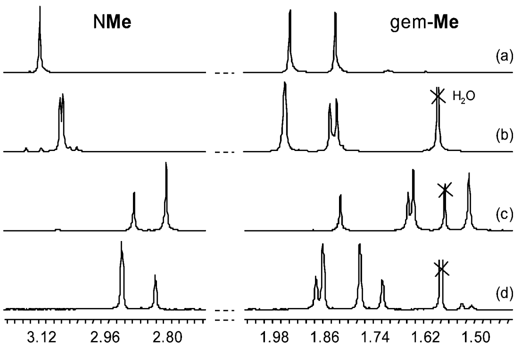

Fig. 1 ^1H NMR ($CDCl_3$, 400 MHz, parts) of (a) [**5**][BF_4], (b) [**5**][Δ-**1**], de 0%, (c) [*M*-**5**][Δ-**2**], de 27% and (d) [*P*-**5**][Λ-**3**], de 34%.

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Notes and references

‡ Halogenated solvents (CH_2Cl_2, $CHCl_3$, *etc.*) should be avoided if a BINPHAT salt has to remain in solution for several days.

§ In diol **4**, the free *cis*-hydroxyl groups adopt a sterically-demanding axial–equatorial arrangement; this and the formation of the rigid, *trans*-decalin like, 1,3-dioxane ring were considered to be favorable factors for a high diastereoselectivity at the P-atom.

¶ Crystal data for [Me_2NH_2][Λ-**3**](C_3H_6O): $C_{31}H_{30}NO_{11}PCl_8$, M = 907.2, monoclinic, a = 18.5028(13), b = 16.1920(8), c = 14.6519(9), β = 110.117(7)° Å, U = 4121.9(5) Å^3, T = 200 K, space group C 2 (no. 5), Z = 4, μ(Mo–K$_\alpha$) = 0.64 mm^{-1}, 31887 reflections measured, 9336 unique (R_{int} = 0.046) from which 5943 were considered as observed ($|F_o| > 4\sigma(F_o)$) and used in all calculations. The final $wR(F)$ was 0.036 and the Flack parameter x = 0.01(7). CCDC 210499. See http://www.rsc.org/suppdata/cc/b3/b305169b/ for crystallographic data in .cif format.

|| As anion **3** is more polar than **1** and **2**, EtOAc (0–10%) is usually added to the mobile phase to elute the corresponding [**5**–**6**][**3**] salts.

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