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Large-Scale Synthesis and Resolution of TRISPHAT [Tris(tetrachlorobenzenediolato) Phosphate(V)] Anion

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Abstract: Both enantiomers of TRISPHAT anion can be obtained on a multigram scale through a novel resolution procedure. The Λ enantiomer is isolated as the tri-*n*-butylammonium salt, [^{n}Bu$_3$NH][Λ-**1**], which is soluble in pure $CHCl_3$ and CH_2Cl_2. The Δ enantiomer is prepared as the cinchonidinium derivative, which is only soluble in polar solvent mixtures (>7.5% DMSO in $CHCl_3$).

Many chemical reactions and processes involve cationic racemic or prochiral reagents, intermediates, or products. To afford nonracemic or enantiopure adducts and benefit from new possible applications, a stereoselective ion pairing of these cations with enantiopure anions can be considered, with the counterions behaving as asymmetric auxiliaries, ligands, or reagents.[1] Recently, the chemistry of hexacoordinated phosphate anions has been rejuvenated for exactly this purpose, as chiral tris(tetrachlorobenzenediolato)phosphate(v) anion **1**, known as TRISPHAT (Figure 1),[2,3] has been shown to be a valuable NMR chiral solvating,[4] resolving,[5] asymmetry-inducing,[6] and solubilizing[7] reagent for organic, organometallic, metallo-organic, and polymeric substances. Since the original report from our group,[2] new aspects about the synthesis and the resolution of ammonium TRISPHAT salts have been found which render the preparation of salts of enantiopure **1** quite easier. They are detailed in the following paragraphs and in the Experimental Section.

The octahedral geometry of pentavalent hexacoordinated phosphorus allows the formation of chiral anions by complexation of a central phosphorus atom with three identical dianionic bidentate ligands. These compounds exist as Λ or Δ enantiomers with left- or right-handed propeller shape (*M* and *P* helicity), respectively.[8] Hellwinkel and co-workers were the first to report the synthesis and resolution of a chiral hexacoordinated phosphate anion, the tris-biphenyl-2,2′-diyl phosphate(V).[9] Tris(benzenediolato) phosphate anion **2** (Figure 1), first identified by Allcock in the crude reaction mixture of tricyclic hexachlorocyclotriphosphazene and pyrocatechol,[10] was later shown to be simply prepared

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(2) Lacour, J.; Ginglinger, C.; Grivet, C.; Bernardinelli, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 608−609.

(3) Anion **1** was mentioned several times in the literature prior to our initial study, but only once fully characterized. In 1992, Schmutzler and co-workers isolated the dimethylammonium salt of **1** as a product of spontaneous decomposition of a spirophosphorane in $CDCl_3$. Shevchenko, I. V.; Fischer, A.; Jones, P. G.; Schmutzler, R. *Chem. Ber.* **1992**, *125*, 1325−1332.

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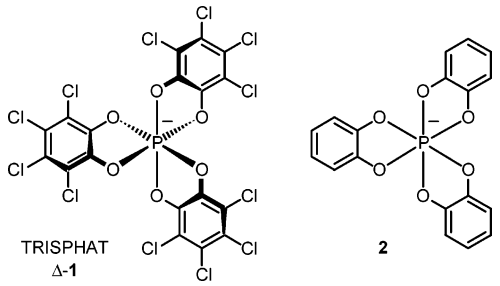

FIGURE 1. Hexacoordinated phosphorus anions **1** (TRISPHAT) and **2**.

as ammonium salts by the reaction of PCl_5 with pyrocatechol and an amine.[11] The anion was isolated in optically enriched form through the use of brucine as a chiral base during the synthesis. Unfortunately, anion **2** is rather configurationally labile, and Koenig, Munoz, Wolf, and co-workers could show that the epimerization is acid-catalyzed and first order in substrate.[12] These, and other mechanistic observations,[13] indicated that a configurationally stable phosphate anion could be in fact prepared if an electron-poor catechol unit was to be chosen in place of pyrocatechol. Readily available tetrachlorocatechol was selected.[14] Ammonium salts of tris-(tetrachlorobenzenediolato) phosphate(V) anion **1** were then prepared and showed to be configurationally stable at room temperature in all common organic solvents.

In our original report,[2] the synthesis and resolution of TRISPHAT **1** were essentially paired together as cinchonidine—chosen in place of brucine as a resolving agent—was introduced in the reaction vessel directly after PCl_5 and tetrachlorocatechol to afford the anion. Mixtures of diastereomeric [cinchonidinium][Δ-**1**] and [cinchonidinium]-[Λ-**1**] salts were obtained with yields ranging from 50 to 70% on a small scale (up to 200 mg). Scale-up became quickly an issue as the poor solubility in CH_2Cl_2/hexane of the resulting cinchonidinium salts limited both the scope of the reaction and the selective isolation of the most crystalline [cinchonidinium][Δ-**1**] pair; this latter isomer being fully characterized by chiroptical measurements and X-ray diffraction analysis.[2] Herein, we report the full details of an improved resolution procedure that decouples the synthesis of TRISPHAT anion from its separation in enantiopure salts; this two-step procedure is easier to scale-up, shows good reproducibility, and allows the isolation of both enantiomers of TRISPHAT—the Λ one in particular.[15]

As mentioned, the poor solubility of the cinchonidinium TRISPHAT salts obtained directly from the one-pot synthetic protocol was problematic for further uses, and NMR enantiodifferentiation studies in particular. We thus looked for a new resolution procedure that would allow the isolation of one enantiomer of TRISPHAT anion as a salt soluble in low polarity solvents. The racemic tri-*n*-butylammonium derivative, salt [^{n}Bu$_3$NH][*rac*-**1**], seemed ideal as a starting material as it dissolves readily in solvents such as $CHCl_3$ or CH_2Cl_2. We imagined that the addition of a substoichiometric amount of a chiral amine to a solution of the adduct would generate a good proportion of diastereomeric chiral ammonium salts by in situ acid—base reaction. Selective precipitation of one diastereomeric ion pair might then occur and leave, in the mother liquor, the antipodal anion associated with the tri-*n*-butylammonium cation. This last salt would then most probably possess the desired solubility. Finally, since effective chiral recognition of D_3-symmetric phosphate[15] and arsenate anions[16] has been show to happen with the conjugated acids of *cinchona* alkaloids, it was decided to keep cinchonidine as a resolving agent.

The synthetic preparation of salt [^{n}Bu$_3$NH][*rac*-**1**] (Scheme 1) was effected following essentially the procedure developed by Koenig, Munoz, and co-workers for the making of ammonium salts of anion **2**. Addition of anhydrous tetrachlorocatechol (3.0 equiv)[17] to a solution of PCl_5 (toluene, 50 °C) and further reaction for several hours (>14 h, 70 °C) afforded a gray suspension, which was concentrated in vacuo. Additions of CH_2Cl_2, *n*-hexane, and ^{n}Bu$_3$N led to the formation of salt [^{n}Bu$_3$NH][*rac*-**1**], which precipitated from the reaction medium (61% on a multigram (40 g) scale).[18] During most of the sequence, care must be taken to perform the reaction under inert atmosphere to avoid hydrolysis of PCl_5 or of subsequent derivatives. However, once the [^{n}Bu$_3$NH][*rac*-**1**] salt has precipitated, there are no particular conditions required for its handling.

Resolution was then afforded as planned (Scheme 1). Addition as a solid of cinchonidine (0.5 equiv) to a CH_2Cl_2 solution of [^{n}Bu$_3$NH][*rac*-**1**] led, after first the dissolution of the alkaloid, to the precipitation of a white compound (fraction **A**) containing predominantly the [cinchonidinium][Δ-**1**] ion pair over the other diastereomer; the CD spectra (EtOH, $\Delta\epsilon_{213} = +197$; $\Delta\epsilon_{222} = -282$, $c = 5.4 \times 10^{-6}$ M) showing unambiguously the preferred Δ configuration of the anion in the precipitate. After filtration and concentration of the mother-liquor, a white solid (fraction **B**) was obtained containing essentially tri-*n*-butylammonium TRISPHAT salt along with 5−10% of cinchonidine/cinchonidinium derivatives; this latter fraction contained logically the Λ enantiomer of **1** of which the enantiomeric excess (ee 70%) could be measured by ^{31}P NMR spectroscopy in the presence of (−)-bis[(*S*)-1-phenylethyl]amine hydrochloride (7−8 equiv) as chiral

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(14) If one considers that pK_a values for the first ionization of catechols can be used as a measure of the electronic effect of the substituents on a catechol, then tetrachlorocatechol (pK_a = 6.63) is definitely more electron-poor than pyrocatechol (pK_a = 10.87): Rosenblatt, D. H.; Epstein, J.; Levitch, M. *J. Am. Chem. Soc.* **1953**, *75*, 3277−3278.

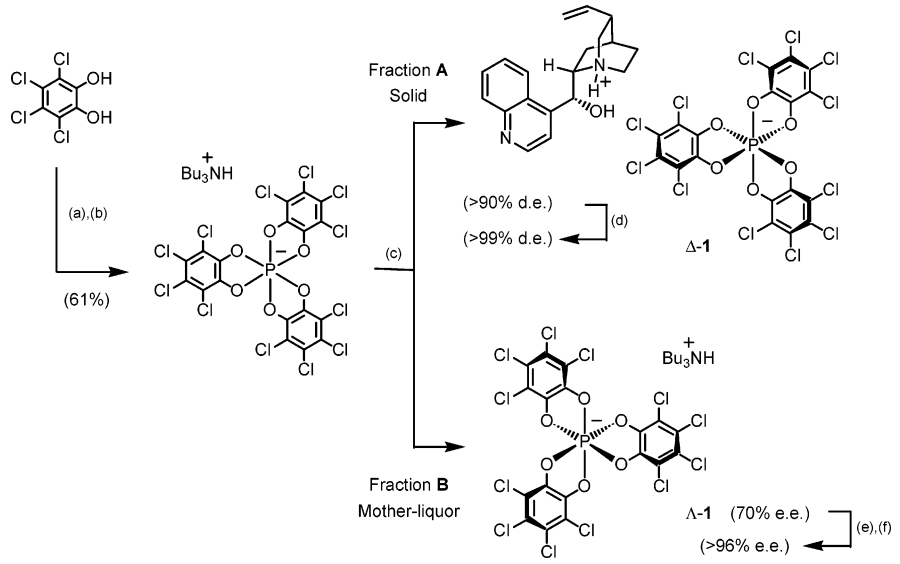
(15) Part of these results were reported as a communication: Lacour, J.; Ginglinger, C.; Favarger, F. *Tetrahedron Lett.* **1998**, 4825−4828.

(16) Ryschkewitsch, G. E.; Garrett, J. M. *J. Am. Chem. Soc.* **1968**, *90*, 7234−7238 and references therein.

(17) Commercial tetrachlorocatechol is usually monohydrated even if the chemical provider does not mention it. Care must be taken to dry the reagent prior to use.

(18) This protocol is rather general and most primary, secondary and tertiary amines can be used. The racemic ammonium [R$_3$NH][**1**] salts, recovered by filtration, are usually afforded in decent to good yields (59−89%). In most instances, *n*- or *c*-hexane is used as a cosolvent to improve the yields at the precipitation stage, as some of the salts are quite soluble in CH_2Cl_2.

SCHEME 1. Synthesis and Resolution of Salt [^{n}Bu$_3$NH][*rac*-1]^a



^{a} Key: (a) PCl_5 (0.33 equiv), Ph-Me, 70 °C; (b) ^{n}Bu$_3$N, CH_2Cl_2/*n*-hexane, 20 °C; (c) cinchonidine (0.50 equiv), CH_2Cl_2, 20 °C; (d) recrystallization in acetone/EtOAc; (e) filtration (SiO_2); (f) recrystallization in CH_2Cl_2 (mother liquor).

solvating agent. Both fractions were then purified, chemically and optically, by chromatographic and/or recrystallization experiments.

Fraction **A** ($[\alpha]^{20}_D = -353$, $c = 0.129$ in EtOH, de > 90%) was simply dissolved in a mixture of acetone and EtOAc, and slow evaporation of the solvents afforded diastereomerically pure [cinchonidinium][Δ-**1**]·EtOAc ($[\alpha]^{20}_D = -375$, $c = 0.111$ in EtOH) as initially reported.[2] To remove the included solvent, the crystals can be placed under high vacuum at 60 °C for 12 h to give pure [cinchonidinium][Δ-**1**] as a white powder.

For the purification of Fraction **B**, a major hurdle was the physical separation of the [^{n}Bu$_3$NH][**1**] salt from the cinchonidine residues. No satisfactory precipitation conditions could be found. However, as TRISPHAT anion confers to most of its salts a poor affinity for polar chromatographic phases[19]—with the welcome exception of the cinchonidinium ion pairs—it was possible to obtain clean enantiomerically enriched [^{n}Bu$_3$NH][Λ-**1**] salt by the rapid elution of this compound over silica gel. With this chemically pure compound in our hands, an optical enrichment was feasible by dissolution of the derivative in CH_2Cl_2 and, upon slow evaporation of the solvent, precipitation of racemic [^{n}Bu$_3$NH][*rac*-**1**] ion pair. After filtration and concentration under reduced pressure of the mother liquor, the desired [^{n}Bu$_3$NH][Λ-**1**] salt ($[\alpha]^{20}_D = +371$, $c = 0.105$ in EtOH) was afforded in good chemical and enantiomeric purity (ee > 96% as checked by ^{31}P NMR in the presence of (−)-bis[(*S*)-1-phenylethyl]-amine hydrochloride).

In conclusion, both enantiomers of the TRISPHAT anion can be obtained on multigram scale through this novel resolution procedure. The Λ enantiomer is isolated as the tri-*n*-butylammonium salt, [^{n}Bu$_3$NH][Λ-**1**], which is soluble in pure $CDCl_3$ and CD_2Cl_2. The Δ enantiomer is prepared as the cinchonidinium derivative, which is only soluble in polar solvent mixtures (>7.5% DMSO in $CDCl_3$).[20]

Experimental Section

Anhydrous Tetrachloropyrocatechol. In a 250 mL round-bottomed flask, commercially available tetrachloropyrocatechol monohydrate[17] (102.6 g, 386 mmol) was suspended in dry toluene (100 mL) and heated at reflux for 1 h. The resulting solution was allowed to cool to room temperature. Spontaneous crystallization occurred, and the crude reaction mixture was filtered over a Büchner funnel. The solid was washed with dry toluene (2×), crushed in a mortar into a fine powder, and dried under reduced to pressure (24 h) to afford anhydrous tetrachloropyrocatechol (80.35 g, 78.5%).

Racemic [Tri-*n*-butylammonium][tris(tetrachloropyrocatecholato)phosphate(V)], [Bu$_3$NH][*rac*-1]. In a two-necked 1-L round-bottomed flask equipped with a septum, a condenser connected via a tap to a double-manifold gas/vacuum Schlenk line, and a magnetic stirring bar was introduced 10.33 g of PCl_5 (49.6 mmol). The reaction was placed under inert atmosphere (N_2), by repeated sequences of vacuum and N_2 flushing, and dry toluene (141 mL, measured with graduated glass cylinder) was added via a cannula. The resulting suspension was heated at 50 °C to give a yellowish colored solution. Under a strong flow of dinitrogen, the septum was replaced by a graduated addition funnel for solid containing anhydrous tetrachloropyrocatechol (38.9 g, 148.8 mmol). The tap on the top of the condenser was replaced by a gas trap filled with concentrated aqueous NaOH. The tetrachloropyrocatechol was then slowly added (~50 min). Care was taken to avoid excessive gas evolution (HCl). After the addition, the funnel was rinsed with dry toluene (4 × 2 mL) and replaced by a tap connected to a double manifold gas/vacuum Schlenk line. During the addition, a precipitate appeared and the suspension turned green. The reaction was then stirred at 50 °C for 22 h.[21] It was then allowed to cool to room temperature, and the toluene was removed slowly under reduced pressure. The resulting light-brown solid was dried under high vacuum

(19) Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567−570.

(20) Previously, it was shown that the [cinchonidinium][Δ-**1**] salt can be transformed in one step into the lipophilic [^{n}Bu$_4$N][Δ-**1**] derivative (ref 4c), which is soluble in chloroform and methylene chloride.

(21) After 3 h, the suspension became blue and then brown after 22 h. The origin of this blue color is unknown to us. We have, however, observed that an early removal of the solvent prior to the disappearance of the blue color leads to reduced yields and lower chemical purity of the product.

at 100 °C for 4 h. Then, at room temperature, dry CH_2Cl_2 (250 mL) and *n*-hexane (260 mL) were added. The suspension was stirred for 15 min. Then, a solution (CH_2Cl_2, 100 mL) of freshly distilled $^nBu_3N$ (11.84 mL, 49.6 mmol) was added resulting in the dissolution of the brownish solid. A novel beige precipitate rapidly appeared, and the reaction was stirred at room temperature for 24 h. The crude reaction mixture was filtered over a Büchner funnel. The solid was washed with *c*-hexane (20 mL) and dried under high vacuum (4 h) to afford chemically pure salt [$^nBu_3NH$][*rac*-**1**] (28.88 g, 30.2 mmol, 61%) as a beige powder: mp 305 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (br, s, 1H, NH^+), 3.03 (m, 6H, NCH_2CH_2−), 1.61 (m, 6H, NCH_2CH_2−), 1.34 (sext, $J_{(H,H)}$ = 7.52 Hz, 6H, CH_2CH_3), 0.93 (t, $J_{(H,H)}$ = 7.52 Hz, 9H, −CH_3); ^{31}P NMR (162 MHz, CD_3CN) δ −79.8; ^{13}C NMR (100 MHz, CD_3CN) δ 142.6 ($^2J_{(C-P)}$ = 6.9 Hz), 123.6, 114.7 ($J_{(C-P)}$ = 19.8 Hz), 54.0, 26.2, 20.4, 13.7; IR (KBr) $\tilde{\nu}$ 3171.7 (w), 2964.7 (m), 2877.5 (w), 1447.1 (s), 1387.1 (m), 1300.0 (w), 1234.6 (m), 989.4 (s), 825.9 (s), 716.9(m), 673.4 (s); UV/vis (EtOH, 1.13 × 10^{-5} M) λ_{max} (ϵ) 300.0 (1.01 × 10^4), 237.0 (3.3 × 10^4), 218.0 (1.68 × 10^5); MS (ES): (+) 186 [$^nBu_3NH^+$], (−) 768.8 [TRISPHAT]; Anal. Calcd for $C_{30}Cl_{12}H_{28}NO_6P$: C, 37.73; H, 2.96; N, 1.47. Found: C, 37.73; H, 3.11; N, 1.44.

Resolution Procedure. In a 2-L round-bottomed flask equipped with a magnetic stirring bar was introduced 10.0 g of [tri-*n*-butylammonium][*rac*-**1**] (10.46 mmol). Dichloromethane (980 mL) was added and the mixture stirred vigorously to dissolve the solid. To the clear solution was then added cinchonidine (1.54 g, 5.24 mmol, 0.5 equiv) in one portion via a funnel, which was rinsed with CH_2Cl_2 (20 mL). The alkaloid dissolved immediately upon strong stirring to give a limpid solution. Two to three minutes later, the formation of a white precipitate was observed, and the reaction was allowed to stand at room temperature for 24 h to ensure maximum precipitation. The crude reaction mixture was filtered over a Büchner funnel. The white powder (fraction A), containing essentially [cinchonidinium][**1**], was washed with dichloromethane and collected (4.39 g, $[\alpha]^{20}_D$ = −353, *c* = 0.129 in EtOH)). The mother liquor, containing enantioenriched [Bu_3NH][Λ-**1**], Bu_3N, and residual cinchonidine products, was concentrated in vacuo and dried under high vacuum (15 min) to afford a light brown powder (fraction B, 7.25 g).[22]

[Cinchonidium][Δ-tris(tetrachloropyrocatecholato)-phosphate(V)], [Cinchonidium][Δ-1]. At room temperature, fraction **A** (4.39 g) was dissolved in a minimum amount of acetone (40−60 mL) and the resulting solution filtered. EtOAc (12 mL) was added, and slow evaporation of the solvents over 15 days afforded pure [cinchonidinium][Δ-**1**]·EtOAc (2.39 g, 2.24 mmol, 21%) as colorless plates: mp 245−260 °C dec; $[\alpha]^{20}_D$ = −375 (*c* = 0.111 in EtOH); CD (EtOH, 1.14 × 10^{-5} M, 20 °C) λ ($\Delta\epsilon$) 244 (−61), 220 (−268), 211 (+195). To remove the included EtOAc, the crystals were placed under high vacuum at 60 °C for 12 h to give pure [cinchonidinium][Δ-**1**] as a white powder: mp 245−265 °C dec; $[\alpha]^{20}_D$ = −378 (*c* = 0.101 in EtOH); ^{31}P NMR (162 MHz, acetone-d_6) δ −79.4; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.91 (d, *J* = 4.4 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 4.4 Hz, 1H), 7.75 (dd, *J* = 8.1, 7.4 Hz, 1H), 7.58 (dd, *J* = 7.4, 7.0 Hz, 1H), 6.29 (br, 1H), 5.83 (ddd, *J* = 10.3, 7.3, 7.0 Hz, 1H), 5.06 (2d, *J* = 17.3, 10.3 Hz, 2H), 6.31 (dd, *J* = 2.6, 2.1 Hz, 1H), 4.47 (ddd, *J* = 12.6, 11.1, 4.9 Hz, 1H), 4.12 (dddd, *J* = 10.6, 7.1, 2.6, 2.0 Hz, 1H), 3.93 (dd, *J* = 13.0, 10.6 Hz, 1H), 3.63 (dd, *J* = 13.0, 5.6 Hz, 1H), 3.62 (dddd, *J* = 12.6, 11.2, 5.7, 2.0 Hz, 1H), 3.3−2.5 (br, 2H, OH and NH^+), 2.38 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.31 (ddd, *J* = 12.7, 11.1, 5.7 Hz, 1H), 2.23 (dd, *J* = 3.8, 2.8 Hz, 1H), 2.10 (dddd, *J* = 12.7, 11.2, 4.9, 2.7 Hz, 1H), 1.84 (dddd, *J* = 13.5, 10.6, 3.8, 2.7 Hz, 1H);[23] ^{13}C NMR (100 MHz, acetone-d_6) δ 150.9, 149.1, 145.8, 142.7 ($^2J_{(C-P)}$ = 6.1 Hz), 138.6, 131.2, 129.9, 127.7, 125.4, 123.2, 122.8, 119.7, 117.1, 114.2 ($J_{(C-P)}$ = 20.6 Hz), 68.4, 61.8, 55.7, 45.7, 37.9, 27.5, 24.8, 19.5; UV/vis (EtOH, 5.40·10^{-6} M) λ_{max} (ϵ) 300.0 (2.09 × 10^4), 217.0 (3.50·10^5); CD (EtOH, 6.01 × 10^{-6} M, 20 °C) λ ($\Delta\epsilon$) 304.0 (−10), 244.0 (−84), 220.0 (−336), 211.0 (+220); MS (ES) (+) 295.1 [cinchonidinium], (−) 767.9 [TRISPHAT]. Anal. Calcd for $C_{37}Cl_{12}H_{23}N_2O_7P$: C, 41.77; H, 2.18; N, 2.63. Found: C, 41.79; H, 2.41; N, 2.69.

[Tri-*n*-butylammonium][Λ-tris(tetrachloropyrocatecholato)phosphate(V)], [Bu_3NH][Λ-1]. The removal of the cinchonidine residues (R_f ~ 0) was realized by chromatography as only [Bu_3NH][**1**] (R_f ~ 0, CH_2Cl_2) elutes over silica gel. Fraction **B** (7.25 g) was thus placed as a solid on top of column (SiO_2, 11 × 3 cm) and eluted with CH_2Cl_2. The light-colored fractions were collected and concentrated in vacuo to afford 5.17 g of a beige solid, which was then dissolved at room temperature in a minimum amount of CH_2Cl_2 (260 mL). The resulting solution was filtered and allowed to slowly evaporate. After 15 days, white crystals were collected by filtration and washed (CH_2Cl_2) to afford racemic [Bu_3NH][*rac*-**1**] (1.88 g, $[\alpha]^{20}_D$ = 0 (*c* = 0.098 in EtOH)). The mother liquor was concentrated in vacuo, dried under high vacuum at room temperature and gave pure [Bu_3-NH][Λ-**1**] (3.11 g, 28%): $[\alpha]^{20}_D$ = +354 (*c* = 0.099 in EtOH). Recrystallization (CH_2Cl_2) of an aliquot afforded a highly enantiomerically enriched sample: $[\alpha]^{20}_D$ = +371 (*c* = 0.105 in EtOH, ee > 96% (NMR)); CD (EtOH, 1.40 × 10^{-5} M, 20 °C): λ ($\Delta\epsilon$) 244.0 (+99), 221.0 (+392), 212.0 (−287).

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Supporting Information Available: General methods and materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The enantiomeric purity of the TRISPHAT anion in this fraction (70% ee) was accessed by ^{31}P NMR in $CDCl_3$ using (−)-bis[(S)-1-phenylethyl]amine hydrochloride (7−8 equiv) as chiral shift agent and its absolute Λ configuration was unambiguously determined by its CD spectrum.

(23) The coupling constants were measured by Dr. D. Jeannerat (University of Geneva) by deconvolution in the frequency domain by using the 'Deco program'.