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Letter

^{19}F NMR-Based Chiral Analysis of Organoboron Compounds via Chiral Recognition of Fluorine-Labeled Boronates with Cobalt Complexes

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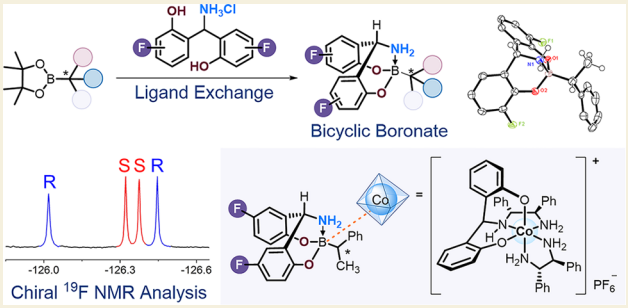
ABSTRACT: This study aims to develop a method for the chiral analysis of organoboron compounds using nuclear magnetic resonance (NMR) spectroscopy. It addresses the longstanding challenge associated with these chiral organoboron compounds, which often require derivatization and pretreatment prior to chromatographic analysis. Our method utilizes tridentate ligands to facilitate effective ligand exchange and incorporates fluorine labels, allowing for the precise discrimination of ^{19}F NMR signals. This is achieved in conjunction with a chiral cationic cobalt complex, serving as the chiral solvating agent. This approach provides reliable and rapid determination of enantiomeric excess in a wide range of organoboron compounds, featuring various functional groups, and establishes a universal tool for assessing the optical purity of these substances.



KEYWORDS: *^{19}F NMR, Chiral analysis, Organoboron, Cobalt complex, Tridentate ligand*

INTRODUCTION

Organoboron compounds containing chiral carbon centers are precious for their biological activities in medicinal chemistry and as key intermediates in organic synthesis.[1−4] Over the past few decades, significant efforts have been made to develop synthetic strategies for optically active organoboron compounds (Figure 1a).[5−9] Due to the inherent instability of boronic acid, the predominant approach involves using air- and moisture-stable boronic acid derivatives with various ligands, such as pinacol boronic ester (Bpin), catechol boronic ester (Bcat), 1,8-diaminonaphthyl boronic acid amide (Bdan), neopentylglycol boronic ester (Bneop), and potassium trifluoroborate (BF_3K).[10,11] Accordingly, the chiral analysis of boronic esters is highly important and currently relies on conventional high-performance liquid chromatography (HPLC) with chiral stationary phases. However, due to the instability of boronic esters, oxidation to alcohols is often required, and the introduction of chromophores is frequently necessary for the facile detection of these alcohol products (Figure 1b).[12]

Despite these challenges, chromatographic methods remain the only available technique for the chiral analysis of organoboron compounds, as there is no alternative direct method.

Nuclear magnetic resonance (NMR) spectroscopy has been employed as a complementary technique for the identification and quantification of chiral compounds. In the context of chiral analysis, the use of chiral derivatizing agents or chiral solvating agents together with analytes is essential to induce anisochronous chemical shifts.[13] According to current knowledge, chiral boronic esters have been utilized as chiral derivatizing agents specifically for the chiral analysis of diols.[14−17] However, despite the extensive preparation of chiral organoboron compounds, a direct method for the chiral analysis of these compounds has not yet been developed.

Motivated by this challenge, we aimed to achieve a chiral analysis of organoboron compounds using NMR spectroscopy. Our strategy involves three main components: (1) ligand exchange, (2) fluorine labeling, and (3) NMR shifting (Figure 1c). To facilitate ligand exchange, we developed a tridentate ligand, 2,2′-(aminomethylene) bisphenol (**1**). Additionally, this ligand incorporates F-groups to simplify the spectral outcomes. In recent years, ^{19}F NMR spectroscopy has become actively used for chiral and metabolite analysis due to its advantages of 100% natural abundance, absence of background signals, and chemical shifts range exceeding 400 ppm.[18−21] Effective ^{19}F NMR signal resolution of enantiomers was achieved using chiral cationic octahedral cobalt complexes.[22,23]

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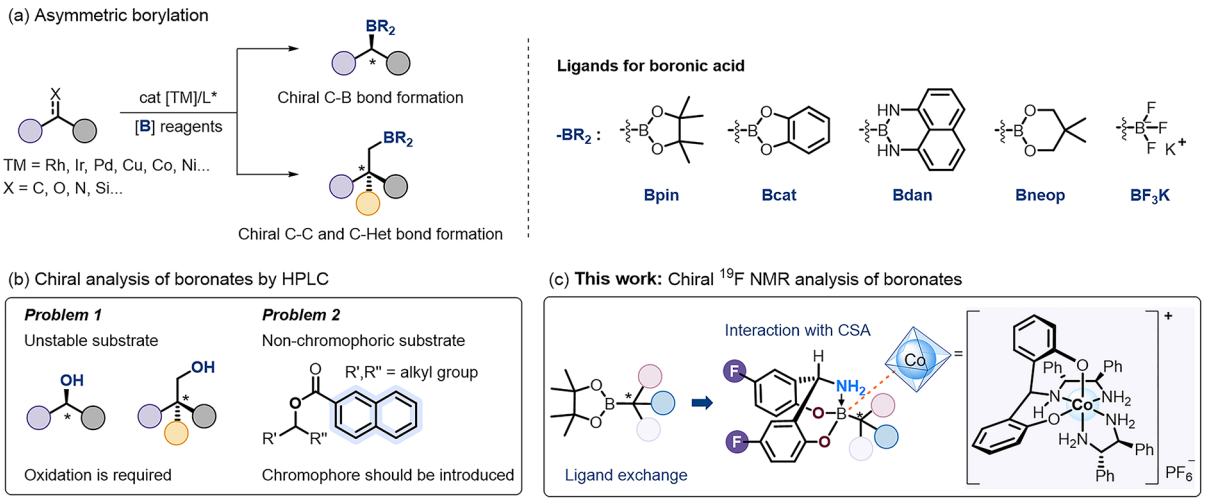

Figure 1. (a) Transition metal-catalyzed asymmetric borylation, (b) conventional chiral analysis of boronates with HPLC, and (c) chiral recognition of boronates by ^{19}F NMR spectroscopy.

Ultimately, we developed a ^{19}F NMR chiral analysis method for organoboron compounds.

RESULTS AND DISCUSSION

We began our study by synthesizing tridentate ligands starting from difluoro-dihydroxy-benzophenones (Figure 2a). Following imine formation with ammonia and subsequent reduction, fluorine-substituted 2,2′-(aminomethylene)bisphenols were isolated as their HCl salt forms with yields of 92% for **1a** and 78% for **1b**. In these compounds, the fluorine groups are located at the 2 positions in **1a** and at the 4 positions in **1b** of the phenol groups. Similar to widely used dianionic boronate ligand structures, ligand **1** contains two anionic phenolate groups. An additional amino group was introduced because the B−N bond formed by these ligands enhances boron stability by donating electron density from nitrogen to the vacant p orbital on boron. This thermodynamic stability, along with the entropic advantage of the tridentate ligand, facilitates easy ligand exchange with reported boronates used in asymmetric reactions.[24]

Using the two synthesized tridentate ligands **1**, we conducted the ligand substitution of 1-phenylethyl boronic acid pinacol ester (**2**) (Figure 2b). When boronic ester **2** was reacted with a neutral form of **1**, prepared by reacting the HCl salt of **1** with an equivalent amount of DBU in $CDCl_3$, the desired ligand exchange did not occur (Table S1). Instead, 3 equiv of DBU were necessary to achieve the ligand exchange, resulting in the formation of the desired bicyclic boronate **2a** with 35% conversion. The yields of **2a** and **2b** were further improved to 52% and 48%, respectively, under optimized conditions: analyte **2** (1 equiv), **1a** or **1b** (1.5 equiv), DBU (4 equiv), CH_3OH (10 μL), and $CDCl_3$ (0.5 mL). The crystal structure **2a** confirmed its bicyclic structure (Figure 2c), where the amino group in its NH_2 form coordinated to the boron center.[25] Both synthesized compounds, **2a** and **2b**, exhibited two distinct fluorine peaks in their ^{19}F NMR spectra due to the tetrahedral boron geometry attached to a chiral carbon center (Figure 2d). DFT calculations helped assign each fluorine peak (Figures S8−10).

Enantiodiscrimination of fluorine signals was tested with a chiral cationic cobalt complex [Co]PF_6, which proved effective for chiral NMR analysis of carbonyl compounds.[23] When **2a** or **2b** was mixed with a stoichiometric amount of [Co]PF_6, four distinct, baseline-separated ^{19}F NMR signals were observed due to diastereomeric ion-pair formation between **2** and [Co]PF_6. Both 2- and 4-positions of the fluorine groups were effective for peak resolution, with $\Delta\Delta\delta$ values of 0.24 and 0.05 ppm for **2a** and 0.30 and 0.07 ppm for **2b**, respectively. These separations are large enough to integrate the separated peaks, enabling the determination of the enantiomeric excess of the analytes.

Notably, distinct peak separation was not observed in the ^{1}H NMR spectra when **2** or **2b** was mixed with [Co]PF_6 (Figure S3). The **1b** ligand was predominantly used in this study due to its slightly superior peak separation. $CDCl_3$ and CD_2Cl_2 provided clean baseline peak separations, and $CDCl_3$ was selected as the reaction solvent due to its optimal peak separation and economic benefits (Figure S4). However, in polar solvents such as CD_3CN, CD_3OD, and DMSO-d_6, peak separation was not observed. Polar solvents proved ineffective as they hindered noncovalent interaction between cobalt complex and **2b**.

We also demonstrated the reliability of chiral analysis through linear correlation. The enantiomeric excess (*ee*) obtained from ^{19}F NMR spectroscopy showed an excellent correlation with the weight % *ee*, as demonstrated in Figure 2e. Additionally, the T1 relaxation values were measured as 0.85 and 0.84 s for **2a**, and 1.31 and 1.32 s for **2b**, respectively (Figure S6). We confirmed that the *ee* values were consistent when using relaxation delays of 1 s (d1= 1 s) and 10 s (d1 = 10 s) (Figure S2). The NMR peak shifts of the bridgehead proton in isolated **2b** were consistent with those observed in the crude reaction mixture, indicating that **2b** remains neutral in the reaction mixture without additional deprotonation. (Figure S3). Furthermore, the binding stoichiometry between [Co]PF_6 and the bicyclic boronate **2b** was determined using the Job plot. Figure 2f shows that the Job plot in $CDCl_3$ had a maximum at 0.5, which implies a 1:1 binding mode between [Co]PF_6 and **2b**. This 1:1 binding is likely due to intermolecular hydrogen bonding interactions between the cobalt complex and the bicyclic boronate.

We also verified the applicability of this method to various chiral boronic esters with different functional groups (Figure 3). ^{19}F NMR chiral analysis was effectively conducted on

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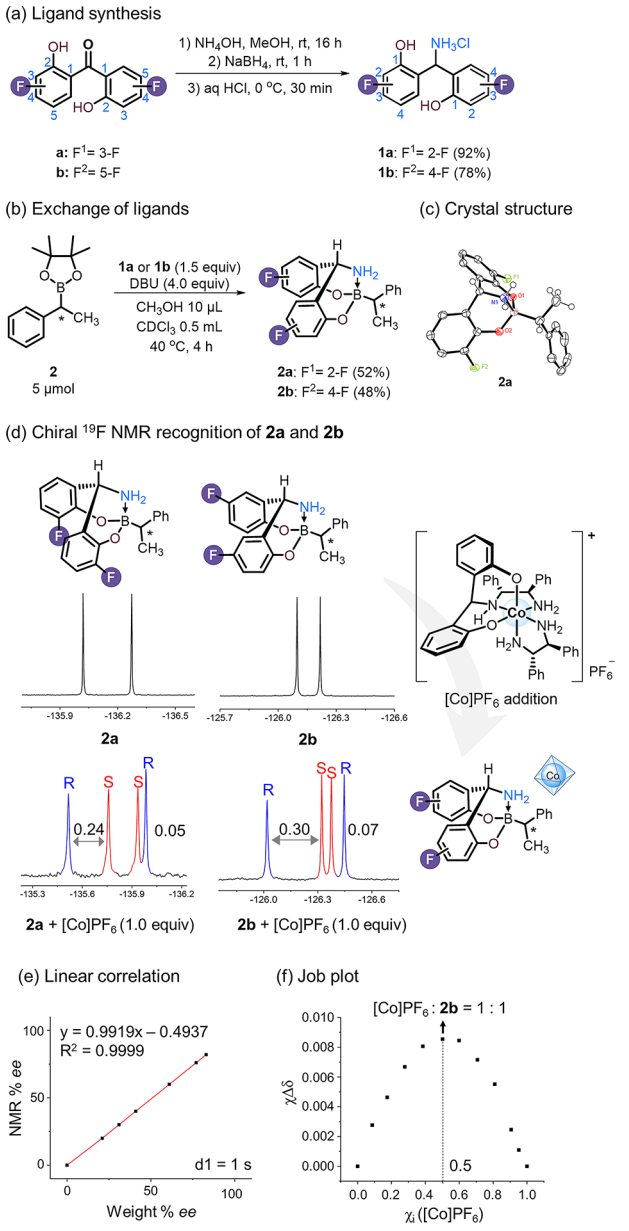

Figure 2. (a) Synthetic procedure of ligand, (b) ligand exchange of analyte **2** using ligands **1a** and **1b**, (c) crystal structure of boronate **2b**, (d) partial $^{19}F\{^{1}H\}$ NMR spectra of the reaction mixture after ligand exchange of **2** and after $[Co]PF_6$ (1.0 equiv) addition to the interconverted mixture, (e) enantiopurity correlation of **2** via ^{19}F NMR analysis and weight-based measurement, and (f) Job plot between **2b** and $[Co]PF_6$ measured in $CDCl_3$.

various α-chiral boronic esters (**3**–**11**), providing clean baseline peak separations. This method demonstrated excellent tolerance to various functional groups, successfully analyzing enantiomers containing ester, cyano, bromo, trifluoro, and ketone groups. Notably, for substrate **7**, which does not contain an aryl group, analysis was possible using ^{19}F NMR. Compounds **10** and **11** required more than one equivalent of $[Co]PF_6$ for effective peak separation. Remarkably, this method was successfully applied for those boronic esters with chiral carbon centers in the β-position (**12**–**15**). Additional functional groups such as chloro, sulfonyl, and phosphine oxide groups were all compatible with the chiral analysis with $[Co]PF_6$. For γ-chiral boronic esters (**16**–**17**), the **1a** ligand was more effective than the **1b** ligand. However, the longer distance between the chiral center and the boron atom makes γ-chiral compounds inherently challenging to analyze, resulting in only partial peak separation for analyte **17**. Measuring the spectra at lower temperatures, specifically at 0 and −20 °C, led to a decrease in peak resolution (Figure S5). When three peaks are observed due to overlapping signals, whether from the same enantiomer or from different enantiomers, the quantification of each enantiomer can be achieved by integrating all three peaks, as demonstrated with analytes **3** and **24**.

The method effectively separated peaks for chiral boron compounds with two stereogenic centers (**18**–**19**). Analyte **18**, displaying a diastereomeric ratio (*dr*) greater than 99:1, presented only one diastereomer, simplifying the analysis of enantiomeric excess. The analysis of analyte **19** was notably effective; despite its uncontrolled *dr* producing two diastereomers, it enabled the simultaneous assessment of enantiomeric excess for each. However, the variable conversions of these diastereomers posed challenges in measuring the diastereoselective ratio using ^{19}F NMR. Effective chiral analysis was accomplished for compounds with alternative ligands (**20**-**21**), such as boronic esters containing methylated acenaphthoquinone and trifluoroborate. For trifluoroborate, optimized conditions were using K_2CO_3 and TMSCl. Compounds containing two Bpin groups (**22**) predominantly yielded products with two fluorine-labeled boronates, resulting in distinct peak separation. For a compound containing Bdan and Bpin (**23**), treatment with KHF_2 selectively converted Bpin to trifluoroborate, as Bdan remained inert under these conditions.[26] Following this, the addition of ligand **1b**, triethylamine, and TMSCl facilitated the selective ligand exchange of the trifluoroboronate moiety. This process allowed for the clear analysis of analyte **23**, both as a racemic mixture and with 82% enantiomeric excess.

Lastly, we demonstrated direct analysis of crude mixtures as illustrated in Figure 4. Hydroboration of styrene was performed using Dppbz and (*R*,*S*)-Josiphos ligands to synthesize chiral boronic esters.[27] The yield of the hydroboration reaction was quantified using ^{1}H NMR, while ^{19}F NMR was utilized to assess enantioselectivity. The ^{19}F NMR analysis was conducted directly on crude mixtures without prior isolation, highlighting the practicality and efficiency of our method. The results showcased effective chiral analysis, with varying enantiomeric excesses depending on the ligand used. Using the Dppbz ligand resulted in racemic products, whereas enantioenriched products with 56–71% *ee* were achieved using the (*R*,*S*)-Josiphos ligand. Due to its simplicity, speed, and convenience, our protocol for chiral solvation using fluorine-labeled boronate holds significant potential for advancing asymmetric reaction development.

CONCLUSION

In conclusion, our approach to the chiral analysis of organoboron compounds using ^{19}F NMR spectroscopy has proven highly effective. This study successfully synthesized tridentate ligands that significantly enhance ligand exchange and incorporated fluorine labels to dramatically improve the resolution of chiral signals. By employing a chiral cationic cobalt complex as a solvating agent, our method achieved distinct and clear separation of ^{19}F NMR signals. Demonstrating versatility, it effectively analyzed various boronic esters, encompassing α, β, and γ chiral centers, as well as compounds

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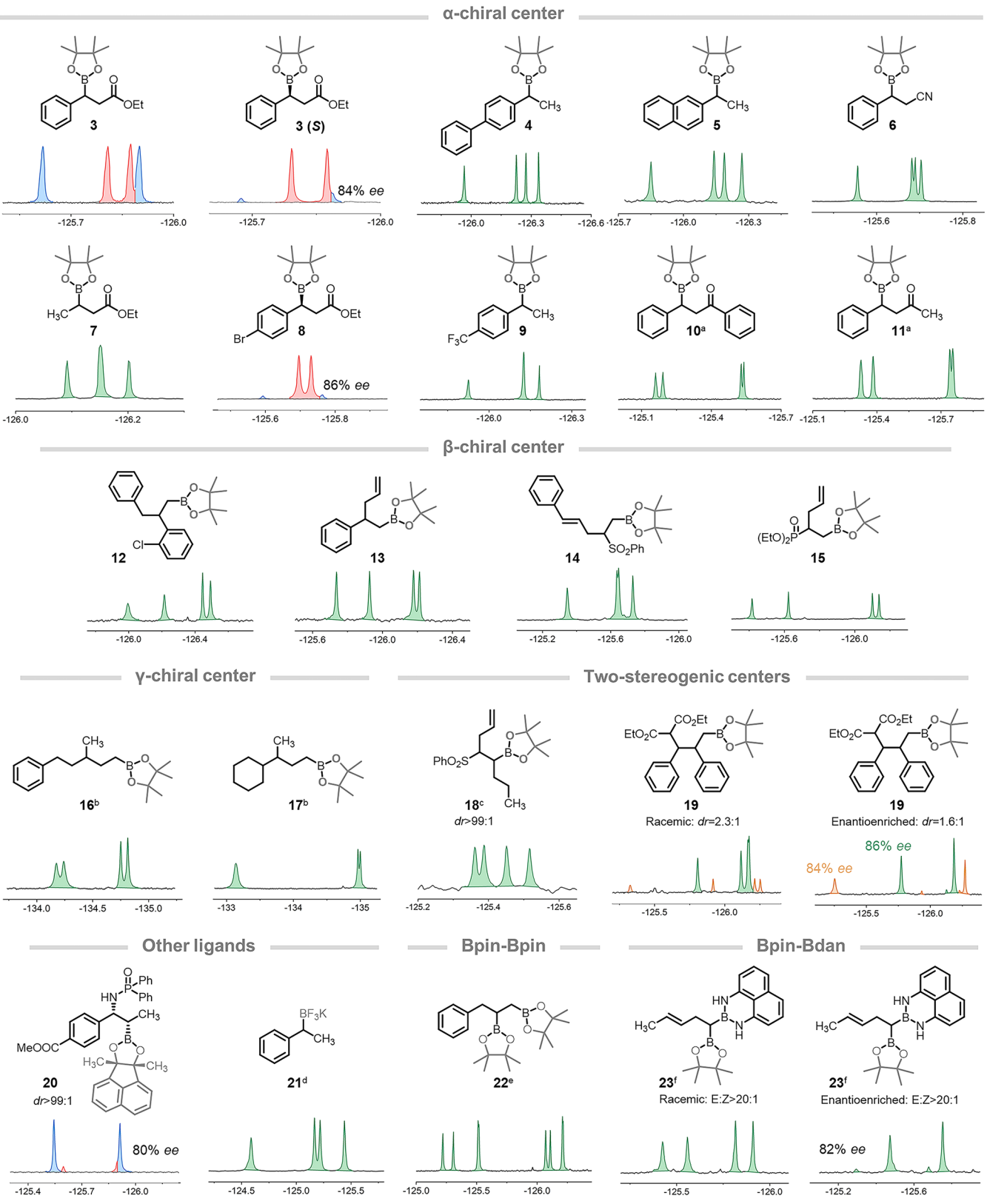

Figure 3. Partial $^{19}F\{^{1}H\}$ NMR spectra of chiral bicyclic boronate with $[Co]PF_6$ (1.0 equiv of the analyte) in $CDCl_3$. Blue: (*R*)-enantiomer; and red: (*S*)-enantiomer. For analyte **20**, blue: (1*R*,2*S*)-enantiomer; and red: (1*S*,2*R*)-enantiomer. [a]$[Co]PF_6$ (4.0 equiv) was used. [b]K_2CO_3 (2.0 equiv) and **1a** ligand (1.5 equiv) were used in methanol. [c]Reaction time: 14 h. [d]K_2CO_3 (2.0 equiv) and TMSCl (3.0 equiv) were used in methanol. [e]**1b** ligand (3.0 equiv) was used. [f]KHF_2 (4.0 equiv) was used in methanol to convert to trifluoroborate, then the resulting trifluoroborate was reacted for 30 min with **1b** ligand (3.0 equiv), TEA (3.0 equiv) and TMSCl (3.0 equiv).

with dual chiral centers. Moreover, the developed approach facilitates direct analysis of crude mixtures, simplifying workflow and enhancing efficiency in synthetic processes. This chiral ^{19}F NMR analysis method has the potential to

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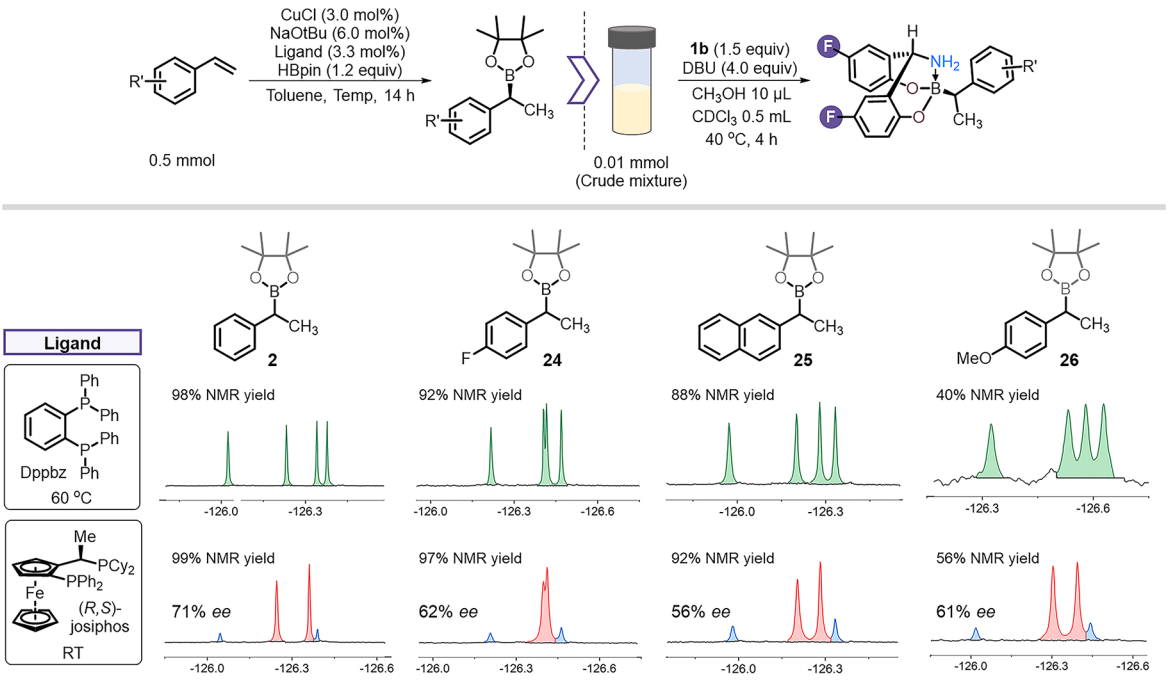

Figure 4. ^{19}F NMR chiral analysis of boronate analyte in crude reaction mixture without isolation. Partial $^{19}F\{^1H\}$ NMR spectra of chiral bicyclic boronate with $[Co]PF_6$ (1.0 equiv). Green: racemic mixture; blue: (*R*)-enantiomer; and red: (*S*)-enantiomer. NMR yields of the hydroboration reaction were determined by ^1H NMR using mesitylene as an internal standard.

overcome the limitations of traditional methods and is expected to become a pivotal tool for precise assessment of the optical purity of chiral organoboron compounds.

METHODS

$^{19}F\{^1H\}$ NMR Measurements

Analytes (5 μmol) were dissolved in $CDCl_3$ (0.4 mL). A stock solution was prepared by dissolving tridentate ligand **1a** or **1b** (0.15 mmol, 21.6 mg) and diazabicyclo(5.4.0)undec-7-ene (DBU, 0.2 mmol, 30.4 mg) in a solvent mixture (CH_3OH:$CDCl_3$ = 1:9, 1 mL) was prepared. Subsequently, 100 μL of the tridentate ligand stock solution was added to the analyte solution. The reaction mixture was stirred at 40 °C for 4 h. Following the reaction, the crude mixture was treated with $[Co]PF_6$ (5 μmol, 4.1 mg, 1.0 equiv). The resulting solution was transferred to a 5 mm NMR tube for recording the $^{19}F\{^1H\}$ NMR spectra. $^{19}F\{^1H\}$ NMR spectra were recorded using Bruker Ascend 400 and Bruker Ascend 500 spectrometers at 298 K, using a default relaxation delay (D1) of 1 s and a total of 16 scans. Spectra acquisition was performed using ^1H decoupled ^{19}F NMR technique, utilizing the Bruker pulse program, zgfhigqn (inverse-gated ^1H decoupled pulse sequence).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c00703.

Experimental procedures, NMR spectroscopic data, crystal structure information, and computational details (PDF)

Crystallographic data for **2a** (CIF)

Accession Codes

CCDC 2360347 contains 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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