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NMR enantiodifferentiation of triphenylphosphonium salts by chiral hexacoordinated phosphate anions

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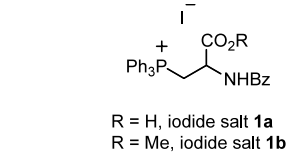
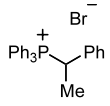
Abstract—BINPHAT anion—rather than TRISPHAT—is an efficient NMR chiral shift reagent for triphenylphosphonium salts containing stereogenic centers on the aliphatic side-chain.

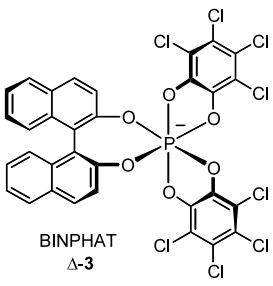
Phosphonium salts are versatile compounds, which have found widespread applications as Wittig reagent precursors,[1,2] but also as ionic liquid,[2] crystal liquid,[3] PTC catalysts,[4] or for their nonlinear optical properties.[5] Since the pioneering works of McEwen, Horner and Luckenbach,[6] few studies have been performed using chiral quaternary phosphonium salts in asymmetric reactions, certainly due to the difficulty of their preparation in enantiopure form. Recently, significant progresses have been made, for the stereoselective synthesis of chiral quaternary phosphonium salts from P-chirogenic phosphine–borane complexes[7] and of triphenylphosphonium salts bearing aminoacid substituents.[8] In this last case, the α-amino acid derivative **1a**, was obtained in 80% overall yield, by ring opening of an oxazoline salt derived from serine, with trimethylsilyl iodide, followed by quaternization with PPh_3. These efficient routes to chiral phosphonium salts open new fields for their use in stereoselective reactions, but also poses the problem of the determination of their enantiomeric purity. Until today, the enantiomeric purity of the acidic compound **1a** was controlled by ^{31}P NMR spectroscopy after its in situ transformation into cinchonidinium salts.[8] An enantiodifferentiation was observed for the diastereomeric ion pairs ($\Delta\Delta\delta \sim 0.06$ ppm, ^{31}P NMR). This method, which requires the presence of a carboxylic acid moiety on the analyte, could not be applied to the ester or the unfunctionalized salts, **1b** or **2**, respectively.



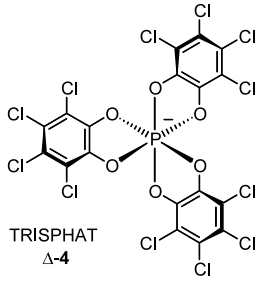
R = H, iodide salt **1a**
R = Me, iodide salt **1b**



bromide salt **2**



salt $[Bu_4N][\Delta\text{-}\mathbf{3}]$



salt $[Bu_4N][\Delta\text{-}\mathbf{4}]$

A more general method to determine the enantiomeric purity of triphenylphosphoniums bearing stereogenic centers on the aliphatic chain, such as in salts **1a**, **1b** and **2**, was thus looked for. Herein, we report that BINPHAT anion **3** is a good NMR chiral shift agent for these cations as it induces an efficient enantiodifferentiation in both ^{1}H and ^{31}P NMR spectroscopy.

In the last decades, NMR has evolved as one of the methods of choice for the determination of the enantiomeric purity of chiral species.[9] Lanthanide reagents, which have been particularly efficient for most applica-

Keywords: NMR enantiodifferentiation; phosphonium salts; amino acids and derivatives; BINPHAT; TRISPHAT; chiral anions.

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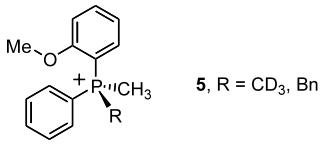
tions, have however been rarely used with chiral cations due to often excessive line broadening and distorted baselines.[10] Previously, chiral hexacoordinated phosphate anions BINPHAT **3** (bis(tetrachlorobenzenediolato) mono([1,1′]binaphthalenyl-2,2′-diolato)-phosphate(V))[11] and TRISPHAT **4** (tris(tetrachlorobenzenediolato)phosphate(V))[12] have been shown to be readily prepared from commercially available starting materials. These diamagnetic anions are effective NMR chiral shift agents for cationic metallo-organic and organo-metallic substrates.[13] Anion **3** often leads to superior NMR enantiodifferentations than **4** when associated with organic cations.[11,14] Most relevance to the present study is the observation that TRISPHAT **4** is an efficient NMR chiral shift agent for P-chirogenic quaternary phosphoniums of type **5**.[15,16] Rather large differences were observed for the enantiomers of these chiral cations in the presence of anion **4** (R = Bn, ^{1}H NMR: $\Delta\Delta\delta_{max}$ 0.065 ppm, ^{31}P NMR: $\Delta\Delta\delta_{max}$ 0.112 ppm, C_6D_6).



5, R = CD_3, Bn

An NMR enantiodifferentiation was therefore expected for the structurally related triphenylphosphoniums of salts **1a**, **1b** and **2** upon the addition of ammonium TRISPHAT salts. However, this was not the case. Addition of [Bu_4N][Δ-**4**] reagent[17] to solutions of racemic salts (±)-**1a**, (±)-**1b** and (±)-**2** ($CDCl_3$:DMSO-d_6 (0–5%)) revealed, in general, little differences in the ^{1}H NMR spectra. This was particularly true for salts (±)-**1a** and (±)-**2** as no split of their signals could be observed, despite the use of an excess of TRISPHAT reagent (up to 4.0 equiv.).

For ester salt (±)-**1b**, the situation was moderately better as pairs of signals could be observed for several of the proton resonances upon addition of the chiral shift TRISPHAT agent. The higher-frequency NH signal was particularly easy to follow as well as the singlet signal of the ester methyl group (Fig. 1, spectra a and b). We could also observe a full separation of the signal of the proton α to the ester side-chain and of one of the diastereotopic methylene hydrogen atoms. Observed chemical shifts (δ), upfield/downfield shifts induced by the phosphate reagent ($\Delta\delta$), and the magnitude of the difference in chemical shifts of analogous protons of

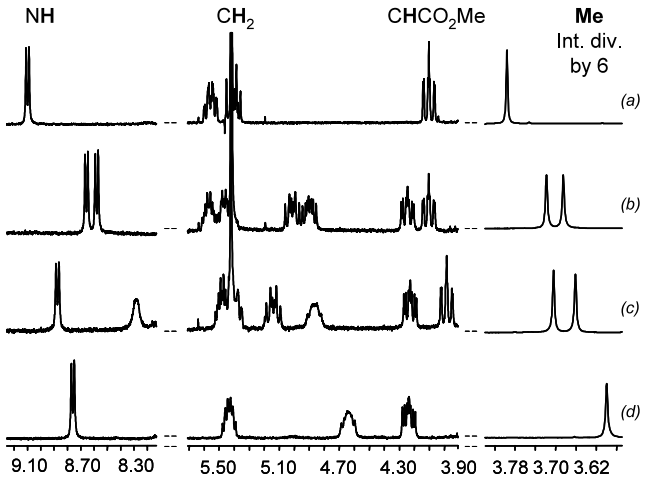


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$, parts) for (a) triphenylphosphonium salt (±)-**1b**, (b) (±)-**1b** and 3.4 equiv. of [Bu_4N][Δ-**4**], (c) (±)-**1b** and 3.0 equiv. of [Bu_4N][Δ-**3**], (d) (−)-**1b** (e.e. >96%) and 3.6 equiv. of [Bu_4N][Δ-**3**].

the two enantiomers of (±)-**1b** upon addition of 3.4 equiv. of [Bu_4N][Δ-**4**] ($\Delta\Delta\delta$) are summarized in Table 1.

In ^{31}P NMR (162 MHz), the situation was better as the NMR signals of the enantiomers of the phosphoniums were split in all cases ($\Delta\Delta\delta_{max}$: (±)-**1a**, 0.040 ppm; (±)-**1b**, 0.061 ppm and (±)-**2**, 0.109 ppm, ~3.0 equiv. of [Bu_4N][Δ-**4**]). However, the moderate efficiency of the TRISPHAT reagent to behave as a chiral shift agent for these cations led us to evaluate the influence of the BINPHAT anion.

As mentioned, recent examples have shown that BINPHAT anion **3** often displays better NMR chiral shift properties than TRISPHAT when associated with organic cations. We decided to test the generality of this observation with triphenylphosphonium salts **1a**, **1b** and **2**. Derivative [Bu_4N][Δ-**3**], rather than [Me_2NH_2][Δ-**3**], was selected for this study due to a higher solubility in low polarity solvents and a better overall chemical stability.[18] Its structural similarity with [Bu_4N][Δ-**4**] was also seen as a beneficial factor as it renders a direct comparison of the results more feasible.

Additions of various amounts of reagent [Bu_4N][Δ-**3**] (1.0–3.5 equiv.) to solutions of salts (±)-**1a**, (±)-**1b** and (±)-**2** were realized. For (±)-**1b** and (±)-**2**, pure $CDCl_3$ was used as solvent, but addition of 5% of DMSO-d_6

Table 1. Selected ^{1}H NMR chemical shifts of (±)-**1b** and effect on the chemical shifts induced by [Bu_4N][Δ-**4**] in $CDCl_3$

Proton	δ^a	δ^b		$\Delta\delta^b$		$\Delta\Delta\delta^b$
N**H**	8.999	8.557	8.480	−0.442	−0.519	0.077
P^+C**H**H′	5.304	4.913	4.798	−0.391	−0.506	0.115
C**H**CO_2Me	4.002	4.144	4.004	+0.142	+0.002	0.140
Me	3.756	3.678	30.646	−0.078	−0.110	0.032

[a] Without chiral anions.
[b] With 3.4 equiv. of [Bu_4N][Δ-**4**].

Table 2. Selected ^{1}H NMR chemical shifts of (±)-**1a** and effect on the chemical shifts induced by [Bu_4N][Δ-**3**] in 5% DMSO-d_6/$CDCl_3$

Proton	δ^a	δ^b		$\Delta\delta^b$		$\Delta\Delta\delta^b$
N**H**	8.633	8.598	8.186	−0.035	−0.447	0.412
P^+C**H**H′	5.000	0.556	4.427	−0.444	−0.573	0.056

[a] Without chiral anions.
[b] With 3.0 equiv. of [Bu_4N][Δ-**3**].

was however necessary to solubilize the (±)-**1a** salt. In all these experiments, an NMR enantiodifferentiation was observed in both ^{1}H and ^{31}P NMR spectroscopy.

For (±)-**1a**, the most efficiently split signals in ^{1}H NMR spectroscopy were those of the NH and of one of the diastereotopic CH_2 protons. Two equivalents of [Bu_4N][Δ-**3**] were sufficient to lead to a sizeable split ($\Delta\Delta\delta$ 0.31 ppm) of amide resonance. A larger excess of chiral shift agent was necessary to lead to a full separation of the more complex signal of the methylene proton. Observed chemical shifts (δ), upfield shifts induced by the phosphate reagent ($\Delta\delta$), and the magnitude of the difference in chemical shifts of analogous protons of the two enantiomers of (±)-**1a** upon addition of 3.0 equiv. of [Bu_4N][Δ-**3**] ($\Delta\Delta\delta$) are summarized in Table 2. In ^{31}P NMR (162 MHz), the signal of the cation was also split in two signals ($\Delta\Delta\delta$ 0.145 and 0.154 ppm with 1.8 and 3.0 equiv. of [Bu_4N][Δ-**3**], respectively, see Fig. 2, spectra b and c).

Testing this protocol in ^{1}H and ^{31}P NMR spectroscopy with an enantioenriched sample of salt (−)-**1a** ($[\alpha]_D$ = −20, *c* 1, MeOH)[19] revealed the presence of both enantiomers of the phosphonium. In ^{1}H NMR, the signal of the minor enantiomer was observed more particularly in the CH_2 region.[20] Accurate determination of the enantiomeric purity of **1a** by integration of the enantiodifferentiated resonances was however difficult; the large signal nature of the methylene proton making it difficult to separate the contribution of the minor enantiomer from the noise of the baseline. However, in ^{31}P NMR spectroscopy, two sharp and well-separated signals were observed for the enantiomers ($\Delta\Delta\delta$ 0.196 ppm with 3.6 equiv. of [Bu_4N][Δ-**3**], Fig. 2, spectrum d). A clean integration could be performed allowing the measurement of a 71% enantiomeric purity.

For methyl ester derivative (±)-**1b** the ^{1}H NMR signals of most of the aliphatic protons were split efficiently in two sets upon addition of [Bu_4N][Δ-**3**]. For most resonances, a single equivalent of chiral shift agent was sufficient to induce a sizeable separation of the signals ($\Delta\Delta\delta$ 0.35 ppm for the NH proton); a larger excess of [Bu_4N][Δ-**3**] improving further the separation (Fig. 1, spectrum c). Observed chemical shifts (δ), downfield/upfield shifts induced by the phosphate reagent ($\Delta\delta$), and the magnitude of the difference in chemical shifts of analogous protons of the two enantiomers of (±)-**1b** upon addition of 3.0 equiv. of [Bu_4N][Δ-**3**] ($\Delta\Delta\delta$), are summarized in Table 3. In ^{31}P NMR (162 MHz), the signal of the phosphonium was also split in two signals (1:1 ratio, $\Delta\Delta\delta$ 0.310, 0.457 and 0.535 ppm with 1.0, 2.2 and 3.0 equiv. of [Bu_4N][Δ-**3**], respectively).

The enantiomeric purity of a non-racemic sample of salt (−)-**1b** ($[\alpha]_D$ = −33, *c* 1.2, $CHCl_3$)[21] was also investigated. The presence of a minor enantiomer could not

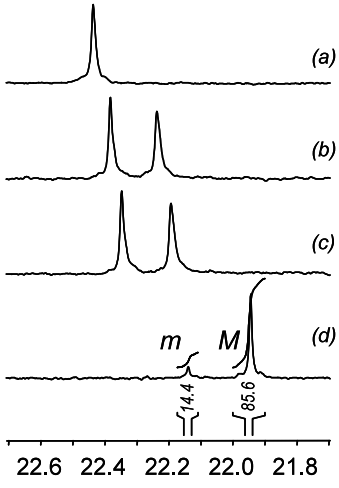


Figure 2. ^{31}P (162 MHz) spectra ($CDCl_3$, parts) for (a) (±)-**1a** and (b) 1.8 or (c) 3.0 equiv. of [Bu_4N][Δ-**3**], (d) (−)-**1a** (e.e. 71%) and 3.6 equiv. of [Bu_4N][Δ-**3**]; *m* and *M* indicate the minor and major enantiomers.

Table 3. Selected ^{1}H NMR chemical shifts of (±)-**1b** and effect on the chemical shifts induced by [Bu_4N][Δ-**3**] in $CDCl_3$

Proton	δ^a	δ^b		$\Delta\delta^b$		$\Delta\Delta\delta^b$
N**H**	9.010	8.775	8.186	−0.235	−0.824	0.589
P^+C**H**H′	5.324	5.038	4.762	−0.286	−0.562	0.276
CHCO_2Me	4.004	4.125	3.883	+0.121	−0.121	0.242
Me	3.761	3.665	3.621	−0.096	−0.140	0.044

[a] Without chiral anions.
[b] With 3.0 equiv. of [Bu_4N][Δ-**3**].

Table 4. Selected ^{1}H NMR chemical shifts of (±)-**2** and effect on the chemical shifts induced by [Bu_4N][Δ-**3**] in $CDCl_3$

Proton	δ[a]	δ[b]		$\Delta\delta$[b]		$\Delta\Delta\delta$[b]
Me	1.848	1.727	1.512	−0.121	−0.336	0.215
ArH	–[c]	6.803	6.749	–[d]	–[d]	0.054
ArH	–[c]	6.955	6.907	–[d]	–[d]	0.048

[a] Without chiral anions.
[b] With 1.6 equiv. of [Bu_4N][Δ-**3**].
[c] The chemical shift could not be determined with precision.
[d] Not applicable.

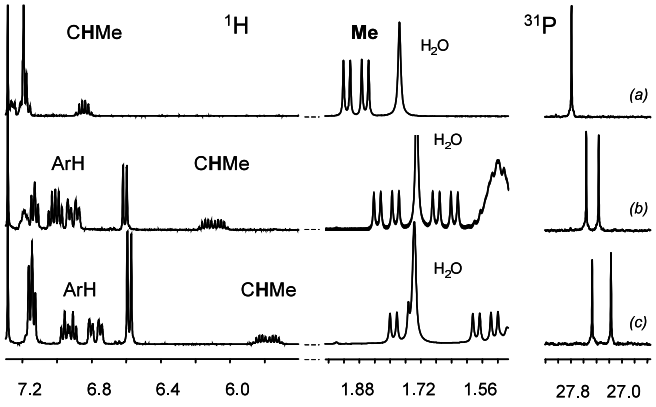


Figure 3. ^{1}H (400 MHz) and ^{31}P NMR (162 MHz) spectra ($CDCl_3$, parts) for (a) (±)-**2** and (b) 0.75 and (c) 1.6 equiv. of [Bu_4N][Δ-**3**].

be detected in both ^{1}H and ^{31}P NMR spectroscopy demonstrating the highly enantioenriched nature of the sample (e.e. >96%, see Fig. 1, spectrum d).

Finally, salt (±)-**2**[22] was analyzed in the presence of [Bu_4N][Δ-**3**]. The signal of the methyl group was efficiently split in two sets. Only a partial separation was achieved for the sextuplet signal of the benzylic proton. Interestingly, we could observe a decent enantiodifferentiation for the lower-frequency aromatic protons of the triphenylphosphonium moiety (Fig. 3, spectra b and c). Observed chemical shifts (δ), downfield/upfield shifts induced by the phosphate reagent ($\Delta\delta$), and the magnitude of the difference in chemical shifts of analogous protons of the two enantiomers of (±)-**2** upon addition of 1.6 equiv. of [Bu_4N][Δ-**3**] ($\Delta\Delta\delta$) are summarized in Table 4. In ^{31}P NMR (162 MHz), the signal of the phosphonium was again split in two signals ($\Delta\Delta\delta$ 0.192 and 0.295 ppm with 0.75 and 1.6 equiv. of [Bu_4N][Δ-**3**], respectively, see Fig. 3 spectra b and c).

Table 5. Largest differences of chemical shift ($\Delta\Delta\delta_{max}$, ^{1}H NMR, 400 MHz) observed for the enantiomers of the racemic triphenylphosphonium salts with [Bu_4N][Δ-**3**]

Salt	No. equiv.	$\Delta\Delta\delta_{max}$	
		^{1}H NMR	^{31}P NMR
(±)-**1a**	3.0	0.412[a]	0.154
(±)-**1b**	3.0	0.589[a]	0.535
(±)-**2**	2.7	0.215[b]	0.358

[a] Amide NH proton.
[b] Methyl protons.

All in all, BINPHAT salt [Bu_4N][Δ-**3**] behaves as a better NMR chiral shift agent for salts **1b** and **2** than for **1a** (see Table 5 for a summary). This is interpreted as the result of looser interactions occurring between the BINPHAT anion and the acidic phosphonium. In the more polar media conditions that are required for the solubilization of salt **1a**, the ion pairs are more separated and this leads to a diminution of the overall efficiency of the anionic chiral shift agent.

In conclusion, a better enantiodifferentiation of the chiral triphenylphosphonium salts **1a**, **1b** and **2** was observed with BINPHAT reagent [Bu_4N][Δ-**3**]. This further demonstrates the higher efficiency of the BINPHAT anion as a NMR shift agent for chiral organic cations.

Acknowledgements

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18. Compound $[Bu_4N][\Delta\text{-}\mathbf{3}]$ was prepared following previously reported guidelines. See the supporting information of Ref. 14a.
19. Prepared following the reported guidelines in ref. 8.
20. The NH signal is too broad to be analyzed with precision.
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22. (±)-(1-Phenylethyl)triphenylphosphonium bromide **2** was obtained by heating triphenylphosphine and (±)-1-phenylethyl bromide: mp = 226–227°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ (ppm) 7.85–7.45 (m, 15H), 7.30–7.00 (m, 5H), 6.59 (m, 1H), 1.78 (dd, 3H, $^3J_{HH} = 7$, $^3J_{HP} = 19$); ^{31}P NMR (101 MHz, $CDCl_3$): δ (ppm) +27.9.