Efficient Resolution of a Dinuclear Triple Helicate by Asymmetric Extraction/Precipitation with TRISPHAT Anions as Resolving Agents**

Jonathan J. Jodry and Jérôme Lacour*[a]

Abstract: Tetradentate 1,2-bis[4-(4′-methyl-2,2′-bipyridyl)]ethane ligand (**3**) and $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ combine in a 3:2 ratio to form the racemic helicate $[Fe_2L_3]^{4+}$ (**4**), as reported by Elliott et al. We now show that the enantiomeric purity of **4** can be efficiently measured by ^1H NMR by the use of the TRISPHAT (**1**) salt as a chiral shift reagent. Large differences in chemical shifts ($\Delta\Delta\delta$ of up to 0.3 ppm, 20% [D$_6$]DMSO in CD_3CN) are observed between the enantiomers of **4** upon addition of [nBu$_4$N][Δ-**1**]. The resolution of **4** by asymmetric extraction was attempted: addition of an organic solution of [cinchonidinium][Δ-**1**] salt (2 equiv) to an aqueous solution of helicate **4**-$(SO_4)_2$ led, after vigorous stirring, to the extraction of the homochiral diastereomer [P-**4**][Δ-**1**]$_4$ into the organic layer along with the precipitation of the heterochiral diastereomer [M-**4**][Δ-**1**]$_4$ at the interface (diastereomeric ratio $>$ 49:1 for both processes). An enantioenriched fraction of [P-**4**][SO_4]$_2$ remained in the aqueous layer. To obtain only two fractions of resolved helicate and develop this procedure into an efficient resolution protocol, four equivalents of [cinchonidinium][Δ-**1**] salt were used as the resolving agent. Chemically and diastereomerically pure [P-**4**][Δ-**1**]$_4$ and [M-**4**][Δ-**1**]$_4$ helicate salts were then obtained in excellent yields.

Keywords: chirality · chiral resolution · helical structures · iron · supramolecular chemistry

Introduction

Helicate derivatives formed by the self-assembly of polydentate organic ligands and transition metal ions have received much attention over the last two decades.[1] Such structures, in which the ligand strands are twisted around a metal–metal axis, are usually chiral and the helical enantiomers are characterized by their *plus* (*P*) or *minus* (*M*) handedness. Each metal center of the helicate is stereogenic and has, in general, the same intrinsic configuration, Δ or Λ, which translates respectively into the *P* or *M* handedness of the helicate (Figure 1).[2]

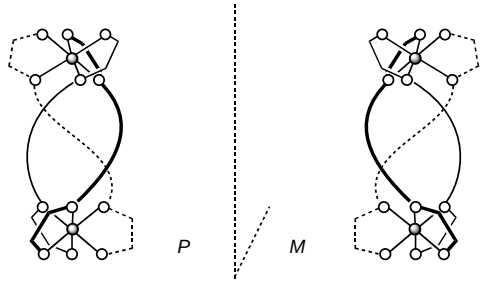

Figure 1. *P* and *M* helicity of a dinuclear helicate.

To obtain chiral helicates in a predominant *P* or *M* configuration, the most common strategy has been to add stereogenic elements to the backbone of the ligands. Intramolecular diastereoselective interactions occur between the enantiopure strands and lead, by self-assembly, to the preferred formation of one diastereomer.[3] This method was first applied in 1978 by Raymond and Carrano, who synthesized a dinuclear iron(III) complex with rhodotorulic acid as the chiral ligand.[4] To date, there are many examples of high selectivity in the formation of double and triple helicates, in which enantiopure ligands completely control the configuration. The stereogenic elements are introduced either on the coordinating units,[5] on the bridging elements,[6] or on a chiral template that links the strands together.[7] This strategy has the advantage of leading to chiral complexes that are configurationally stable in solution as the ratio between the diastereomers is thermodynamically controlled by the chiral ligands.

When achiral ligands are used, helicates are obtained as racemic mixtures, as no enantioselective method of synthesis has yet been reported. Chemists must then rely on resolution procedures to obtain the helicates in an enantioenriched or enantiopure form. Only a few examples of such enantiomeric

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[**] TRISPHAT = tris(tetrachlorobenzenediolato)phosphate(v) anion

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separations have been reported and they are usually based on the formation of diastereomeric ion pairs between cationic helicates and anionic chiral resolving agents. Williams et al. reported the resolution of a dinuclear cobalt(III) helicate by ion-pair chromatography with a concentrated solution of enantiopure sodium (+)-tartratoantimonate(III) as the eluent.[8] Similarly, the groups of Lehn, Sauvage, and Keene resolved iron(II) tri- and dinuclear helicates by chromatography.[9] Selective crystallization in the presence of an enantiopure anion can also lead to resolution; Sauvage et al. applied this method to a chiral dicopper(I) trefoil knot.[10] Finally, Lehn et al. reported that the crystallization of a nickel(II) trinuclear helix can occur with a spontaneous partial resolution; however, this process was random and difficult to reproduce.[11] In all these examples, the determination of the enantiomeric purity of the resolved helicate has been challenging. NMR experiments were attempted with chiral shift reagents and low separation of the signals of the enantiomers[10] or partial precipitation of the cationic helicate during the analysis[8] were observed. Authors have also relied on X-ray diffraction analysis of crystals of the resolved complexes to confirm their enantiomeric purity.

Recently, we have shown that the readily prepared and resolved tris(tetrachlorobenzenediolato)phosphate(V) anion (**1**) (Figure 2), or TRISPHAT, is configurationally stable as an ammonium salt in solution.[12] The Λ enantiomer can be isolated as the tri-*n*-butylammonium salt.[13] The Δ enantiomer is prepared as the cinchonidinium ion pair, which in turn can be transformed into [nBu$_4$N][Δ-**1**].[14] This anion is an efficient NMR chiral shift reagent for chiral cations, particularly mononuclear ruthenium(II) complexes.[15] Anion **1** was also shown to be an efficient chromatographic resolving agent for mononuclear $[Ru(diimine)_3]^{2+}$ complexes (SiO_2, CH_2Cl_2)[16] and an asymmetric inducer onto the configurationally labile $[Fe(\mathbf{2})_3]^{2+}$ derivative (diastereomeric ratio (dr) > 49:1 in $CHCl_3$, **2**: 4,4′-dimethyl-2,2′-bipyridine).[17] The efficiency of **1** as an NMR shift reagent or chiral auxiliary was explained by the formation of diastereomeric contact ion pairs with the chiral cations. However, the complexes studied were all mononuclear and of simple D_3 symmetry, similar to that of **1**. It was then debatable whether **1** would behave as a good NMR chiral shift reagent and/or resolving agent for polynuclear helicates of more complex structure and geometry.[18] We here report that the determination of the enantiomeric purity of a dinuclear iron(II) triple helix can be conveniently carried out by ^{1}H NMR analysis with [nBu$_4$N][Δ-**1**] as a chiral shift reagent. We also present a novel resolution procedure which is based on an asymmetric extraction/precipitation with lipophilic TRISPHAT anions as resolving agents. Simple stirring of an aqueous solution of the $[Fe_2(\mathbf{3})_3][SO_4]_2$ helicate (**3** = 1,2-bis[4-(4′-methyl-2,2′-bipyridyl)]ethane) with an organic solution of TRISPHAT salts leads to the simultaneous asymmetric extraction/precipitation of the P and M enantiomers of $[Fe_2(\mathbf{3})_3]^{4+}$ with selectivity ratios higher than 49:1.

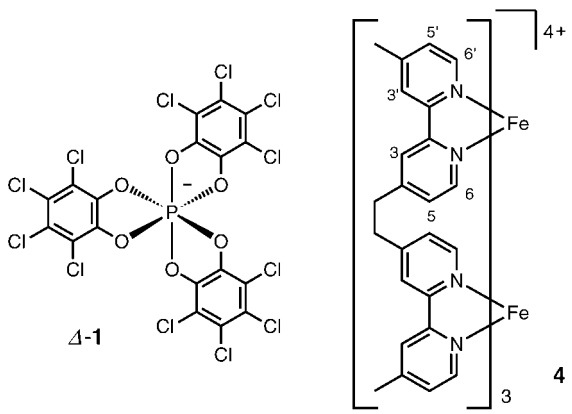

Figure 2. Chiral TRISPHAT anion **1** (Δ) and helicate **4**.

Abstract in French: *Le ligand tétradentate 1,2-bis[4-(4′-méthyl-2,2′-bipyridyl)]éthane **3** et le sel de Mohr $[Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O]$ s'assemblent dans un rapport 3:2 pour former un triple hélicate racémique $[Fe_2L_3]^{4+}$ **4**, précédemment décrit par Elliott. Dans cet article, nous montrons que la pureté énantiomérique de **4** peut être efficacement mesurée en RMN ^{1}H, en utilisant un sel de TRISPHAT (**1**) comme agent de dédoublement. D'importantes différences de déplacements chimiques ($\Delta\Delta\delta$ jusqu'à 0.3 ppm, 20% [D$_6$]DMSO dans CD_3CN) sont observées entre les énantiomères de **4** après l'ajout de [nBu$_4$N][Δ-**1**]. Un dédoublement de l'hélicate **4** par extraction asymétrique est possible: l'addition d'une solution organique du sel [cinchonidinium][Δ-**1**] (2 équiv) à une solution aqueuse de l'hélicate $[\mathbf{4}][SO_4]_2$ conduit, après une agitation soutenue, à l'extraction du diastéréoisomère homochiral $[P\text{-}\mathbf{4}][\Delta\text{-}\mathbf{1}]_4$ vers la phase organique et à la précipitation simultanée du composé hétérochiral $[M\text{-}\mathbf{4}][\Delta\text{-}\mathbf{1}]_4$ à l'interface (rapport diastéréoisomérique > 49:1 pour chaque processus). Dans la phase aqueuse, une fraction énantiomériquement enrichie du sel $[P\text{-}\mathbf{4}][SO_4]_2$ est isolée. Pour obtenir seulement deux fractions de l'hélicate diastéréomériquement pur, et convertir ainsi cette procédure en une méthode efficace de dédoublement, il suffit d'utiliser 4 équivalents du sel [cinchonidinium][Δ-**1**]. Les sels $[P\text{-}\mathbf{4}][\Delta\text{-}\mathbf{1}]_4$ et $[M\text{-}\mathbf{4}][\Delta\text{-}\mathbf{1}]_4$ sont alors obtenus chimiquement et optiquement purs avec d'excellents rendements.*

Results and Discussion

Choice of a helicate: The purpose of our study was to estimate the interactions of a chiral cationic helicate and anions **1**. We decided to prepare a helicate already reported in the literature, rather than create a novel derivative, to gain rapid access to valuable information. We selected the $[Fe_2(\mathbf{3})_3]^{4+}$ helicate **4**—reported by Elliott et al. in 1988—for its ease of preparation from readily accessible ligands and unambiguous structural determination both in solution and in the solid state (Figure 2 and Figure 3).[19] This chiral derivative had never been resolved and no attempt had been made to determine a possible enantiomeric purity. Furthermore, this complex is formally an "extended dimer" of mononuclear cation $[Fe(\mathbf{2})_3]^{2+}$ for which we have observed a high diastereoselectivity in asymmetric induction experiments with TRISPHAT anions.[17] For all these reasons, helicate **4** was chosen to be the investigated substrate.

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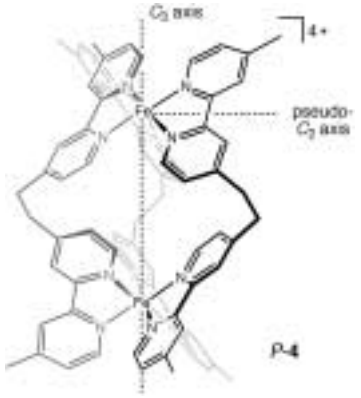
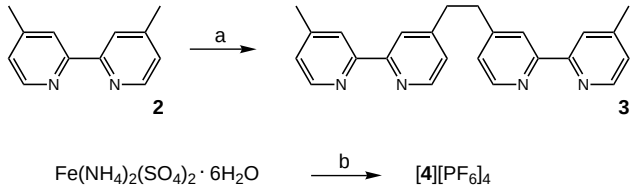


Figure 3. *P* enantiomer of **4** (from the X-ray structural analysis of Elliott,[19] Cambridge crystallographic database [SADMIT]).

Tetradentate ligand **3** was prepared in a single step by reaction of **2**[20] with *n*BuLi and 1,2-dibromoethane as previously described (Scheme 1).[21] Treatment of **3** (1.5 equiv)



Scheme 1. Preparation of ligand **3** and helicate **4**. Reaction conditions: a) i) LDA (1.5 equiv), THF, −78 °C; ii) $BrCH_2CH_2Br$ (2.1 equiv), −78 °C to RT, 30 %. b) i) **3** (1.5 equiv), H_2O/EtOH (1:1), reflux, 3h; ii) $[NH_4][PF_6]$ (excess), RT, 100 %.

with $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ salt (1.0 equiv) in H_2O/EtOH and addition of excess $[NH_4][PF_6]$ afforded the racemic $[\mathbf{4}][PF_6]_4$ salt as a red solid in a quantitative yield.

Enantiomeric purity determination by NMR spectroscopy: With cationic helicate **4** in our hands, our first goal was to demonstrate that anion **1** could be used as an NMR chiral shift reagent for the determination of the enantiomeric purity of **4**. The conditions reported in an earlier work were used:[15a] we added the $[n\mathrm{Bu_3NH}][\Lambda\text{-}\mathbf{1}]$ salt to a solution of $[\mathbf{4}][PF_6]_4$ in 20 % $[D_6]$DMSO/CD_3CN. To our surprise, the ^{1}H NMR spectrum showed a large broadening of the signals of **4**, instead of the expected split in a 1:1 ratio (Figure 4, spectrum g) which prevented any quantitative measurement.[22] However, upon addition of the newly prepared $[n\mathrm{Bu_4N}][\Lambda\text{-}\mathbf{1}]$ reagent,[14] a clean nonmagnetic equivalency for the *P* and *M* enantiomers of **4** was observed. The signals remained sharp and were split. The differences in chemical shifts ($\Delta\Delta\delta$) for the protons of **4** were sufficient to integrate the respective signals of each enantiomer (1:1 ratio). The spectra of $[\mathbf{4}][PF_6]_4$ without (a) and with (b–f) various amounts of $[n\mathrm{Bu_4N}][\Lambda\text{-}\mathbf{1}]$ are shown in Figure 4.

Upon addition of $[n\mathrm{Bu_4N}][\Lambda\text{-}\mathbf{1}]$, only one of the enantiomers of **4** (that of *P* configuration[23]) showed strong shifts of some of its signals. The aromatic protons H6′ and H5′ of this enantiomer, which are located at the periphery of the helicate along its C_3 axis, are shifted the most (see Figure 2 for the

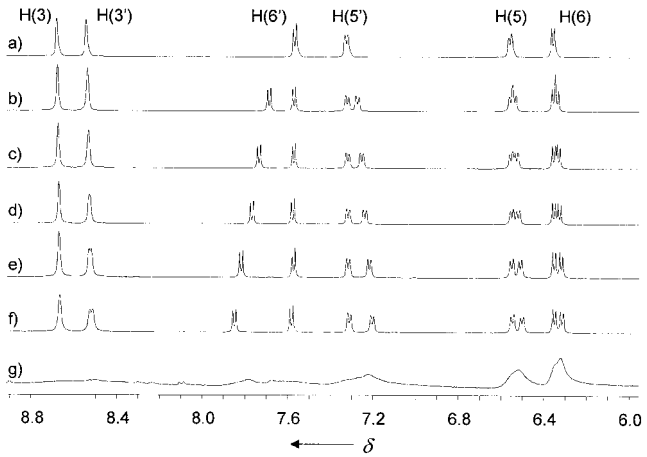


Figure 4. ^{1}H NMR spectra (400 MHz) of helicate $[\mathbf{4}][PF_6]_4$ in 20 % $[D_6]$DMSO/CD_3CN: a) without additive, b)–f) with respectively 1.5, 2.3, 3.1, 4.3, and 5.5 equivalents of $[n\mathrm{Bu_4N}][\Lambda\text{-}\mathbf{1}]$, g) with 2.2 equivalents of $[n\mathrm{Bu_3NH}][\Lambda\text{-}\mathbf{1}]$.

assignment of the protons). The other protons remained essentially unchanged (Table 1, $\Delta\delta$). The H6′ protons are shifted downfield ($\Delta\delta_{max} = 0.249$ with 4.3 equivalents of $[n\mathrm{Bu_4N}][\Delta\text{-}\mathbf{1}]$ salt) contrary to the others. Analogous protons

Table 1. Chemical shifts (δ), induced changes ($\Delta\delta$) and difference in chemical shifts ($\Delta\Delta\delta$) for the enantiomers of **4** upon the addition of 4.3 equivalents of $[n\mathrm{Bu_4N}][\Lambda\text{-}\mathbf{1}]$ to $[\mathbf{4}][PF_6]_4$ (400 MHz, 20 % $[D_6]$DMSO/CD_3CN).

Proton	δ_P[b]	δ_M[b]	$\Delta\delta_P$	$\Delta\delta_M$	$\Delta\Delta\delta$[c]
H6′	7.817	7.576	0.249	0.008	0.241
H5′	7.216	7.316	−0.109	−0.009	−0.100
Me	2.541	2.466	−0.026	−0.102	0.076
H3′	8.669	8.669	−0.014	−0.023	0.009
H3	8.529	8.520	−0.010	−0.010	0.000
*CH*H′[a]	3.512	3.471	−0.002	−0.043	0.041
CH*H*′[a]	2.860	2.883	−0.034	−0.011	−0.023
H5	6.319	6.353	−0.041	−0.008	−0.033
H6	6.511	6.551	−0.050	−0.009	−0.040

[a] The methylene protons are diastereotopic and easily distinguished. [b] See ref. [23]. [c] $\Delta\Delta\delta = \Delta\delta_P - \Delta\delta_M$.

H6, which occupy positions close to the C_3 axis but inside the helicate, only changed a little. These larger differences in chemical shifts $\Delta\Delta\delta$ of H6′ and H5′ and smaller $\Delta\Delta\delta$ of the other hydrogen atoms are consistent, for this enantiomer *P*, with an ion-pairing model in which anions **1** and cation **4** interact at the periphery along the C_3 axis. For this reason, the protons away from the C_3 axis (i.e. H3′, H3 and CH_2, and the ones located inside the helicate, H5 and H6) remain more or less unchanged. For the other enantiomer *M*,[23] the methyl and methylene groups carry the most perturbed protons. This might indicate an approach of anions **1** along the "*pseudo*-C_2" axes[24] of each individual metal coordination center rather than an approach along the C_3 axis.

As expected, increasing the amount of added $[n\mathrm{Bu_4N}][\Lambda\text{-}\mathbf{1}]$ reagent (1.5–5.5 equivalents) increases the magnetic nonequivalency of the protons (Figure 4 and Table 2). In more polar solvents, smaller separations of the signals were

Table 2. Proton H6′ of **4**. Chemical shifts (δ), induced changes ($\Delta\delta$), and differences in chemical shifts ($\Delta\Delta\delta$) of the enantiomers as a function of the number of equivalents of [nBu$_4$N][Δ-**1**] added (400 MHz, 20% [D$_6$]DMSO/CD$_3$CN).

Added equiv [nBu$_4$N][Δ-**1**]	δ_P[a]	δ_M[a]	$\Delta\delta_P$	$\Delta\delta_M$	$\Delta\Delta\delta$[b]
0.0	7.568		–	–	–
1.53	7.688	7.571	0.120	0.003	0.117
2.33	7.735	7.572	0.167	0.004	0.164
3.13	7.768	7.576	0.200	0.008	0.192
4.32	7.817	7.576	0.249	0.008	0.241
5.54	7.848	7.582	0.280	0.014	0.267

[a] See ref. [23]. [b] $\Delta\Delta\delta = \Delta\delta_P - \Delta\delta_M$.

observed. For proton H6′ of the enantiomer *P* which undergoes the greatest shift, the $\Delta\Delta\delta$ value is reduced from 0.267 to 0.081 in 20% [D$_6$]DMSO/CD$_3$CN and pure [D$_6$]DMSO, respectively, on addition of 5.5 equivalents of [nBu$_4$N][Δ-**1**]. This decrease in chiral shift efficiency as the polarity increases is interpreted as the result of looser interactions between the ions.[25] However, in pure [D$_6$]DMSO, the separation remains sufficient to allow a clean integration of the signals of the enantiomers. With this quantitative method of determination of the enantiomeric purity of helicate **4**, we turned our attention to the development of a resolution procedure.

Chromatographic resolution: To resolve the racemic helicate **4**, we first attempted to use the ion-pair chromatographic conditions we reported earlier for the enantiomeric separation of configurationally stable mononuclear ruthenium tris(diimine) complexes.[16] The potential of anions **1** to serve as chromatographic resolving agents was evaluated by thin-layer chromatography. We added four equivalents of [nBu$_3$NH][Λ-**1**] to a solution of [*rac*-**4**][PF$_6$]$_4$ in CH$_2$Cl$_2$ and spotted the resulting mixture. No migration of **4** was observed on either silica gel or on alumina (all grades) with eluents CH$_2$Cl$_2$ or more polar mixtures of solvents (up to 10% MeOH/EtOAc). A similar result was observed in preparative experiments. This absence of migration could be explained by the higher polarity of helicate **4**, which has a charge of 4+, compared to [Ru(diimine)$_3$]$^{2+}$ complexes.

Asymmetric extraction: We then explored the possibility to resolve helicate **4** by an asymmetric extraction procedure with anions **1** as lipophilic chiral selectors. The [cinchonidinium][Δ-**1**] salt is soluble in polar solvent mixtures (>5% DMSO/CHCl$_3$ or 10% acetone/CH$_2$Cl$_2$). More importantly, the lipophilic TRISPHAT anion confers to this salt an affinity for organic solvents and, once dissolved, the [cinchonidinium][Δ-**1**] pair does not partition in aqueous layers.[26] This affinity of anions **1** for organic layers led us to consider using them as chiral selectors in an asymmetric extraction procedure of helicate **4**. The resolution of racemic substrates by preferential extraction of one enantiomer from water into immiscible organic solvents has been well studied.[27] The extraction and the resulting selectivity arise from the preferential binding in the organic phase of one enantiomer of the substrate with a chiral lipophilic selector. The racemic substrates are traditionally ammonium salts or zwitterionic amino acids.[28] Crown ethers with chiral elements in or around the backbone are usually used to ensure asymmetric discrimination. Selectivity ratios as high as 99:1 have been obtained.[28g] Recent studies have described the use of unusual selectors, such as lanthanide tris(β-diketonate) and polymeric columnar aggregates of deoxyguanosine.[29] Of most relevance to the current work is the observation by Lindoy and Everett that chiral cobalt(III) amine complexes can be successfully extracted from aqueous layers into CHCl$_3$ with Lasalocid A as the chiral host (*dr* up to 2.6:1).[30]

Asymmetric extraction experiments were first attempted in the following manner: a solution of [cinchonidinium][Δ-**1**] salt (2.0 equivalents) in 5% acetone/CH$_2$Cl$_2$ was added to an aqueous solution of [rac-**4**][SO$_4$]$_2$ in 5% EtOH/H$_2$O (0.35 mM) and the resulting biphasic mixture was stirred vigorously for 3 h at room temperature. Partial transfer of red coloration—corresponding to helicate **4**—from the aqueous layer (AL) to the organic layer (OL) was observed (Figure 5). Unfortunately, the simultaneous formation of a red suspension (SU) at the interface was also observed. This red solid was collected by filtration, and the resulting limpid phases were separated. Addition of a solution of [NH$_4$][PF$_6$] to the AL led to the precipitation of [**4**][PF$_6$]$_4$, which was isolated by filtration. Concentration of the OL in vacuo afforded a red solid that contained helicate **4**. Three fractions that contained helicate **4** were thus obtained and analyzed separately (Table 3).

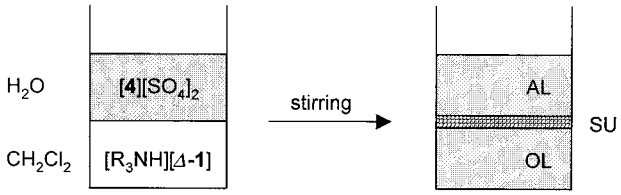


Figure 5. Schematic representation of the asymmetric extraction/precipitation of [rac-**4**][SO$_4$]$_2$ by [cinchonidinium][Δ-**1**] salt (2.0 equiv). Aqueous layer (AL), organic layer (OL), and suspension (SU).

^{1}H and ^{31}P NMR, as well as ES-MS revealed an association of helicate **4** with anions Δ-**1** in the solids which were obtained from the OL and SU fractions. The ratio between diastereomers [*P*-**4**][Δ-**1**]$_4$ and [*M*-**4**][Δ-**1**]$_4$ was measured by integration of the peaks in the ^{1}H NMR spectra, as the anions behave as NMR chiral shift reagents; in the fraction from the OL, we detected only one set of signals which indicated the presence of only one diastereomer (Figure 6, *dr* > 49:1). For the

Table 3. Composition and selectivity ratio of the three fractions obtained from the organic layer (OL), the suspension (SU), and the aqueous layer (AL) after stirring solutions of [rac-**4**][SO$_4$]$_2$ and [cinchonidinium][Δ-**1**] salt (2.0 equiv).

Fraction	Composition	Selectivity ratio	Yield
OL	[*P*-**4**][Δ-**1**]$_4$	*dr* > 49:1[b]	10%
SU	[*M*-**4**][Δ-**1**]$_4$	*dr* > 49:1[b]	36%
AL	[**4**][PF$_6$]$_4$[a]	*er* = 2.8:1[c]	48%

[a] The major enantiomer has the *P* configuration. [b] Diastereomeric ratio (*dr*) measured by ^{1}H NMR (400 MHz). [c] Enantiomeric ratio (*er*) measured by ^{1}H NMR (400 MHz) after addition of [nBu$_4$N][Δ-**1**] as the chiral shift reagent.

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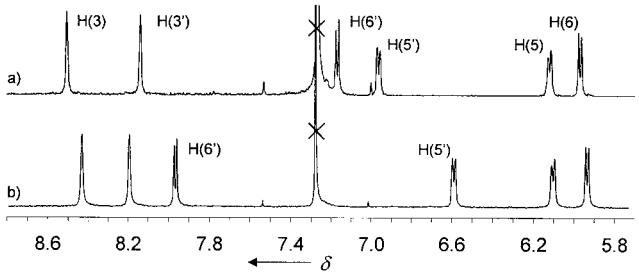

Figure 6. ^{1}H NMR spectra (400 MHz, 20% [D$_6$]DMSO/CDCl$_3$) of the [*M*-**4**][*Δ*-**1**]$_4$ and [*P*-**4**][*Δ*-**1**]$_4$ salts obtained a) from the SU fraction and b) from the OL fraction.

fraction from the SU, a similar result was obtained ($dr > 49{:}1$); however, the signals corresponded to the other diastereomer. The nature—homochiral [*P*-**4**][*Δ*-**1**]$_4$ or heterochiral [*M*-**4**][*Δ*-**1**]$_4$—of the diastereomers within the OL or SU fractions was determined by CD analysis (Figure 7). For the diastereomer

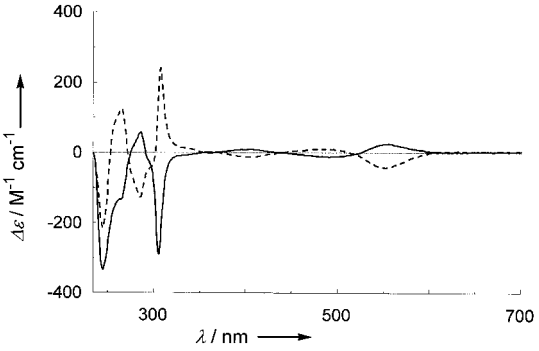

Figure 7. CD spectra (5.5×10^{-6} M in 0.5% DMSO/CH$_3$CN) of the OL (——) and SU (– – –) fractions.

from the OL, strong exciton couplings were observed in the $\pi-\pi^*$ and the MLCT regions ($\Delta\varepsilon_{307} = -290$ and $\Delta\varepsilon_{554} = +23$) which indicated a *P* configuration of the helicate **4**.[5a] For the *M* diastereomer in the SU, opposite Cotton effects were observed ($\Delta\varepsilon_{307} = +240$, $\Delta\varepsilon_{554} = -45$), as expected.

In the AL, spectral analyses indicated an association of helicate **4** with hexafluorophosphate anions. The ratio between the *P* and *M* enantiomers was determined after addition of the [*n*Bu$_4$N][*Δ*-**1**] salt, following the procedure described above. Integration of the respective signals indicated a moderate enantiomeric ratio (*er*) of 2.8:1 (Figure 8).

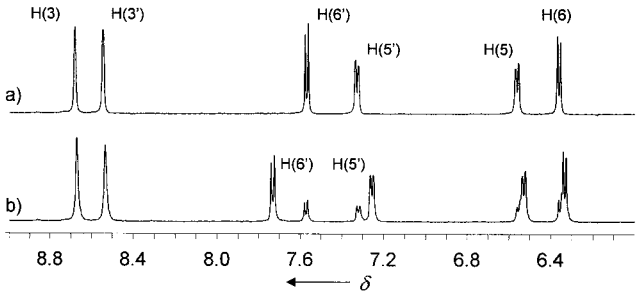

Figure 8. ^{1}H NMR spectra (400 MHz, 20% [D$_6$]DMSO/CD$_3$CN) of the salt obtained in the AL ([*P*-**4**][PF$_6$]$_4$): a) before and b) after the addition of 2.9 equivalents of [*n*Bu$_4$N][*Δ*-**1**] (*er* = 2.8:1).

The absolute configuration *P* of the major enantiomer of helicate **4** in the AL was determined by CD analysis ($\Delta\varepsilon_{304} = -255$, $\Delta\varepsilon_{547} = +15$, $c = 2.5 \times 10^{-6}$ M).

We thus achieved the separation of the enantiomers of chiral helicate **4** in the form of the heterochiral [*M*-**4**][*Δ*-**1**]$_4$ and homochiral [*P*-**4**][*Δ*-**1**]$_4$ diastereomers, in the suspension (by precipitation) and in the organic layer (by extraction), respectively. Although efficient, this process did not correspond to our initial goal as we were looking for a clean asymmetric extraction procedure that would have given only the aqueous and organic fractions in high enantiomeric and diastereomeric excesses. Despite all our efforts, we did not find the experimental conditions—solvents, temperature, concentration—which would allow a clean extraction of the homochiral diastereomer into the OL without some degree of precipitation of the heterochiral diastereomer. Three fractions were always obtained with low enantiomeric purity for helicate [**4**][PF$_6$]$_4$ from the AL because of the competing extraction and precipitation—the AL being depleted of the *P* and *M* enantiomers simultaneously. Therefore, to maximize the yield of resolved helicate and simplify the procedure, we attempted experiments with four equivalents of [cinchonidinium][*Δ*-**1**] to try to drive the extraction/precipitation processes to completion. This would leave only two diastereomeric fractions to separate.

High-yielding resolution: Extraction experiments were then repeated with 4.0 equivalents of [cinchonidinium][*Δ*-**1**] and, as expected, water-soluble helicate [rac-**4**][SO$_4$]$_2$ completely separated into two fractions: the [*P*-**4**][*Δ*-**1**]$_4$ salt was extracted to the organic layer and the insoluble [*M*-**4**][*Δ*-**1**]$_4$ salt precipitated as a suspension. ^{1}H NMR spectroscopy proved again that both fractions were diastereomerically pure ($dr >$ 49:1) and were obtained in excellent yields of 50 and 48%, respectively (Table 4).

Table 4. Composition and selectivity ratio of the two fractions obtained from the organic layer (OL) and the suspension (SU) after stirring solutions of [rac-**4**][SO$_4$]$_2$ and [cinchonidinium][*Δ*-**1**] salt (4.0 equiv).

Fraction	Composition	Selectivity	Yield
OL	[*P*-**4**][*Δ*-**1**]$_4$	$dr > 49{:}1$[a]	50%
SU	[*M*-**4**][*Δ*-**1**]$_4$	$dr > 49{:}1$[a]	48%

[a] Diastereomeric ratio (*dr*) measured by ^{1}H NMR spectroscopy (400 MHz).

Configurational stability: As observed by Williams et al. for a dicobalt(II) triple helicate,[18] the configurational stability of Elliott's derivative **4**, compared to the mononuclear analogue [Fe(**2**)$_3$]$^{2+}$, has strongly increased. No epimerization was observed after two weeks at 25 °C for solutions of salts [*P*-**4**][*Δ*-**1**]$_4$ or [*M*-**4**][*Δ*-**1**]$_4$ in 20% [D$_6$]DMSO/CDCl$_3$ or 20% [D$_6$]DMSO/CD$_3$CN. To induce complete epimerization, the diastereomerically pure salts were heated in pure [D$_6$]DMSO (80 °C, 15 min) and the outcome of the reaction was easily monitored by ^{1}H NMR. At 80 °C (Figure 9b), new signals corresponding to free ligand **3** appeared. Upon cooling to 25 °C, both diastereomers were formed in a 1:1 ratio and most

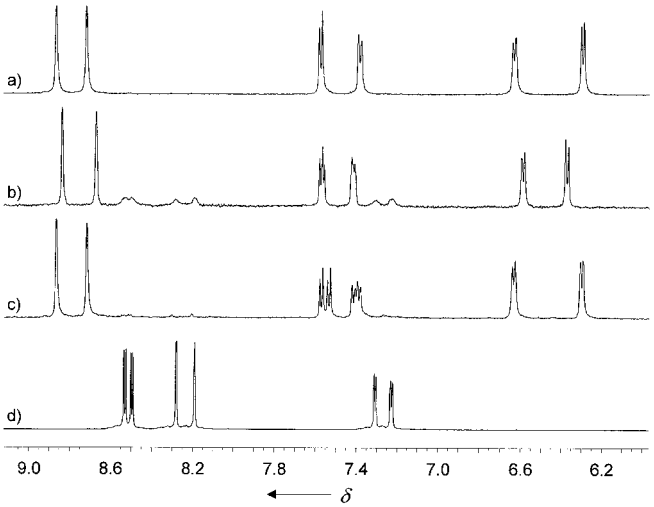

Figure 9. ^{1}H NMR (400 MHz) spectra of [*P*-**4**][*Δ*-**1**]$_4$ in [D$_6$]DMSO: a) at 25 °C ($dr > 49{:}1$), b) at 80 °C, c) after cooling again at 25 °C ($dr = 1{:}1$). d) ^{1}H NMR (400 MHz) spectrum of ligand **3** in [D$_6$]DMSO at 80 °C.

of **3** disappeared (Figure 9c).[31] The appearance of the free ligand at higher temperatures suggests a racemization pathway which involves the complete loss of one ligand around the metal centers. Racemization might then occur at the stage of a double-stranded intermediate, which would recombine randomly with **3** to form a 1:1 mixture of diastereomeric salts.

Conclusions

In conclusion we have shown that the [*n*Bu$_4$N][*Δ*-**1**] salt is a valuable NMR chiral shift reagent for Elliott's iron(II) dinuclear helicate **4**. An efficient resolution of **4** was developed based on an asymmetric extraction/precipitation procedure with lipophilic TRISPHAT anions.

Experimental Section

General: Solvents (SDS and Fluka) were used without further purification, except chloroform (Fluka) and $CDCl_3$ (CIL) which were filtered through a plug of basic alumina prior to use. Deionized water was used for aqueous solutions. The iron(II) salt $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (Fluka) and the solution of [*n*Bu$_4$N][OH] in water (40%, Fluka) were used without further purification. The [NH$_4$][PF$_6$] salt (Fluka) was used as a solution in water (4.9 M). 1,2-Bis[4-(4′-methyl-2,2′-bipyridyl)]ethane (**3**) was prepared following the procedure given in the literature[21] starting from 4,4-dimethylbipyridine (**2**).[20] The [cinchonidinium][Δ-**1**] salt was obtained with our previously described procedure.[12]

Analytical thin-layer chromatography (TLC) was performed on Macherey-Nagel 0.25 mm silica gel plates. Visualization was accomplished with UV light. Melting points (M.p.) were measured in open capillary tubes with a Stuart Scientific SMP3 melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX-400 spectrometer at 25 °C (unless otherwise specified). ^{1}H NMR shifts are given relative to the internal standard tetramethylsilane. Mixtures of solvents were calibrated with $CDCl_3$ ($\delta = 7.27$) or CD_3CN ($\delta = 1.93$). When necessary, assignment of the signals was achieved with NOESY and/or COSY experiments. A standard concentration of 5×10^{-4} M was used for the ^{1}H NMR spectra of the helicates. The ^{31}P NMR (162 MHz) shifts are given relative to H_3PO_4. Infrared spectra were recorded on a Perkin Elmer 1600 Series FT-IR spectrophotometer in a NaCl cell or KBr; absorption intensities are represented as strong (s), medium (m) and weak (w). UV spectra were recorded on a UVIKON 860 spectrometer in a 1.0 cm quartz cell. Circular dichroism spectra were recorded on a JASCO J-715 spectropolarimeter in a 1.0 cm quartz cell. Optical rotations were measured on a Perkin – Elmer 241 polarimeter in a thermostated (20 °C) microcell (length: 10.0 cm) with high pressure lamps of sodium or mercury and are reported as follows: $[\alpha]_\lambda^{20}$ (c [g 100 mL^{-1}], solvent). Electrospray mass spectra were obtained on a Finnigan SSQ 7000 spectrometer by the Department of Mass Spectroscopy by Mr. W. Kloeti and Mrs E. Sandmeyer. Elemental analyses were performed by Dr. H. Eder at the Institut de Chimie Pharmaceutique de l'Université de Genève.

[Tris(1,2-bis(4′-methyl-2,2′-bipyridyl-4-yl)ethane)diiron][tetrakis(hexafluorophosphate)] salt, 4-(PF$_6$)$_4$: In a 100 mL conical flask equipped with a condenser, a suspension of $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (55.6 mg, 141.8 μmol, 2.0 equiv) and the ligand 1,2-bis[4-(4′-methyl-2,2′-bipyridyl)]ethane (**3**; 78.0 mg, 3.0 equiv) in water/acetone (1:2, 60 mL) was heated at 65 °C for 3 h. At room temperature, a solution of ammonium hexafluorophosphate in water (50 equiv) was added to the red solution, and the resulting precipitate **4**-(PF$_6$)$_4$ was filtered (125.6 mg, 99%). No further purification was needed. M.p. 270 °C (decomp); ^{1}H NMR (400 MHz, 20% [D$_6$]DMSO/$CDCl_3$): $\delta =$ 8.32 (s, 6H; H3), 8.18 (s, 6H; H3′), 7.12 (d, ^3J(H,H) = 5.9 Hz, 6H; H6′), 6.91 (d, ^3J(H,H) = 5.9 Hz, 6H; H5′), 6.10 (d, ^3J(H,H) = 5.5 Hz, 6H; H5), 5.99 (d, ^3J(H,H) = 5.5 Hz, 6H; H6), 3.13 (d, ^3J(H,H) = 7.4 Hz, 6H; CH_2), 2.65 (d, 6H; CH_2), 2.23 (s, 18H; CH_3); ^{1}H NMR spectra in mixtures of [D$_6$]DMSO/$CDCl_3$, see Table 5; ^{31}P NMR (162 MHz, 20% [D$_6$]DMSO/$CDCl_3$): $\delta =$ −143.6 (septet, ^1J(P,F) = 712.8 Hz); IR (KBr): $\tilde{\nu} =$ 3662 (w), 3082 (w), 1621 (m), 1485 (m), 1421 (m), 1247 (w), 846 (s), 558 (w) cm^{-1}; MS (ES): positive-ion mode : 1645.1 ([Fe$_2$L$_3$]$^{4+}$(PF$_6^-$)$_3$), 750.3 ([Fe$_2$L$_3$]$^{4+}$(PF$_6^-$)$_2$), 451.8 ([Fe$_2$L$_3$]$^{4+}$(PF$_6^-$)); negative-ion mode: 144.4 (PF$_6^-$).

Table 5. ^{1}H NMR chemical shifts of [**4**][PF$_6$]$_4$ as a function of the percentage of [D$_6$]DMSO in $CDCl_3$.

DMSO [%]	10	20	30	50
H6′	7.317	7.127	6.964	6.733
H6	6.203	6.006	5.822	5.551
H5′	7.073	6.916	6.785	6.583
H5	6.304	6.120	5.985	5.808
H3′	8.311	8.194	8.091	7.915
H3	8.395	8.330	8.259	8.085
H(CH_2)	3.283	3.179	2.990	2.713
H(CH_2)	2.873	–[a]	2.444	2.133
H(Me)	2.430	2.243	2.068	1.801

[a] Not measurable.

[*n*Bu$_4$N][*Δ*-TRISPHAT] salt: To a solution of [cinchonidinium][*Δ*-**1**] in a minimum of EtOH was added [*n*Bu$_4$N][OH] (2 equiv), followed by water (≈2%) to ensure complete precipitation. The solid was filtered, redissolved in acetone, and concentrated in vacuo to afford the [*n*Bu$_4$N][*Δ*-**1**] salt (100%). $R_f = 0.86$ (SiO_2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.3 – 3.1 (m, 8H; H1), 1.8 – 1.6 (m, 8H; H2), 1.4 – 1.2 (m, 8H; H3), 0.90 (t, ^3J(H,H) = 7.3 Hz, 12H; HCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.7$ (d, ^2J(C,P) = 6.6 Hz, 6C), 122.6 (6C), 113.7 (d, ^3J(C,P) = 19.8 Hz, 6C), 59.2 (4CH_2), 23.8 (4CH_2), 19.7 (4CH_2), 13.4 (4CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): $\delta = -79.2$; $[\alpha]_D^{20} = -368$, $[\alpha]_{578}^{20} = -380$, $[\alpha]_{546}^{20} = -437$, $[\alpha]_{436}^{20} = -820$, $[\alpha]_{365}^{20} = -1506$ ($c = 0.10$, EtOH); MS (ES): positive-ion mode: 242.3 ([Bu$_4$N]$^+$); negative-ion mode: 768.5 (TRISPHAT$^-$).

Asymmetric extraction procedure: In a conical flask equipped with a condenser, a suspension of $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (55.6 mg, 141.8 μmol, 2.0 equiv) and ligand 1,2-bis[4-(4′-methyl-2,2′-bipyridyl)]ethane (**3**; 78.0 mg, 3.0 equiv) in water/ethanol (1:1, 20 mL) was heated at reflux (90 °C) for 3 h. The resulting red solution was cooled to 20 °C and diluted with water to a volume of 200 mL. A solution of [cinchonidinium][*Δ*-TRISPHAT] salt (2.0 equiv) in 5% acetone/CH_2Cl_2 (200 mL) was then added. The resulting biphasic mixture was stirred vigorously for 3 h. A partial transfer of the coloration from the aqueous to the organic layer was observed, while a suspension formed at the interface. The solid was filtered, washed with a large amount of water and CH_2Cl_2, and then dried to afford the heterochiral salt [*M*-**4**][*Δ*-**1**]$_4$ (110.4 mg; 36%). After separation of the

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limpid phases, the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). Addition to the aqueous layer of a solution of $[NH_4][PF_6]$ in water (50 equiv) led to the formation of the enantioenriched **4**-$(PF_6)_4$ salt (predominant *P* enantiomer) obtained as a red precipitate (60.4 mg, 48 %). The combined organic layers were washed with 10 % acetone/water (4 × 200 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the homochiral diastereomer salt [*P*-**4**][*Δ*-**1**]$_4$ as a deep red solid (31.7 mg, 10 %).

Heterochiral [*M*-4][*Δ*-1]$_4$ salt: $R_f = 0.0$ (SiO_2, CH_2Cl_2); m.p. 330 °C (decomp); ^{1}H NMR (400 MHz, 20 % [D$_6$]DMSO/$CDCl_3$): $\delta = 8.50$ (s, 6H; H3), 8.14 (s, 6H; H3′), 7.17 (d, ^3J(H,H) = 5.5 Hz, 6H; H6′), 6.96 (d, ^3J(H,H) = 5.5 Hz, 6H; H5′), 6.12 (d, ^3J(H,H) = 5.9 Hz, 6H; H5), 5.98 (d, ^3J(H,H) = 5.9 Hz, 6H; H6), 3.35 (d, ^3J(H,H) = 7.4 Hz, 6H; CH_2), 2.53 (d, ^3J(H,H) = 8.1 Hz, 6H; CH_2), 2.15 (s, 18H; CH_3); ^{31}P NMR (162 MHz, 20 % [D$_6$]DMSO/$CDCl_3$): $\delta = -80.1$; IR (KBr): $\tilde{\nu} = 3459$ (w), 1618 (w), 1452 (s), 1390 (m), 1302 (w), 1236 (w), 992 (m), 826 (s), 720 (w), 676 (m) cm^{-1}; UV/Vis (1 % DMSO/$CHCl_3$, 2.89×10^{-6} M): λ_{max} (ε) = 300.0 (7.3×10^4 M), 532.0 nm (4.8×10^3 cm^{-1}dm^{3}mol^{-1}); CD (0.5 % DMSO/CH_3CN, 5.58×10^{-6} M, 19.5 °C): λ ($\Delta\varepsilon$) = 245.5 (−217), 265.5 (124), 285.5 (−129), 307.5 (240), 407.5 (−14), 489.5 (8), 552.5 nm (−45 cm^{2}mmol^{-1}); $[\alpha]_D^{20} = -1075$, $[\alpha]_{578}^{20} = -1075$ and $[\alpha]_{436}^{20} = -212$ ($c = 0.015$, 10 % DMSO/CH_3CN); MS (ES): positive-ion mode: 1374.7 ($[Fe_2L_3]^{4+}$(TRISPHAT$^-$)$_2$), 1188.6 ($[Fe_2L_2]^{4+}$(TRISPHAT$^-$)$_2$), 535.0 ($[Fe_2L_2]^{4+}$(TRISPHAT$^-$)), 394.1 ($[FeL_2]^{2+}$); negative-ion mode: 768.4 (TRISPHAT$^-$); elemental analysis calcd for $C_{144}H_{66}Cl_{48}Fe_2N_{12}O_{24}P_4$ (4285.45) (%): C 40.36, H 1.55, N 3.92; found: C 40.85, H 2.37, N 3.72.

Enantioenriched [4][PF$_6$]$_4$ salt: $R_f = 0.0$ (SiO_2, CH_2Cl_2); m.p. 300 °C (decomp); ^{1}H NMR (400 MHz, 20 % [D$_6$]DMSO/$CDCl_3$): $\delta = 8.33$ (s, 6H; H3), 8.20 (s, 6H; H3′), 7.15 (d, ^3J(H,H) = 5.5 Hz, 6H; H6′), 6.93 (d, ^3J(H,H) = 5.5 Hz, 6H; H5′), 6.13 (d, ^3J(H,H) = 5.9 Hz, 6H; H5), 6.02 (d, ^3J(H,H) = 5.9 Hz, 6H; H6), 3.15 (d, ^3J(H,H) = 7.3 Hz, 6H; CH_2), 2.6 (d, 6H; CH_2), 2.26 (s, 18H; CH_3); ^{31}P NMR (162 MHz, 20 % [D$_6$]DMSO/$CDCl_3$): $\delta = -143.6$ (septet, ^1J(P,F) = 713.4 Hz); IR (KBr): $\tilde{\nu} = 3436$ (m), 2963 (w), 1621 (m), 1485 (w), 1420 (w), 1261 (w), 1094 (m), 845 (s), 558 (m) cm^{-1}; UV/Vis (0.5 % DMSO/CH_3CN, 2.51×10^{-6} M): λ_{max} (ε) = 300.0 (1.3×10^5), 531.0 nm (1.2×10^4 cm^{-1}dm^{3}mol^{-1}); CD (0.5 % DMSO/CH_3CN, 2.51×10^{-6} M, 19.5 °C): λ ($\Delta\varepsilon$) = 303.5 (−255), 547.0 (15), 645.5 nm (−31 cm^{2}mmol^{-1}); $[\alpha]_D^{20} = 1036$, $[\alpha]_{578}^{20} = 1014$ ($c = 0.009$, 10 % DMSO/CH_3CN); MS (ES): positive-ion mode: 1645.1 ($[Fe_2L_3]^{4+}(PF_6^-)_3$), 750.3 ($[Fe_2L_3]^{4+}(PF_6^-)_2$), 451.8 ($[Fe_2L_3]^{4+}(PF_6^-)$); negative-ion mode: 144.4 (PF_6^-); elemental analysis calcd for $C_{72}H_{66}F_{24}Fe_2N_{12}P_4$ (1790.92) (%): C 48.29, H 3.71, N 9.39; found: C 47.46, H 4.22, N 8.79.

Homochiral [*P*-4][*Δ*-1]$_4$ salt: $R_f = 0.0$ (SiO_2, CH_2Cl_2); m.p. 300 °C (decomp); ^{1}H NMR (400 MHz, 20 % [D$_6$]DMSO/$CDCl_3$): $\delta = 8.44$ (s, 6H; H3), 8.20 (s, 6H; H3′), 7.97 (d, ^3J(H,H) = 5.5 Hz, 6H; H6′), 6.57 (d, ^3J(H,H) = 5.9 Hz, 6H; H5′), 6.08 (d, ^3J(H,H) = 5.5 Hz, 6H; H5), 5.91 (d, ^3J(H,H) = 5.5 Hz, 6H; H6), 3.17 (d, ^3J(H,H) = 7.7 Hz, 6H; CH_2), 2.55 (d, ^3J(H,H) = 7.4 Hz, 6H; CH_2), 1.95 (s, 18H; CH_3); ^{1}H NMR spectra in mixtures of [D$_6$]DMSO/$CDCl_3$, see Table 6; ^{31}P NMR (162 MHz, 20 % [D$_6$]DMSO/$CDCl_3$): $\delta = -80.2$; IR (KBr): $\tilde{\nu} = 3062$ (w), 1618 (w), 1452 (s), 1390 (m), 1302 (w), 1236 (w), 992 (m), 826 (s), 720 (w), 675 (m) cm^{-1}; UV/Vis (0.5 % DMSO/CH_3CN, 1.82×10^{-6} M): λ_{max} (ε) = 300.0 (1.2×10^5), 532.0 nm (8.8×10^3 cm^{-1}dm^{3}mol^{-1}); CD (0.5 % DMSO/CH_3CN, 5.41×10^{-6} M, 19.5 °C): λ ($\Delta\varepsilon$) = 245.0 (−334), 286.0 (56), 305.5 (−290), 408.0 (8), 491.0 (−14), 565.0 nm (23 cm^{2}mmol^{-1}); $[\alpha]_{D^-}^{20} = 282$, $[\alpha]_{578}^{20} = 256$ and $[\alpha]_{436}^{20} = 833$ ($c = 0.016$, 10 % DMSO/CH_3CN); MS (ES): postive-ion mode: 1373.3 ($[Fe_2L_3]^{4+}$(TRISPHAT$^-$)$_2$), 1190.6 ($[Fe_2L_2]^{4+}$(TRISPHAT$^-$)$_2$), 659.7 ($[Fe_2L_3]^{4+}$(TRISPHAT$^-$)), 394.2 ($[FeL_2]^{2+}$), 302.3 ($[Fe_2L_3]^{4+}$); negative-ion mode: 768.4 (TRISPHAT$^-$); elemental analysis calcd for $C_{144}H_{66}Cl_{48}Fe_2N_{12}O_{24}P_4$ (4285.45) (%): C 40.36, H 1.55, N 3.92; found: C 39.60, H 1.80, N 3.71.

Table 6. ^{1}H NMR chemical shifts of [*P*-**4**][*Δ*-**1**]$_4$ as a function of the percentage of [D$_6$]DMSO in $CDCl_3$.

DMSO [%]	10	15	20	30	50
H6′	8.230	8.114	7.974	7.632	7.059
H6	6.182	6.143	6.121	6.008	5.516
H5′	6.758	6.668	6.585	6.478	6.404
H5	6.116	6.019	5.934	5.761	5.809
H3′	8.306	8.262	8.208	8.102	7.918
H3	8.526	8.493	8.446	8.338	8.114
H(CH_2)	3.375	3.282	3.187	2.999	2.707
H(CH_2)	2.701	–[a]	2.582	2.404	2.129
H(Me)	2.107	2.034	1.963	1.841	1.684

[a] Not measurable.

Resolution procedure: In a conical flask equipped with a condenser, a suspension of $Fe(NH_4)_2(SO_4)_2 \cdot 6H_2O$ (36.2 mg, 92.41 μmol, 2.0 equiv) and ligand **3** (50.8 mg, 3.0 equiv) in water/ethanol (1:1, 20 mL) was heated at reflux (90 °C) for 3 h. The resulting red solution was cooled to 20 °C and diluted with water to a volume of 100 mL. A solution of [cinchonidinium][*Δ*-TRISPHAT] salt (4.0 equiv) in 5 % acetone/CH_2Cl_2 (100 mL) was then added. The resulting biphasic mixture was stirred vigorously for 3 h. A complete transfer of the coloration from the aqueous to the organic layer was observed, while a suspension formed at the interface. The solid was filtered, washed with a large amount of water and CH_2Cl_2 and then dried to afford the heterochiral salt [*M*-**4**][*Δ*-1]$_4$ (95.8 mg; 48 %). After separation of the limpid phases, the aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL). The combined organic layers were washed with a 10 % acetone/water (3 × 60 mL), dried (Na_2SO_4), and concentrated in vacuo to afford the homochiral diastereomer salt [*P*-**4**][*Δ*-**1**]$_4$ as a deep red solid (98.9 mg, 50 %). Analyses for homochiral [*P*-**4**][*Δ*-**1**]$_4$ and heterochiral [*M*-**4**][*Δ*-**1**]$_4$ salts obtained by this procedure were identical to the those already reported.

Acknowledgements

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