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Chiral ^{1}H NMR Analysis of Carbonyl Compounds Enabled by Cationic Cobalt Complex

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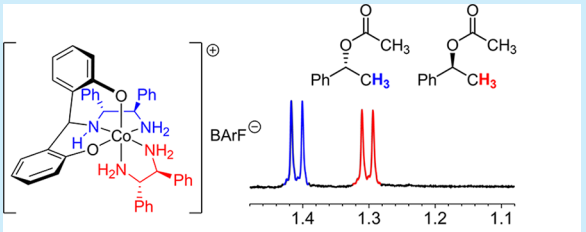
ABSTRACT: We report a newly prepared cationic cobalt(III) complex as a general and efficient chiral solvating agent that discriminates carbonyl compounds including esters, amides, ketones, and aldehydes. This cobalt(III) complex was further utilized to directly analyze both the conversion and the enantiomeric excess at once in the asymmetric fluorination.



^{1}H NMR chiral analysis of carbonyl compounds: 32 examples including esters, amides, ketones, and aldehydes.

The great importance of optically active (chiral) compounds in synthetic, medicinal, and biological chemistry continues to advance the search for rapid and facile methods to determine the identity, concentration, and relative ratio of chiral molecules.[1] Such chiral analysis has been successfully performed with conventional chromatographic methods using high-performance liquid chromatography (HPLC) or gas chromatography (GC).[2] However, the utilization of ^{1}H nuclear magnetic resonance (^{1}H NMR) spectroscopy with chiral solvating agents (CSAs) has gained continuous attention as a complementary analytical technique.[3,4] In principle, the CSAs provide distinctive ^{1}H NMR signals obtained from two *in-situ*-formed diastereomeric adducts between the enantiopure CSA and the two enantiomers of the analyte of interest through noncovalent interactions, such as ion pairing, H bonding, or dipole−dipole interactions.[3] Over the last few decades, several classes of CSAs such as (1) small- to medium-sized organic-based reagents,[4b,d,5] (2) lanthanides or unsaturated transition-metal complexes,[6] and (3) host compounds, such as cyclodextrins, crown ethers,[7] and synthetic macrocycles,[8] have been developed. Many of them are practically optimized and commercialized, but the analyte scope is mainly limited to amines or carboxylic acids, which can establish relatively strong intermolecular interactions. It has been a great challenge to develop CSAs effectively working for other types of analytes. Because ^{1}H NMR spectroscopy is a fundamental analytical technique, CSAs with a wide range of analyte scope and functional group compatibility should promote the routine application of ^{1}H NMR chiral analysis.

Chiral carbonyl compounds are ubiquitous and widely utilized as pharmaceuticals.[9] Besides, they have been a common substrate platform for asymmetric synthesis, as exemplified by the carbonyl α-substitution reactions.[10,11] However, to the best of our knowledge, there are no CSAs that are broadly applicable for carbonyl compounds, probably due to the weak intermolecular interactions between CSA and carbonyl analytes. The dirhodium complex and modified Kagan's amide were used as CSAs for amides or esters with limited examples.[12] We have reported anionic chiral octahedral Al complexes as general and efficient CSAs for amines and carboxylic acids (Figure 1a).[13] With the optimized pK_a value, the anionic Ga complex was successfully used for the ^{1}H NMR chiral analysis of alcohols at room temperature (Figure 1a).[4c] These anionic CSAs employ strong intermolecular interactions such as ion pairing or charged H-bonding interactions with analytes. However, our anionic CSAs were not active toward carbonyl analytes because they can only form weak intermolecular interactions. (See the Supporting Information.) In 2018, Gladysz and coworkers reported a Werner-type octahedral Co complex, $[Co(dpen)_3]^{3+}$, as an efficient CSA for various chiral analytes, including a few carbonyl compounds.[14] This tricationic Co complex could establish a cationic ion−dipole interaction with carbonyl compounds, found to be suitable for ^{1}H NMR chiral analysis. Inspired by this seminal work, we here designed cationic octahedral Co complexes by combining N_2O_2 ligands (**L1**−**L2**) and 1,2-diphenylethylenediamine (**1**). In the formation of the metal-centered chirality, Werner complexes with chiral diamines showed a moderate selectivity (83:17) at room temperature.[15] In comparison with this, our Co complexes were readily synthesized by the

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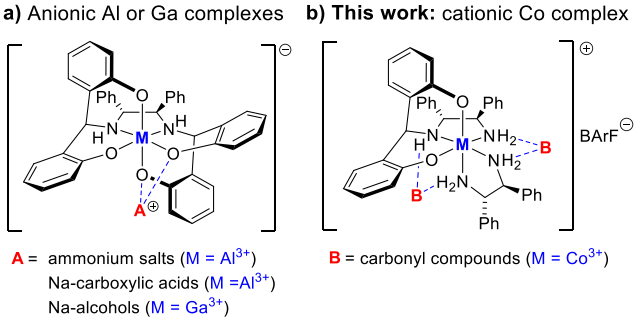
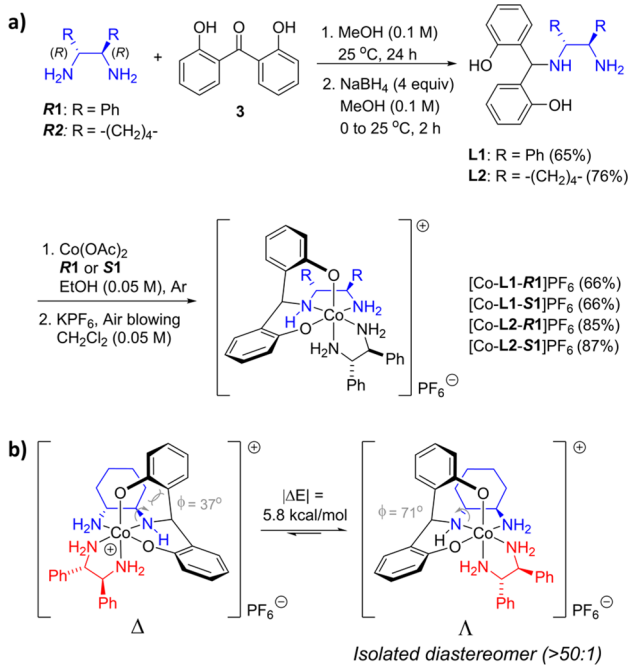


Figure 1. ^{1}H NMR chiral analysis with (a) anionic Al and Ga complexes and (b) cationic Co complex.

Scheme 1. (a) Synthetic Procedure for Cationic Cobalt Complexes and (b) Stereoselective Assembly of [Co-L2-*S*1]PF_6



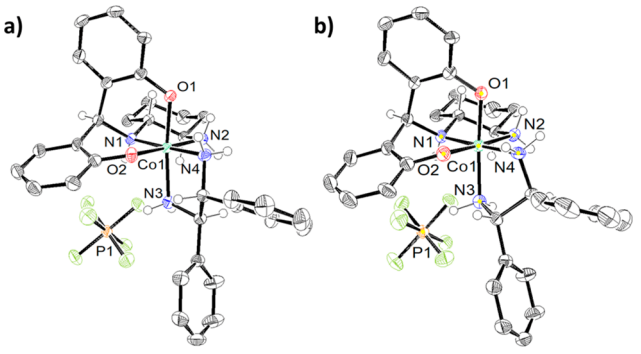


Figure 2. Crystal structures of (a) [Co-**L2**-***R*1**]PF_6 and (b) [Co-**L2**-***S*1**]PF_6 (thermal ellipsoids at 50% probability).

assembly of the metal and the two ligands with excellent stereoselectivity (>50:1). Further experimental and computational analysis of the Co complexes enabled us to develop a highly efficient CSA for esters, amides, ketones, and aldehydes. This analytical method allows the real-time measurement and

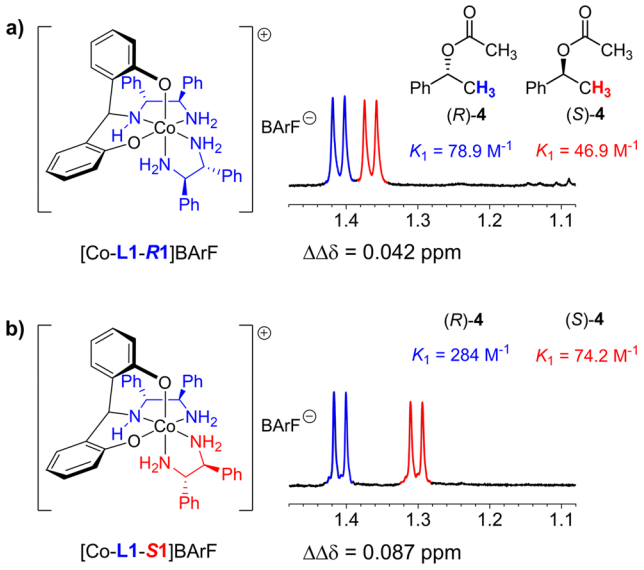


Figure 3. Chiral solvation and binding constant of 1-phenylethyl acetate (**4**) with (a) [Co-**L1**-***R*1**]BArF and (b) [Co-**L1**-***S*1**]BArF.

the direct analysis of both the conversion and the enantiomeric excess at once in asymmetric reactions.

Chiral cobalt complexes were prepared by combining tetradentate N_2O_2 ligands (**L1** and **L2**) and chiral 1,2-diphenylethylenediamine (**1**), which provide diamagnetic octahedral d^6-Co(III) complexes compatible for ^{1}H NMR measurement (Scheme 1a). The tetradentate N_2O_2 ligands (**L1** and **L2**) were readily synthesized from (*R*,*R*)-1,2-diamines (***R*1** and ***R*2**) and 2,2′-dihydroxybenzophenone (**3**). Octahedral cobalt complexes were then prepared by the reaction of the N_2O_2 ligand (**L1** and **L2**), Co(acac)$_2$, and (*R*,*R*)- or (*S*,*S*)-1,2-diphenylethylenediamine (***R*1** or ***S*1**) to yield neutral Co(II) complexes that were further oxidized to cationic Co(III) complexes in the presence of KPF_6 under aerobic conditions (Scheme 1a). The reaction sequence was completed to provide four Co(III) complexes in 66−87% isolated yields.

The tetradentate N_2O_2 ligands (**L1** and **L2**) are crucial for determining the metal-centered chirality of the Co complexes (Scheme 1b). In principle, two diastereomeric Δ and Λ complexes can be prepared in the formation of the octahedral complexes with chiral N_2O_2 ligand (**L1** and **L2**) and 1,2-diamine (**1**). Interestingly, only the Λ form of Co complexes was isolated to a detectable extent in the ^{1}H NMR spectra (>50:1). The density functional theory (DFT) computation indicates that the Λ-form is more stable than the Δ form by ∼5.8 kcal/mol, in agreement with the experimental results. (See the Supporting Information.) This energy value translates to an equilibrium constant of ∼1.8 × 10^5. The steric repulsion due to the torsional strain appears to be responsible for the energy difference of the two diastereomers: The torsion angle C−N−C−C is found to be 37 and 71° for the Δ and Λ complexes, respectively (Scheme 1b). A severe torsional strain makes the minor Δ form highly unstable compared with the major Λ form. In addition, the chirality of the 1,2-diamine (**1**) did not affect the metal-centered chirality of the Co(III) complexes, as shown in Figure 2.

All cationic Co(III) complexes were initially prepared and isolated with a PF_6 anion. However, they were insoluble or only partially soluble in CH_2Cl_2, $CHCl_3$, or C_6H_6, which limits the solvent usage and prevents a broad application for ^{1}H

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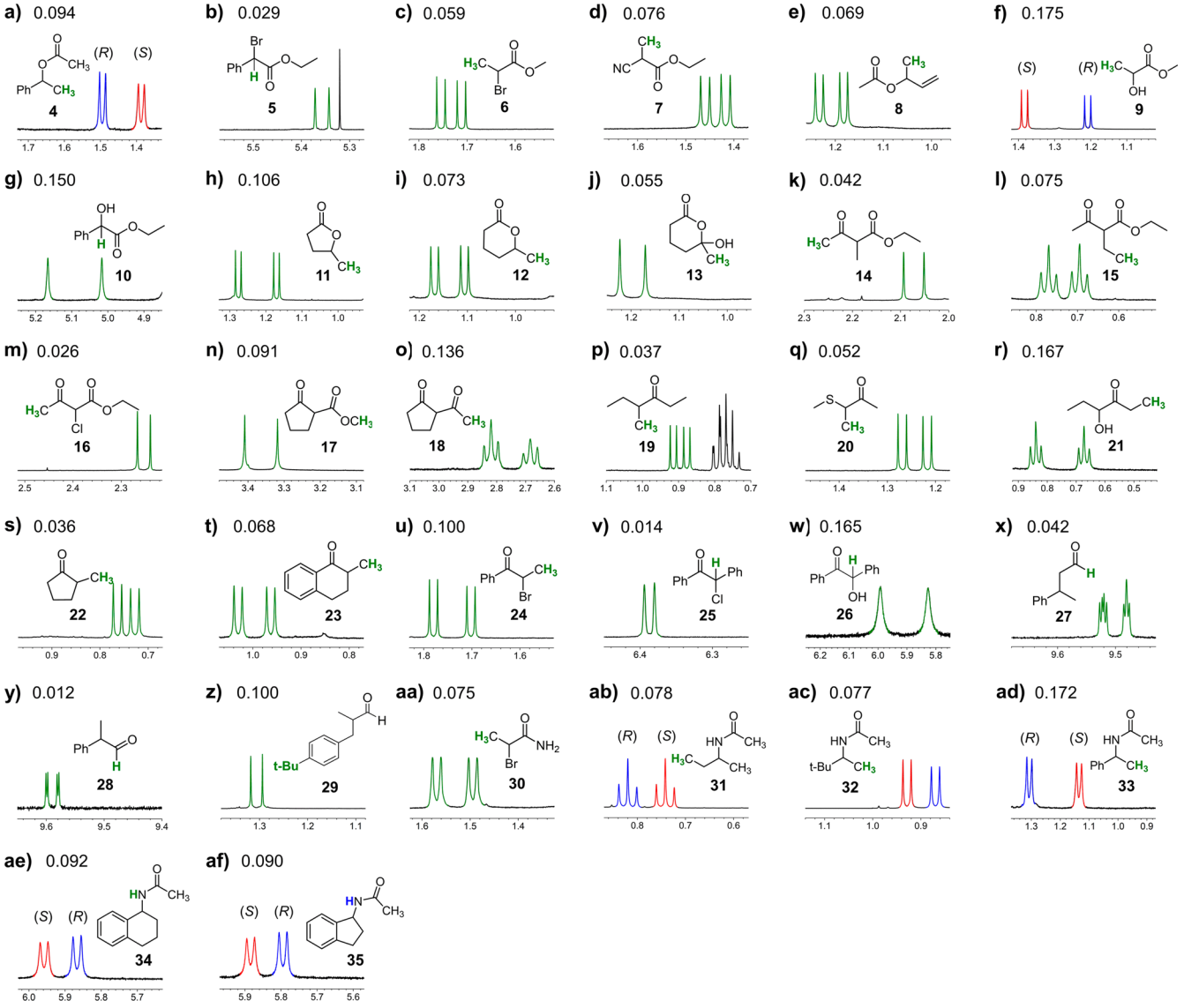

Figure 4. Partial ^{1}H NMR (400 MHz, 298 K) spectra of carbonyl compounds with [Co-**L1**-*S***1**]BArF in $CDCl_3$. $\Delta\Delta\delta$ values are shown in ppm.

NMR chiral analysis. To increase their solubility, we changed the counteranion to tetrakis(3,5-bis(trifluoromethyl)phenyl)-borate (BArF) by the addition of an equimolar amount of NaBArF. The BArF salts of all cobalt metal complexes showed excellent solubility in organic solvents such as CH_2Cl_2, $CHCl_3$, and C_6H_6. They were even soluble in diethyl ether and partially soluble in *n*-hexane.

With several chiral Co(III) complexes, we first tested the ^{1}H NMR chiral solvation of 1-phenylethyl acetate (**4**) in $CDCl_3$. When an equimolar amount of [Co-**L1**-*R***1**]BArF or [Co-**L1**-*S***1**]BArF was mixed with *rac*-**4** in $CDCl_3$ (20 mM), we were pleased to find that both complexes could give rise to a baseline separation of the methyl peak of *rac*-**4** in the ^{1}H NMR spectra (Figure 3). Interestingly, [Co-**L1**-*S***1**]BArF was more efficient than [Co-**L1**-*R***1**]BArF, with $\Delta\Delta\delta$ ($\Delta\Delta\delta = |\Delta\delta_R - \Delta\delta_S|$) values of 0.087 and 0.042 ppm, respectively. Both [Co-**L1**-*S***1**]BArF and [Co-**L1**-*R***1**]BArF with the metal-centered chirality of the Λ form showed the same sense of peak resolution, where the methyl signal of (*S*)-**4** is more low-frequency-shifted than that of (*R*)-**4**. It is quite evident that the metal-centered chirality of the Co complexes plays a significant role in resolving the ^{1}H NMR signals of the analytes. However, the resolution ability was more enhanced with opposite (*S*,*S*)-1,2-diamine chirality in combination with the (*R*,*R*)-chirality of N_2O_2 ligand in [Co-**L1**-*S***1**]BArF. Compared with the Werner-type ML_3 chiral complexes synthesized with the same absolute configuration of the ligands,[14] our chiral Co(III) complex was optimized to improve the chiral solvation ability by the combination of (*R*,*R*)- and (*S*,*S*)-diamine-based ligands.

We tested the chiral solvation of *rac*-1-phenylethyl acetate (**4**) with [Co-**L1**-*S***1**]BArF in various deuterated solvents. We were pleased to find that our cationic cobalt complex [Co-**L1**-*S***1**]BArF was effective toward the carbonyl compound **4**, giving a clean baseline ^{1}H NMR peak separation in CD_2Cl_2, $CDCl_3$, C_6D_6, and toluene-d_8. (See the Supporting Information.) In polar organic solvents, CD_3CN, acetone-d_6, DMSO-d_6, and CD_3OD, we could not achieve the peak separation. It is evident that the polar solvent molecules prevent the formation of diastereomeric mixtures between the Co complex and the carbonyl analyte. In this regard, we have chosen $CDCl_3$ as the optimal NMR solvent because it gave the most significant peak separation and it is also economically beneficial.

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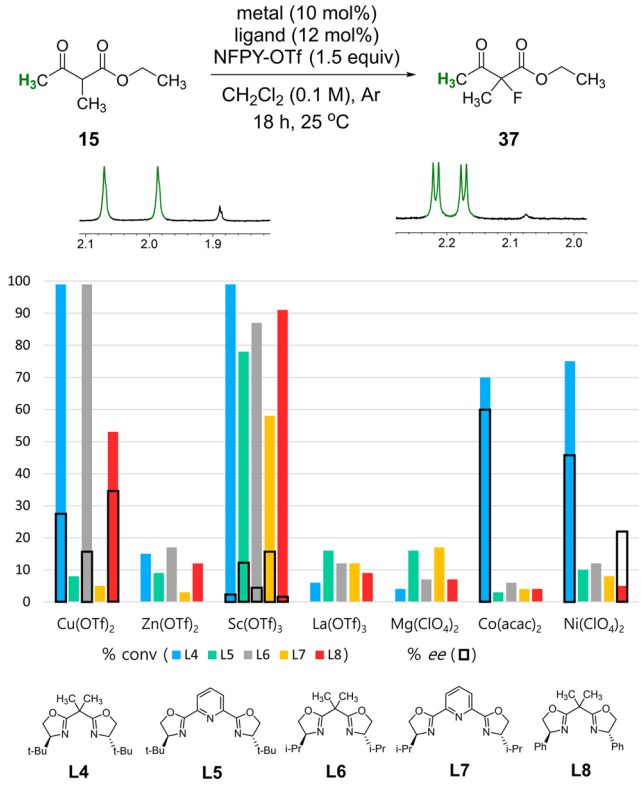

Figure 5. Screening of metals and ligands for asymmetric fluorination by ^{1}H NMR spectroscopy.

We investigated the chiral solvating ability of the optimal cationic cobalt complex for a series of chiral carbonyl-containing compounds **4**−**35** (Figure 4). When several carbonyl analytes were mixed with a stoichiometric amount of [Co-**L1**-*S1*]BArF in $CDCl_3$ (20 mM), full baseline separations were achieved. The esters bearing aromatic (**4**, **5**) and aliphatic groups (**6**−**8**) were successfully analyzed. In addition, α-hydroxy esters (**9**, **10**), lactones (**11**−**13**), and β-keto esters (**14**−**17**) gave an efficient peak separation with the cobalt complex. Moreover, various ketones, including β-diketone (**18**), aliphatic linear ketones (**19**−**21**), cyclic ketone (**22**), and ketones bearing aromatic groups (**23**−**26**), were prone to the ^{1}H NMR chiral analysis. Furthermore, aldehydes (**27**−**29**) and amides (**30**−**35**) were well resolved in the ^{1}H NMR spectra. Because there are few signals of [Co-**L1**-*S1*]BArF with chemical shifts in the range of 0−4 ppm, there was no overlap with the ^{1}H NMR signals belonging to the sp^3 C−H of the analytes. Given the broad analyte scope shown in Figure 4, the chiral solvation with the cationic cobalt complex can be a general method for the chiral analysis of carbonyl-containing compounds.

Our cationic cobalt complex can be used for the chiral analysis of ketoesters. To further demonstrate its utility, we have chosen the asymmetric fluorination of ethyl-2-methyl-acetoacetate[16] (Figure 5). The enantioselective introduction of the fluorine atom is of significant synthetic interest due to its unique properties in drugs and agricultural agents.[17] Both the starting material (**14**) and the product (**36**) can be directly analyzed with our cobalt complex (Figure 5). Because **14** and **36** give distinctive signals with [Co-**L1**-*S1*]BArF in $CDCl_3$, we can measure the conversion and the enantiomeric excess with one measurement. Using this method, we tested the reaction conditions with six different Lewis-acidic metals and five different bisoxazoline ligands, a total of 30 reaction conditions, and the resulting % conversion and % *ee* are summarized in Figure 5. The crude mixture was directly analyzed in the cases of the diamagnetic metal catalysts, whereas paramagnetic metal salts were removed by silica-gel filtration prior to the analysis. Enantiomeric excess with >20% conversion was measured. (See the Supporting Information.)

As shown in Figure 5, a rapid chiral analysis of asymmetric fluorination was successfully performed by ^{1}H NMR with [Co-**L1**-*S1*]BArF. We could easily identify that $Cu(OTf)_2$ and $Sc(OTf)_3$ showed high conversion but low stereoselectivity, whereas $Co(acac)_2$ with ligand **L3** gave the highest enantioselectivity of 60% *ee*. Therefore, ^{1}H NMR chiral analysis with [Co-**L1**-*S1*]BArF can be a simple and efficient method for determining the conversion and the enantiomeric excess in asymmetric reactions involving chiral carbonyl compounds.

In summary, we have demonstrated a ^{1}H NMR chiral analysis of carbonyl compounds with our newly prepared cationic Co(III) complex. The Co complexes were readily prepared by a stereoselective assembly of two ligands with excellent stereoselectivity (>50:1). The chiral solvation ability of the Co complexes was improved by the choice of BArF anion and the combination of ligands with opposite diamine chiralities. The optimal CSA, [Co-**L1**-*S1*]BArF, was successfully used for the ^{1}H NMR chiral analysis of 32 carbonyl compounds including esters, amides, ketones, and aldehydes. Furthermore, an asymmetric fluorination of ethyl-2-methyl-acetoacetate was readily analyzed by ^{1}H NMR spectroscopy with [Co-**L1**-*S1*]BArF, determining the conversion and the enantiomeric excess in a single measurement. This cationic Co complex can be a general and efficient CSA for various carbonyl compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01256.

Experimental procedures, spectroscopic and calculation data, and crystallographic details (PDF)

Accession Codes

CCDC 1987461 and 1987467 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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