The robust, readily available cobalt(III) trication [Co(NH₂CHPhCHPhNH₂)₃]³⁺ is a progenitor of broadly applicable chirality and prochirality sensing agents†

Quang H. Luu, Kyle G. Lewis,‡ Anik Banerjee, Nattamai Bhuvanesh and John A. Gladysz *

When NMR spectra of chiral racemic organic molecules containing a Lewis basic functional group are recorded in the presence of air and water stable salts of the cobalt(III) trication [Co(S,S)-NH₂CHPhCHPhNH₂]³⁺ (2⁻), separate signals are usually observed for the enantiomers (28 diverse examples, >12 functional groups). Several chiral molecules can be simultaneously analyzed, and enantiotopic groups in prochiral molecules differentiated (16 examples). Particularly effective are the mixed bis(halide)/tetraarylborate salts L³⁺ 2X⁻ or L³⁺ 3I⁻ (X = Cl⁻, Br⁻, I⁻), which are applied in CD₂Cl₂ or CDCl₃ at 1–100 mol% (avg 34 and 14 mol%). Job plots establish 1 : 1 binding for L³⁺ 2Cl⁻ and 1-phenylethyl acetate (4) or 1-phenylethanol (10), and 1 : 2 binding with DMSO (CD₂Cl₂). Selected binding constants are determined, which range from 7.60–2.73 M⁻¹ for the enantiomers of 10 to 28.1–22.6 M⁻¹ for the enantiomers of 4. The NH moieties of the C₂ faces of the trications are believed to hydrogen bond to the Lewis basic functional groups, as seen in the crystal structure of a hexakis(DMSO) solvate of L³⁺ 3⁻. These salts rank with the most broadly applicable chirality sensing agents discovered to date.

1. Introduction

Ever since the recognition of molecular chirality, chemists have sought to quantify enantiomer ratios in non-racemic samples.¹ For more than a century, the dominant method was polarimetry, despite many intrinsic limitations.²,³ Today, nearly every analytical technique is being brought to bear on the problem, often in a quest for high throughput screening.⁴ Two broad classes of assays see the most use: “chiral” chromatography⁵,⁶ and NMR spectroscopy.⁷–¹¹

NMR methods can be divided into three principal categories: chiral derivatizing agents (CDAs),¹²–¹⁴,¹⁷ paramagnetic chiral lanthanide shift reagents (CLSRs),¹⁶ and chiral solvating agents (CSAs).¹⁶,¹⁰–¹¹ Over the past few years, the last approach has attracted increasing attention.¹⁷–³⁰ Many but not all of the CSAs are hydrogen bond donors, often with two-four NH or OH groups.¹⁷,²¹,²²,²⁵–²⁸,³⁰ Some of these have been tailored to recognize a specific functional group,¹⁹,²³,²⁴,²⁶–²⁸ while others have wider applicability.¹⁷,²⁰,²²,²⁵,²⁹,³⁰

The first chiral inorganic compounds to be isolated in enantiomerically pure form were reported by Werner some 105 years ago, and included salts of the trication [Co(en)₃]³⁺ (1³⁺; en = ethylenediamine).³¹–³⁵ We have recently found that lipophilic salts of this trication¹⁰ and the related species [Co(S,S)-NH₂CHArCHArNH₂]³⁺ (2⁻ for Ar = Ph)³⁷–³⁹ and [Co(en)₂(NH₂CH₂CH[(CH₃)₂N(CH₃)₂]NH₂)]³⁺ (3⁻)⁴₀ – all of which are depicted in Fig. 1 – serve as hydrogen bond donor catalysts for a variety of organic transformations. The trication 1³⁺ features only metal centered chirality, for which the absolute configurations are traditionally designated Δ and Δ.⁴¹ In the trications 2⁻ and 3⁻, the three ethylenediamine ligands are substituted with six aryl groups⁴² or a single (CH₃)₂N(CH₃)₂ moiety, respectively.⁴³ The latter constitutes a bifunctional catalyst.⁴⁴ Both enantiomers of the NH₂CHPhCHPhNH₂ (dpen) ligand in 2⁻ are commercially available at modest prices.⁴⁵

Although the mechanisms of these transformations are still under investigation, their effectiveness is thought to be rooted in the large number of NH groups (twelve). Those of one diastereomer of 2⁻ are depicted in Fig. 1 (bottom). As many as five to six might play a role in transition state assemblies,⁴⁵ as opposed to a maximum of two with most literature catalysts such as thioureas.⁴⁶ As such, they might possess unique
Fig. 1 (Top) Chiral hydrogen bond donor catalysts based upon cobalt(III) tris(ethylenediamine) trications. (Bottom) Space filling representations of the trication of $\Lambda$-2$^{2+}$ 3Cl$^-$·2H$_2$O·2CH$_2$OH: A, view down the idealized C$_3$ axis; B, view down one of three idealized C$_2$ axes.

2. Results

2.1. Syntheses of cobalt(III) CSAs

Enantiopure $\Lambda$-1$^{3+}$ 3BAr$_f^-$ and diastereopure $\Lambda$-2$^{2+}$ 2Cl$^-$ BAr$_f^-$, $\Lambda$-2$^{2+}$ 2Cl$^-$(C$_6$F$_5$)$_3$B, $\Lambda$-2$^{2+}$ 3BAr$_f^-$, and $\Delta$-2$^{2+}$ 2Cl$^-$(BAr$_f$)$_2$ were prepared according to previously reported procedures.$^{36,42}$ Those for the BAr$_f^-$ salts of $\Lambda$-2$^{2+}$ are summarized in Scheme 1. The key precursor $\Lambda$-2$^{2+}$ 3Cl$^-$ is easily synthesized from CoCl$_2$ or Co(OAc)$_2$, O$_2$, and (S,S)-dpen.$^{42}$

The new triiodide salt $\Lambda$-2$^{2+}$ 3I$^-$ was isolated in 97% yield from the reaction of $\Lambda$-2$^{2+}$ 3Cl$^-$ and KI in acetone.$^{38}$ Addition of 1.0 equiv. of Na$^+$ BAr$_f^-$ afforded the mixed bis(iodide)/tetraarylborate salt $\Lambda$-2$^{2+}$ 2I$^-$(BAr$_f$)$_2$ in 99% yield after workup. This complex could also be isolated in >99% yield from the reaction of excess NaI and $\Lambda$-2$^{2+}$ 2Cl$^-$(BAr$_f$)$_2$. It possessed the advantage of being – unlike the other salts – soluble in the inexpensive deuterated solvent CDCl$_3$.

2.2. Screening of cobalt(III) CSAs

The efficacies of the preceding complexes as CSAs were screened with racemic 1-phenethyl acetate (4). As presented in Table 1, 0.0071 M solutions of the CSAs in various solvents were combined with neat 4 (1.0 equiv.). In favorable cases, the chemical shifts of all of the aliphatic NMR signals of the enantiomers differed, as detailed in Table S1 of the ESI.$^\dagger$ In all of these cases, the methine (PhC$\equiv$H)-dpen.

2.2.1. NMR Analysis

Separate signals for the enantiomers were not differentiated (Table 1). The new triiodide salt $\Lambda$-2$^{2+}$ 3I$^-$ (entry 1) was ineffective in all assays, including additional analytes such as 1-phenethyl amine (5), phenyl methyl sulfoxide (6), and 2-carbomethoxycyclopentanone (7).

In contrast, the bis(chloride) tetraarylborate salts $\Delta$-2$^{2+}$ 2Cl$^-$(BAr$_f$)$_2$ and $\Lambda$-2$^{2+}$ 2Cl$^-$(C$_6$F$_5$)$_3$B gave widely separated methine proton signals in CD$_2$Cl$_2$ (entries 2 and 4; $\Delta\delta$ 1.37–1.32 ppm). The opposite diastereomer of the former, $\Delta$-2$^{2+}$ 2Cl$^-$(BAr$_f$)$_2$, was much less effective (entry 3, $\Delta\delta$ 0.15 ppm).

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$^a$ Samples were prepared in 5 mm NMR tubes as described in the Experimental section. $^b$ Separate signals for the enantiomers were not observed, although line widths increased from 0.6–0.9 to 1.0–2.0 Hz.
Interestingly, the corresponding tris(tetraarylborate) salt $\Lambda-2^{3+}$ 3$\text{BARf}_2$ was also less effective (entry 5; $\Delta \delta = 0.34$ ppm), despite the removal of all counter anions that can hydrogen bond to the NH groups of the trication.

The bis(iodide) salt $\Lambda-2^{3+}$ 2$I^{-}$ $\text{BARf}$ gave a high $\Delta \delta$ value (entry 6; 1.30 ppm), comparable to that of $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}_2$. Happily, when $\Lambda-2^{3+}$ 2$I^{-}$ $\text{BARf}$ was applied in the less polar and coordinating solvent CDCl$_3$, the $\Delta \delta$ value increased by 33% (entry 7, 1.75 ppm). Finally, when either $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}_2$ or $\Lambda-2^{3+}$ 2$I^{-}\text{BARf}$ were employed in the more polar and coordinating solvents acetone-$d_6$, CD$_3$CN, or DMSO-$d_6$, the enantiomers of 4 were no longer differentiated (entries 8–13).

It was sought to establish the minimum CSA loading needed to resolve the NMR signals of the enantiomers. Accordingly, an NMR tube was charged with a 0.036 M CD$_2$Cl$_2$ solution of $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}_2$ (0.70 mL, 0.025 mmol). Then neat 4 was added in increments (0.0050 mL; ca. 0.0012 g, 0.0050 mmol). As shown in Fig. 2, the $\Delta \delta$ values for all three aliphatic signals were plotted against the mol% of the CSA, which is in great excess at the start. The data spanned a range of 500 mol% down to 5 mol% (total volume of liquids: 0.7005 to 0.7500 mL, or less than a 7% concentration change). Although the $\Delta \delta$ values monotonically decreased, all signals maintained baseline separations.

The concentration dependence of the efficacies of the CSAs was also probed. For this purpose, a NMR tube was charged with a CD$_2$Cl$_2$ solution that was 0.040 M in a CD$_2$Cl$_2$ solution of $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}_2$ (0.70 mL, 0.025 mmol), or a CSA loading of 25 mol%. Then increments of CD$_2$Cl$_2$ were added, giving more dilute solutions. As shown in Fig. 3, there was little change in the $\Delta \delta$ values over a two fold dilution. However, up to a 30% decrease could be seen at the lower concentration ranges investigated.

### 2.3. Functional group scope, chirality sensing

As summarized in Table 2, racemic chiral organic compounds with a variety of Lewis basic functionalities ([4–31]) were treated with the most effective CSAs, $\Lambda-2^{3+}$ 2$I^{-}\text{BARf}$ (CDCl$_3$ solution) and $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}$ (CD$_2$Cl$_2$ solution). The former could differentiate the $^1$H NMR signals of the enantiomers in every case, and the latter failed with only three analytes. The signals employed are denoted in red in Table 2. With fluorine (15) or phosphorus (19, 20) containing analytes, $^{19}$F{1H} or $^{31}$P{1H} NMR was used instead. In cases where signals have been assigned to specific enantiomers, the samples were spiked with 0.50 equiv. of an authentic sample of one of the enantiomers.

With $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}$, the loadings required for baseline to near-baseline signal separations ranged from 1 to 100 mol%, with an average of 34 mol%. With $\Lambda-2^{3+}$ 2$I^{-}\text{BARf}$, the loading range was identical, but the average decreased to 14 mol%. It was sought to verify that reliable quantitative data could be obtained from this new class of CSAs. Thus, scalemic samples of 4 were prepared and the ee values assayed using both $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}$ and chiral HPLC, as described in the Experimental section. As depicted in Fig. S1 (ESI†), the two methods were essentially in perfect agreement.

When a chiral arene lacking a Lewis basic functional group, sec-butyl benzene (PhCH(CH$_3$)CH$_2$CH$_3$), was similarly investigated ($\Lambda-2^{3+}$ 2$I^{-}\text{BARf}$, CDCl$_3$), only a single set of (broadened) NMR signals was observed. Other analytes that gave only one set of signals included the benzylic chloride 1-phenyl-1-chloroethane, BINOL and its diacetate, and (surprisingly) the amide 5-hydroxymethyl-2-pyrrolidinone. However, the enantiomers of alkyl halides that contained additional Lewis basic functional groups, such as 29 and 30 (Table 2), were easily differentiated.

### Fig. 2 Dependence of the separation of the aliphatic $^1$H NMR signals of the enantiomers of 4 ($\Delta \delta$, CD$_2$Cl$_2$) upon concentration using the CSA $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}$ (constant at 25 mol%).

### Fig. 3 Dependence of the separation of the aliphatic $^1$H NMR signals of the enantiomers of 4 ($\Delta \delta$, CD$_2$Cl$_2$) upon concentration using the CSA $\Lambda-2^{3+}$ 2Cl$^-\text{BARf}$ (constant at 25 mol%).
Table 2: Separation of key NMR signals of the enantiomers of various analytes in the presence of the CSAs $\Lambda^{-2\text{, 5}(+\text{)}^{-2\text{, 1}}\text{BARf}} \text{, (CDCl}_3\text{)}$ or $\Lambda^{-2\text{, 5}(+\text{)}^{-2\text{, 1}}\text{BARf}} \text{, (CD}_2\text{Cl}_2\text{)}\text{a}

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<th>$\Delta\delta''$, $\text{mol}%$</th>
<th>Analyte/NMR signals$^b$</th>
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a Samples were prepared in 5 mm NMR tubes as described in the Experimental section. b The spectra depicted (\(^1^H\) unless noted) were obtained with \( \Lambda^\ddagger^\dagger 2^\dagger \) \( \text{BARf}^- \) in CDCl\(_3\). c Signal separation (ppm)/mol% using \( \Lambda^\ddagger^\dagger 2^\dagger \) \( \text{BARf}^- \). d Signal separation (ppm)/mol% using \( \Lambda^\ddagger^\dagger 2^\dagger \) \( 2\text{Cl}^- \) \( \text{BARf}^- \). e \(^3^1^P\{^1^H\} \) NMR spectra were utilized. f \(^3^1^P\{^1^H\} \) NMR spectra were utilized. g Separate signals for the enantiomers were not observed.

2.4. Prochirality sensing

The types of experiments in the previous section were repeated with achiral molecules using a CSA loading of 100 mol% (1.0 equiv.). As summarized in Table 3, in many cases different signals were observed for enantiotopic groups. Enantiotopic geminal or vicinal hydrogen atoms also became coupled to each other. Achiral molecules in which enantiotopic groups were not differentiated include nitroethane, propionitrile, propionic acid, methyl isovalerate, tetrahydrofuran, and diethyl phosphate.

2.5. Enhanced throughput sensing

Higher throughput variants of the above methodology would be desirable. Thus, it was tested whether the enantiomeric purities of two or more analytes could be simultaneously determined. A CDCl\(_3\) solution of racemic 4, 2-carbethoxyxyclopentanone (7), 1-phenylethanol (10), and two hydroxyphenylmethyl dialkyl phosphonates (19, 20) was prepared (2.0 : 2.0 : 2.0 : 1.0 : 2.0 mol ratio). Then \( \Lambda^\ddagger^\dagger 2^\dagger \) \( \text{BARf}^- \) was added (100 mol% with respect to 19; 50 mol% with respect to the other analytes; average loading per analyte 11 mol%).

As shown in Fig. 4, the enantiomers of all five analytes were differentiated by NMR. Such experiments are potentially complicated by overlapping signals, but this is sidestepped in Fig. 4 by using a second nucleus, \(^3^1^P\), to assay the phosphonates 19 and 20. Some practical uses of simultaneous enantiomeric purity assays would include kinetic resolutions, \(^{57-59}\) for example the acetylation of 10 to 4 or vice versa, \(^{57-60}\) and enantioselective reactions that afford two or more diastereomers. To date, the closest approximation to this capability seems to involve covalent adducts of CDAs where all analytes contain a common functional group (e.g., a primary amine).\(^{61}\)

2.6. Mechanism of chirality and prochirality sensing

Some insight has been previously acquired regarding hydrogen bonding between the twelve NH protons of the triations \(^3^+\) and \( \Lambda^\ddagger^\dagger \) and various counter anions.\(^{37,42,45}\) For example, data for \( \Lambda^\ddagger^\dagger 2^\dagger \) \( 2\text{Cl}^- \) \( \text{BARf}^- \) indicate that the two chloride anions strongly bind to the two \( C_3 \) faces (Fig. 1, bottom left), shifting the \(^1^H\) NMR signals of six NH protons markedly downfield (ca. \( \delta \) 8 ppm). The other six NH protons, which occupy the three \( C_2 \) faces (Fig. 1, bottom right), have only the solvent or the very poorly coordinating \( \text{BARf}^- \) anion to interact with. Accordingly, their \(^1^H\) NMR signals remain upfield (ca. \( \delta \) 4 ppm).\(^{37}\) These trends are illustrated in the bottom spectrum in Fig. 5, although it deserves emphasis that the signal separation is both concentration and temperature dependent.\(^{62}\)

As exemplified by the other spectra in Fig. 5, CD\(_2\)Cl\(_2\) solutions of \( \Lambda^\ddagger^\dagger 2^\dagger \) \( 2\text{Cl}^- \) \( \text{BARf}^- \) have been titrated with various analytes, such as dimethyl malonate, \( \text{trans}-\beta\)-nitrostyrene, methyl ethyl ketone, and both enantiomers of 4. In proceeding from one to 10 equivalents, appreciable downfield shifts of the upfield \( C_2 \) NH signals are observed. The downfield \( C_2 \) NH signals are much less affected. Often there is virtually no shift, as seen with dimethyl malonate (Fig. 5, \( \Delta \delta = 0.07 \) ppm), \( \text{trans}-\beta\)-nitrostyrene, and methyl ethyl ketone; with the enantiomers of 4, there is a modest upfield trend (0.13–0.33 ppm). Although these shifts may reflect a combination of phenomena, it seems assured that the donor functionalities in the analytes hydrogen bond to the \( C_2 \) faces.

Next, Job plots\(^{62}\) were constructed using \(^1^H\) NMR data (CD\(_2\)Cl\(_2\)) for \( \Lambda^\ddagger^\dagger 2^\dagger \) \( 2\text{Cl}^- \) \( \text{BARf}^- \) and the enantiopure analytes (\( S \)) -4 and (\( S \)) -10 as described in the Experimental section. As shown in Fig. 6, both exhibited maxima when the mol fraction of both components was 0.50, indicative of 1 : 1 adducts. Analogous experiments with the prochiral analyte DMSO showed
Table 3  Separation of $^1$H NMR signals of enantiotopic groups of various achiral analytes in the presence of 100 mol% (1.0 equiv.) of the CSAs Λ-2$^{3+}$ 2I$^-$/BAr$_F^-$(CDCl$_3$) or Λ-2$^{3+}$ 2Cl$^-$/BAr$_F^-$(CD$_2$Cl)$_2$.

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$^a$ Samples were prepared in 5 mm NMR tubes as described in the Experimental section. $^b$ The spectra depicted were obtained with Λ-2$^{3+}$ 2I$^-$/BAr$_F^-$ in CDCl$_3$. $^c$ Signal separation (ppm) using Λ-2$^{3+}$ 2I$^-$/BAr$_F^-$. $^d$ Signal separation (ppm) using Λ-2$^{3+}$ 2Cl$^-$/BAr$_F^-$. $^e$ Separate signals for the enantiomers were not observed in the presence of 100–500 mol% of Λ-2$^{3+}$ 2I$^-$/BAr$_F^-$.

a maximum when the mol fraction of the CSA was 0.3, indicative of a ca. 2 : 1 DMSO/Λ-2$^{3+}$ 2Cl$^-$/BAr$_F^-$ adduct.

In an established protocol for obtaining binding constants ($K$), $^{12}$ 0.0050 M CD$_2$Cl$_2$ solutions of Λ-2$^{3+}$ 2Cl$^-$/BAr$_F^-$ and Λ-2$^{3+}$ 2I$^-$/BAr$_F^-$ were titrated with (S)-4, (R)-4, (S)-10, and (R)-10. The concentrations of the analytes were plotted vs. the change in chemical shift of the C$_2$ NH protons. The $K$ values were calculated by nonlinear least-square curve fitting using the 1 : 1 stoichiometry established from the Job plots and standard equations and software (Experimental section and Fig. S7 (ESI†)).

As can be seen in Table 4, the alcohol 10 exhibited the lowest $K$ values (7.60–2.73 M$^{-1}$), while those of the corresponding acetate 4 were somewhat higher (124–22.6 M$^{-1}$). Whereas (R)-4 gave somewhat higher $K$ values than (S)-4, (S)-10 (which has the same relative configuration as (S)-4) gave higher $K$ values than (R)-10. The $K$ values for Λ-2$^{3+}$ 2I$^-$/BAr$_F^-$ and either enantiomer of 4 were considerably higher than those with Λ-2$^{3+}$ 2Cl$^-$/BAr$_F^-$. |
However, they were much more comparable for the other analytes.

2.7. Crystal structure of a DMSO adduct

Efforts were made to cocrystallize salts of $\text{L}^2^{3+}$ with analytes from Tables 2 and 3. This proved to be much more challenging than anticipated. Finally, diethyl ether was allowed to vapor diffuse into a DMSO solution of $\text{L}^2^{3+} \cdot \text{C}_0^{6+}$ and $\text{C}_0^{6+}$. This gave yellow blocks of the hexakis(DMSO) solvate $\text{L}^2^{3+} \cdot \text{C}_0^{6+} \cdot \text{C}_0^{6+}$. X-ray data were acquired and the structure was solved as outlined in Table S3 (ESI†) and the Experimental section. The unit cell contained two independent molecules. Their structures were quite similar, so only one is depicted in Fig. 7.

Although there was no crystallographic symmetry, the trication exhibited an idealized $C_3$ axis. This lies perpendicular to the plane of the paper in the top view in Fig. 7. Furthermore, three idealized $C_2$ axes lie in the plane of the paper. The bottom view in Fig. 7 is oriented so that one $C_2$ axis runs perpendicular to the plane of the paper. Since the CHPh–CHPh bonds of each chelate are parallel to the $C_3$ axis (Fig. 7, top), the trication is said to exhibit a $lel_{3}$ orientation, as previously found in the crystal structure of $\Lambda^2^{3+} \cdot \text{C}_0^{6+}$ (Fig. 1, bottom).

As illustrated in Fig. S8 (ESI†), two of the three iodide anions hydrogen bond to the three NH groups on opposite $C_3$ faces, consistent with the rationale for the downfield NH $^1$H NMR signals in Fig. 5. The I···HN and I···N distances (2.725–2.835 Å; avg 2.767 Å) and 3.612–3.712 Å (avg 3.648 Å) are in typical ranges. The closest contacts for the third iodide anion (see Fig. S9 and S10†) involve the hydrogen atoms of DMSO molecules (2.996–4.043 Å; avg 3.330 Å) and phenyl rings of adjacent trications (3.027–3.285 Å; avg 3.121 Å).
As shown in Fig. 7 (top) and Table S4,† the oxygen atoms of all six DMSO molecules make a single hydrogen bond to a different NH group associated with the three C₃ faces. The O•••HN and O•••N distances (1.975–2.290 Å (avg 2.132 Å)⁶³–⁶⁵ and 2.869–3.006 Å (avg 2.929 Å)) are close to those found in other crystallographically characterized adducts of DMSO with NH hydrogen bond donors (for five typical examples⁶⁷–⁷¹ 1.81–2.10 Å (avg 1.97 Å) and 2.65–2.85 Å (avg 2.77 Å)). For further validation, the sums of the relevant van der Waals radii can be considered (oxygen/hydrogen, 1.52 + 1.20–1.10 Å; oxygen/nitrogen, 1.52 + 1.55 Å).⁷²–⁷⁴ The closer contacts in Λ-2⁺ 3I⁻·6DMSO confirm bonding interactions by both classical⁷⁵ and modern⁷⁶ criteria.

Over 150 crystal structures of salts of the trication [Co(en)₃]³⁺ have been determined, and the diverse types of NH/anion hydrogen bonding interactions observed have been reviewed and classified.⁴⁵ The bonding motifs exhibited by the two proximal iodide anions in Λ-2⁺ 3I⁻·6DMSO are quite common and have been given the designation [C₃C₃C₃][1]. Those for the DMSO molecules would be abbreviated [C₂][1].

### Table 4 Binding constants (K) for CSAs and representative analytes in CD₂Cl₂ at 23 °C

<table>
<thead>
<tr>
<th>Entry</th>
<th>CSA</th>
<th>analyte</th>
<th>K (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Λ-2⁺ 2Cl⁻·BArф⁻</td>
<td>(S)-4</td>
<td>22.6</td>
</tr>
<tr>
<td>2</td>
<td>Λ-2⁺ 2Cl⁻·BArф⁻</td>
<td>(R)-4</td>
<td>28.1</td>
</tr>
<tr>
<td>3</td>
<td>Λ-2⁺ 2I⁻·BArф⁻</td>
<td>(S)-4</td>
<td>104</td>
</tr>
<tr>
<td>4</td>
<td>Λ-2⁺ 2I⁻·BArф⁻</td>
<td>(R)-4</td>
<td>124</td>
</tr>
<tr>
<td>5</td>
<td>Λ-2⁺ 2Cl⁻·BArф⁻</td>
<td>(S)-10</td>
<td>7.60</td>
</tr>
<tr>
<td>6</td>
<td>Λ-2⁺ 2Cl⁻·BArф⁻</td>
<td>(R)-10</td>
<td>2.73</td>
</tr>
<tr>
<td>7</td>
<td>Λ-2⁺ 2I⁻·BArф⁻</td>
<td>(S)-10</td>
<td>5.60</td>
</tr>
<tr>
<td>8</td>
<td>Λ-2⁺ 2I⁻·BArф⁻</td>
<td>(R)-10</td>
<td>4.28</td>
</tr>
</tbody>
</table>

*See Experimental section including the ESI for details.*

3. Discussion

3.1. New CSAs vs. literature systems

The preceding data document an impressive efficacy of Λ-2⁺ 2Cl⁻·BArф⁻ and Λ-2⁺ 2I⁻·BArф⁻ as CSAs. The former has the advantage of being commercially available, whereas the latter (easily synthesized from the former) exhibits superior performance characteristics apparently connected to its solubility in CDCl₃. The data for Λ-2⁺ 2Cl⁻·B(C₆F₅)₄⁻ in Table 1 suggest that salts with related tetraarylborate anions may be comparably effective. The mechanism of action (following section) clearly involves hydrogen bonding between the C₃ NH donor groups of the CSAs and the analytes.

Most of the other CSAs described in the literature also feature hydrogen bond donor groups,¹⁷,¹⁹–²¹,²³–²⁶ although many possess acceptor groups as well.¹⁷,²⁶,²¹,²³,²⁹ Typical donor groups include ureas or chalcogenoureas,²⁵,²⁶,²⁸ squaramides,²⁷...
secondary amines,24 amides of primary amines,17,23,29 sulfonamides,19 and BINOL derivatives.29 However, many of these have only been applied to one or two functional groups.

The most broadly applicable CSAs for chirality sensing reported to date have been developed by Ema, Sakai and coworkers.17 Their lead system, 48 (Fig. 8), was applied to ten functional groups, three of which were not assayed with \( \Lambda ^{-} 2^{+} \) \( 2X^- \) BARf (oxazolidinone, sulfoximine, isocyanate). Their typical loadings were 100–200 mol%, although a chiral sulfone was found to require only 5 mol%. Conversely, Tables 2 and 3 contain several functional groups that they did not study (ester/β-ketoester, amine, amide/sulfonamide, hydroxypophonate, ketone/1,3-diketone, ether). Furthermore, with our lead CSA, \( \Lambda ^{-} 2^{+} 21' \) BARf, the average loading is 14% (range 1–100%).

There is a wider selection of CSAs that have been applied to four-seven functional groups.21,22,25,26 These generally require loadings of 100–300 mol%, although with one analyte the CSA 49 (Fig. 5, \( R = \text{Ph} \)) was shown to be effective at 60 mol%. None of these CSAs are commercially available. However, another group has assembled a library of 32 commercial CSAs, and developed high throughput protocols for identifying optimal partners for specific analytes.77 Far fewer CSAs have been applied to pro-chirality sensing, and the eight functional groups represented in Table 3 exceed the sum of all those in the literature we have been able to locate.48–54

To our knowledge, the above salts of \( \Lambda ^{-} 2^{+} \) represent the first CSAs that are based upon transition metals. However, transition metals are well represented among chiral derivatizing agents (CDAs).21,28,79 The salt 49 (ref. 22) in Fig. 8 is based upon a main group metal, aluminum, and displays several conceptual similarities with our cobalt(ni) systems. First, both metals are octahedral and constitute stereocenters. Second, the anion of 49 has \( C_2 \) symmetry, vs. \( D_3 \) symmetry for the trication 2\(^+\). Third, 49 has two Al–NH groups that can serve as hydrogen bond donors (as well as four Al–O groups that can serve as hydrogen bond acceptors).

### 3.2. Analyte binding to \( \Lambda ^{-} 2^{+} \)

There is a variety of evidence that the enthalpy of hydrogen bonding to a \( C_3 \) face of \( \Lambda ^{-} 2^{+} \) (A, Fig. 1) is much greater than that to a \( C_2 \) face (B, Fig. 1). For example, the solid state structures of the diastereomeric trichloride salts \( \Lambda ^{-} \) and \( \Delta ^{-} 2^{+} \) 3Cl\(^-\) show the three chloride ions to be distributed over two \( C_3 \) faces and one \( C_2 \) face (as opposed to, for example, three \( C_2 \) faces).37 Scheme 1 shows that one chloride ion – presumably that associated with the \( C_2 \) face – can more easily be replaced by the very poor hydrogen bond acceptor BARf\(^-\) than the other two.37 As illustrated by the bottom trace in Fig. 5, the \(^1\)H NMR spectra of mixed salts \( \Lambda ^{-} 2^{+} 2X^- \) BARf\(^-\) always show two NH signals of equal area (6H/6H), with the downfield signal moving upfield as \( X^- \) becomes a poorer hydrogen bond acceptor (e.g., BF\(_4^-\), PF\(_6^-\)).37,42 These observations are consistent with two “occupied” \( C_3 \) faces and three “free” \( C_2 \) faces.

When \( \Lambda ^{-} 2^{+} 2Cl^- \) BARf\(^-\) is titrated with suitable substrates, such as dimethyl malonate in Fig. 5, the upfield NH groups shift markedly downfield, but the downfield NH groups are much less affected. This indicates dominant analyte binding at the \( C_2 \) faces. In accord with the Job plots (Fig. 6), we presume that the binding constants for the first one ([S]4, [S]10) or two (35) analyte molecules are much greater than those for additional molecules. This may seem at odds with the crystal structure in Fig. 7, in which the three \( C_2 \) faces engage in hydrogen bonding with six DMSO molecules (one per NH group). However, interactions that may be very weak in solution are often expressed in the solid state, where physical packing effects may also play roles. For example, one could speculate that a crystal lattice grows faster when comprised of more symmetrical entities derived from six-fold DMSO binding.

The binding constants (K) in Table 4 track the order found for the hydrogen bond donor \( \mu \)-fluorophenol and the analytes ethyl acetate and benzyl alcohol (CCl\(_4\), 25 °C; 11.7 and 7.24 M\(^{-1}\)).40 Those for the acetate 4 (22–124 M\(^{-1}\)) are in the range of values measured for other CSAs and cyclic esters,17,19 and those for the benzyl alcohol 10 (2.7–7.6 M\(^{-1}\)) likewise compare well with values obtained with other benzylic alcohols.26

The loss of efficacy of \( \Lambda ^{-} 2^{+} 2Cl^- \) BARf\(^-\) and \( \Delta ^{-} 2^{+} 21' \) BARf\(^-\) in coordinating solvents (entries 8–13, Table 1) presumably reflects the saturation of the \( C_2 \) faces, obstructing access by the analytes. The halide free salt \( \Lambda ^{-} 2^{+} 3\text{BARf}^-\), with three very poorly hydrogen bond accepting anions, gives much lower \( \Delta \delta \) values (entry 5, Table 1). We speculate that the analyte now preferentially binds to an “unoccupied” \( C_3 \) face, which for some reason gives diminished chiral recognition. Naturally, the cocystallization of additional analytes with all of the preceding cobalt(ni) complexes remains a goal. Crystal structures have been reported for analyte adducts of only a few other CSAs.72,24 Alternatively, insight can be gained by computational studies;22,23,36,38 and a series of DFT investigations are currently underway.

### 3.3. Conclusion

The new cobalt based CSAs described above offer unparalleled functional group applicability, effectiveness at significantly lower loadings and in the presence of multiple analytes, extended stability to air and water, and ready availability from inexpensive building blocks. Their success reflects the
4. Experimental section

4.1. General

The CSAs $\Lambda^2-3+2\text{Cl}^-\text{BAr}_7^-$, $\Lambda^2-3+2\text{Cl}^-\text{B}(\text{CF}_3)_2\text{C}_6^-$, $\Lambda^2-3+3\text{BAr}_7^-$, and $\Lambda^2-3+2\text{Cl}^-\text{BAr}_7^-$ were synthesized as reported earlier, and $\Lambda^2-3+3\text{BAr}_7^-$ was prepared as described for the enantiomer; $\Lambda^2-3+2\text{Cl}^-\text{BAr}_7^-$ is also commercially available. All abbreviations are defined in the introduction. All reactions and worked-ups were conducted in air.

4.2. $\Lambda^2-3^+ 31^-$

A round bottom flask was charged with a suspension of $\Lambda^2-3^+3\text{Cl}^-\cdot3\text{H}_2\text{O}$ (0.170 g, 0.199 mmol) in acetone (20 mL) and KI (0.099 g, 0.597 mmol) was added with vigorous stirring. A suspension of white particles in an orange solution formed. After 1 h, the mixture was filtered. The solvent was removed from the filtrate by rotary evaporation and oil pump vacuum (20 h, rt) to give $\Lambda^2-3^+3\text{Cl}^-\cdot3\text{H}_2\text{O}$ (0.219 g, 0.194 mmol, 97%) as an orange solid, mp 200–202 °C (open capillary). Anal. calc. for C$_{42}$H$_{48}$CoI$_3$N$_6$: C 48.88, H 3.61, N 4.60 (found C 49.17, H 3.50, N 4.46). NMR (CD$_3$OD/acetone-$_d_6$): $^1$H (500 MHz) 7.51–7.49 (m, 12H, o-Ph), 7.38–7.37 (m, 18H, m-Ph, p-Ph), 6.75 (br s, 6H, NH), 5.95 (br s, 6H, NH), 5.26 (s, 6H, CHPh), 2.83 (br s, 7H, H$_2$O); $^{13}$C($^1$H) (125 MHz) 136.4 (s, i-Ph), 130.1 (s, p-Ph), 129.9 and 129.7 (2 s, o- and m-Ph), 62.8 (s, CHPh). IR (powder film, cm$^{-1}$): 3032 (m, $\nu$NH), 1638 (m, $\delta$NH), 1041 (s, $\delta$CCN).

4.3. $\Lambda^2-3^+ 2\text{I}^-\text{BAr}_7^-$

A. A round bottom flask was charged with $\Lambda^2-3^+3\text{I}^-\cdot3\text{H}_2\text{O}$ (0.117 g, 0.104 mmol), CH$_2$Cl$_2$ (20 mL), H$_2$O (20 mL), and Na$_2$BAr$_7^-$ (0.099 g, 0.597 mmol) was added with vigorous stirring. A red solid, mp 107–109 °C dec (black liquid, open capillary). Anal. calc. see above; found C 49.17, H 3.50, N 4.46.

Data for $\Lambda^2-3^+ 2\text{I}^-\text{BAr}_7^-$·0.5H$_2$O. NMR ($^3$H in ppm): $^1$H (500 MHz, CDCl$_3$, or CD$_2$Cl$_2$) $\text{BAr}_7^-$ at 7.69 or 7.71 (s, 8H, o), 7.49 or 7.55 (s, 4H, p); ($S$/S)-$\text{dpen}$ at 7.37–7.27 or 7.44–7.29 (m, 30H, ArH), 6.98 or 7.88 (br s, 6H, NH), 4.86 or 4.21 (br s, 6H, NH), 4.60 (s, 6H, CHPh); 2.22 or 1.78 (br s, 5H or 2H, H$_2$O). $^{13}$C($^1$H) (126 MHz, CD$_2$Cl$_2$) $\text{BAr}_7^-$ at 162.3 (q, $^1$JC = 49.5 Hz, i), 135.4 (s, o), 129.4 (q, $^1$JC = 31.5 Hz, m), 125.2 (q, $^1$JC = 272.3 Hz, CF$_3$), 118.1 (s, p); ($S$/S)-$\text{dpen}$ ligand at 134.6 (s, i-Ph), 130.8 (s, p-Ph), 130.3 (s, o-Ph), 128.7 (s, m-Ph), 62.7 (s, CHPh). IR (powder film, cm$^{-1}$): 3064 (m, $\nu$NH), 1608 (m, $\delta$NH), 1354 (s, $\nu$Ar-CF$_3$), 1275 (vs, $\nu$CF$_3$), 1117 (vs, $\delta$CCN).

4.4. Dependence of $\Delta\delta$ upon CSA and solvent (Table 1)

A 5 mm NMR tube was charged with a 0.0071 M solution of a CSA (0.70 mL, 0.0049 mmol) in the indicated solvent. Neat 1-phenylethyl acetate (4, 0.00050 mL, 0.00012 g, 0.00050 mmol) was added and a 1H NMR spectrum was recorded.

4.5. Dependence of $\Delta\delta$ upon mol% of CSA (Fig. 2)

A 5 mm NMR tube was charged with a CD$_3$Cl$_2$ solution of $\Lambda^2-3^+2\text{Cl}^-\text{BAr}_7^-$·2H$_2$O (0.70 mL, 0.036 M, 0.025 mmol). Neat 4 was then added in 0.0050 mL increments (ca. 0.0012 g, 0.0050 mmol). A 1H NMR spectrum was acquired after each addition. The total volume of 4 added from the first data point (500 mol%) to the final data point (5 mol%) was 0.050 mL.

4.6. Dependence of $\Delta\delta$ upon concentration (Fig. 3)

A 5 mm NMR tube was charged with a CD$_3$Cl$_2$ solution of $\Lambda^2-3^+2\text{Cl}^-\text{BAr}_7^-$·2H$_2$O (0.0050 mmol, 25 mol%). A 1H NMR spectrum was recorded. Then CD$_3$Cl$_2$ was added in increments so as to attain total volumes of 0.60, 0.70, 0.80, 0.90, 1.00, 1.10, 1.50, 2.00, 3.00, 4.00, and 5.00 mL. After each addition, a 1H NMR spectrum was recorded.

4.7. Chirality sensing (Table 2)

A (liquid analytes 4–7, 10, 14–18, 21–25, 27–29, 31). 5 mm NMR tubes were charged with CD$_3$Cl$_2$ solutions of $\Lambda^2-3^+ 2\text{Cl}^-\text{BAr}_7^-$·2H$_2$O or CD$_3$Cl$_2$ solutions of $\Lambda^2-3^+ 2\text{I}^-\text{BAr}_7^-$·0.5H$_2$O (0.70 mL, 0.0071 M, 0.0049 mmol). The samples were titrated with neat liquid analytes in increments of 0.0050 mmol (1.0 equiv.) and monitored by 1H NMR. Experiments were halted when separate signals for the enantiomers were not longer observed. The total volume of liquids added usually ranged from 0.72 to 0.80 mL (solid analytes 8, 9, 11–13, 19–20, 26, 30). Procedure A was repeated, but with the analytes added as 10.0 M CD$_3$Cl$_2$ or CD$_3$Cl$_2$ solutions in increments of 0.00050 mL (0.0050 mmol).

4.8. Enhanced throughput sensing (Fig. 4)

A 5 mm NMR tube was charged with a CD$_3$Cl$_2$ solution (0.70 mL) that was 0.029 M in 4, 7, 10, and 20 (0.020 mmol each), and 0.014 M in 19 (0.010 mmol). Then $\Lambda^2-3^+ 2\text{I}^-\text{BAr}_7^-$·0.5H$_2$O...
(0.018 g, 0.010 mmol) was added, and \(^1\)H and \(^{31}\)P\(^{[\text{H}]}\) NMR spectra were recorded.

4.9. Prochirality sensing (Table 3)

A 5 mm NMR tube was charged with a CD\(_2\)Cl\(_2\) solution of \(\text{A} - 2 + \text{S}\) \(2\text{Cl}^- \text{BAr}^- \cdot \text{H}_2\text{O}\) or a CDCl\(_3\) solution of \(\text{A} - 2 + \text{S}\) \(2\text{I}^- \text{BAr}^- \cdot 0.5\text{H}_2\text{O}\) (0.70 mL, 0.0071 M, 0.0049 mmol). The analyte (1.0 equiv.) was added as a neat liquid (32–38, 40–42, 44, 46) or solid (39, 43, 45, 47) and \(^1\)H NMR spectra were recorded.

4.10. Titration of a CSA with dimethyl malonate (Fig. 5)

A 5 mm NMR tube was charged with a CD\(_2\)Cl\(_2\) solution of 0.019 M CD\(_2\)Cl\(_2\) (0.49 mL) and the concentration of the adduct CSA was determined using a 1H NMR spectrum. A 0.91 M CD\(_2\)Cl\(_2\) solution of 4.10. Titration of a CSA with dimethyl malonate (Fig. 5) was prepared and mixed at nine volume ratios (mL/mL: 0.050/0.10, 0.15/0.35, 0.20/0.30, 0.25/0.25, 0.30/0.20, 0.35/0.15, 0.40/0.10, 0.45/0.05). 1H NMR spectra were recorded and the concentration of the adduct CSA was determined.

4.11. Job plots (Fig. 6)\(^{52}\)

0.010 M CD\(_2\)Cl\(_2\) solutions of \(\text{A} - 2 + \text{S}\) \(2\text{Cl}^- \text{BAr}^- \cdot \text{H}_2\text{O}\) and (S)-4 were prepared and mixed at nine volume ratios (mL/mL: 0.050/0.45, 0.10/0.40, 0.15/0.35, 0.20/0.30, 0.25/0.25, 0.30/0.20, 0.35/0.15, 0.40/0.10, 0.45/0.05). 1H NMR spectra were recorded (500 MHz) and the concentration of the adduct CSA was calculated from the equation\(^{53,84}\)

\[
[\text{CSA} - (S)-4] = \left[\frac{\delta_{\text{obs}} - \delta_0}{\delta_c - \delta_0}\right] \times [\text{CSA}]
\]

where \([\text{CSA}]\) is the concentration of the \(\text{C}_2 \text{NH}\) protons in the sample, \(\delta_{\text{obs}}\) is the chemical shift of the \(\text{C}_2 \text{NH}\) protons in the sample (always upfield from the \(\text{C}_3 \text{NH}\) protons),\(^{42}\) \(\delta_c\) is the chemical shift of the \(\text{C}_2 \text{NH}\) protons of \(\text{A} - 2 + \text{S}\) \(2\text{Cl}^- \text{BAr}^- \cdot \text{H}_2\text{O}\), and \(\delta_0\) is the chemical shift of the \(\text{C}_2 \text{NH}\) protons in the complex \(\text{CSA} - (S)-4\). The values for \([\text{CSA} - (S)-4]\) were then plotted versus the mol fraction \(x\) of \(\text{A} - 2 + \text{S}\) \(2\text{Cl}^- \text{BAr}^- \cdot \text{H}_2\text{O}\) per Fig. 6. This procedure was repeated with 0.010 M CD\(_2\)Cl\(_2\) solutions of \(\text{A} - 2 + \text{S}\) \(2\text{Cl}^- \text{BAr}^- \cdot \text{H}_2\text{O}\) and (S)-10 or 35.

4.12. Binding constants (Table 4)\(^{52}\)

0.0050 M CD\(_2\)Cl\(_2\) solutions of \(\text{A} - 2 + \text{S}\) \(2\text{Cl}^- \text{BAr}^- \cdot \text{H}_2\text{O}\) and \(\text{A} - 2 + \text{S}\) \(2\text{I}^- \text{BAr}^- \cdot 0.5\text{H}_2\text{O}\) were prepared. One 5 mm NMR tube was charged with 1.0 mL of one solution, and another tube with 1.0 mL of the other. Reference 1H NMR spectra were recorded. Analytes were then added in 0.0050 mmol increments (1.0 equiv.) using a microsyringe, and a 1H NMR spectrum was recorded after each addition. The concentrations of the analytes were plotted versus the change in chemical shift of the \(\text{C}_2 \text{NH}\) protons (\(\Delta \delta = \delta_{\text{obs}} - \delta_0\)) as in Fig. S7.\(^1\) The binding constants \(K\) were calculated by nonlinear least-square curve fitting using Origin Pro 8.0,\(^{86}\) the 1 : 1 stoichiometry established from the Job plots, and the equation\(^{86}\)

\[
[\text{Analyte}] = \left(\frac{1}{K}\right) \times [x(1 - x)]
\]

where \(x = (\delta_{\text{obs}} - \delta_0)/(\delta_c - \delta_0)\).
18 Representative papers that have appeared since 2014 and describe new CSAs are given in ref. 19–30. For a complete bibliography for this period, see the additional ref. S14–S29 (ESI†).
35 A. Werner, *Chem. Ber.*, 1911, 44, 1887–1898. V. L. King is listed as an author for the Experimental section.
44 The best prices in effect as of the submission date of this manuscript are from Oakwood Chemical (http://www.oakwoodchemical.com) (R,R-dpen; S359/100 g) and Ark Pharm (http://www.arkpharmacinc.com) (S,S-dpen; $420/100 g). Accessed 13 February 2018.
48 For a brief review of the differentiation of enantiotopic (prochiral) groups by NMR, see pp. 339–341 of ref. 8. For prochirality sensing using CSAs, see ref. 49–54. For prochirality sensing using CLSAs and CDAs, see ref. S30 and S31.† For prochirality sensing using chiral liquid crystals and other chiral media see ref. 55 and S32–S35.†
56 All cobalt(II) complexes are isolated as hydrates, consistent with the appreciable hydrogen bond donor strengths of the NH groups. To aid readability, these are not specified in the formulae in the main text or graphics, but are given in the Experimental section. The additional mass is taken into account in the stoichiometries and yield calculations. For additional related remarks, see ref. 23 in ref. 42.
63 The C–H and N–H bond lengths determined from X-ray crystal structures are usually ca. 10% too short. See, inter alia, ref. 64 and 65.
78 See pp. 365–398 of ref. 8.
81 When the CH3OH treatment was omitted, the toluene solvate Δ±212 21− BA p −0.8C8H4 was isolated, mp 110–112 °C (black liquid, open capillary). Anal. calcd for C74H68BCOF24I6N6: 0.8C8H4 (1885.85): C 50.68, H 3.55, N 4.45; found C 50.09, H 3.63, N 4.38. 1H NMR (500 MHz, CD3Cl2, δ in ppm) BA p at 7.71 (s, 8H, o), 7.54 (s, 4H, p); (S,S)-dpen at 7.29–7.45 (m, 30H, ArH), 5.31 (br s, 6H, NHH); partial overlap, CDHCl2), 4.88 (br s, 6H, NHH), 4.69 (s, 6H, CHPh); 2.01 (br s, 18H, H2O)32 toluene at 7.15–7.23 (m, 4H, C6H5), 2.33 (s, 2.4H, CH3).
82 The increased level of water over that derived from the microanalysis is believed to originate from solvent.
83 See pp. 24–28 of ref. 62.
86 See pp. 189–194 of ref. 62.
87 APEX3, Program for Data Collection on Area Detectors, BRUKER AXS Inc., 5465 East Cherry Parkwy, Madison, WI, USA, pp. 53711–5373.
88 G. M. Sheldrick, SADABS, Program for Absorption Correction of Area Detector Frames, BRUKER AXS Inc., 5465 East Cherry Parkwy, Madison, WI, USA, pp. 53711–5373.