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# A simple quantitative chiral analysis of amino acid esters by fluorine-19 nuclear magnetic resonance using the modified James–Bull method

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**Abstract**

A simple chiral analysis of amino acid esters by fluorine-19 nuclear magnetic resonance ($^{19}$F NMR) through the modified James–Bull method is described. Thus, amino acid ester acid salt was treated with 5-fluoro-2-formylphenylboronic acid and (S)-BINOL in the presence of triethylamine (TEA) and MS4A for 10 minutes. The reaction mixture was analysed by $^{19}$F NMR directly to afford good quantifications.

**KEYWORDS**

$^{19}$F NMR, amino acids, James-bull assembly, quantification

## 1 | INTRODUCTION

α-Amino acids form the proteins in living organisms. Therefore, the natural forms (usually L-amino acids) are easily available and very useful as chiral building blocks.[1] In addition, D-amino acids, which are commonly known as an unnatural form, are currently recognized as a useful indicator of various changes such as ageing and diseases in mammals.[2] Therefore, quantitative chiral analysis of amino acids and their derivatives is highly important.

Chiral analysis of biogenic compounds by use of fluorine-19 nuclear magnetic resonance ($^{19}$F NMR) is currently attracting much attention because of the high sensitivity of $^{19}$F NMR and very low background signals.[3] For example, Zhao et al reported the simultaneous analysis of chiral amines using a pincer-type palladium complex in which various types of primary amines including amino alcohols can be sensed. This method can be expanded to amine sensing in foods and drinks.[4] For discrimination of chiral amines by hydrogen-1 ($^{1}$H) NMR, the method for assembly of a chiral amine, a chiral diol and *o*-formylphenylboronic acid, so-called the James–Bull method, is very useful.[5] Various types of chiral amines can be analyzed qualitatively by $^{1}$H NMR analysis. Although it is considered that the expansion of this method to $^{19}$F NMR analysis would provide a highly effective analytical method by accompanying with the strong points of $^{19}$F NMR described above, the quantitative analysis by $^{19}$F NMR through the James–Bull method was scarcely investigated in detail. In 2009, James and Bull's group reported that ee of several chiral diols can be determined through the similar derivatization of the diol, 4-fluoro-2-formylphenylboronic acid and (*R*)-1-phenylethylamine (**(*R*)-2a**).[6] However, only one amine **(*R*)-2a** was demonstrated; nevertheless, various chiral amines were tested in their quantitative analysis by $^{1}$H NMR. Chaudhari and Suryaprakash independently reported the discrimination of chiral 1-arylethylamines by $^{19}$F NMR through a modified James–Bull method using (*R*,*R*)-cyclohexane-1,2-dicarboxylic acid as a chiral source and 3-fluoro-2-formylphenylboronic acid in 2012.[7] However, unequal intensity pattern of $^{19}$F NMR signals of the reaction mixture with several racemic amines was observed and the quantitative analysis failed. We investigated a detailed investigation of stoichiometric chiral analysis of α-amino acid esters by $^{19}$F NMR through a modified James–Bull method, in which triethylamine (TEA) was found to be a very useful additive for successful assembly. Here, we will present a simple chiral analysis of amino acid esters by $^{19}$F NMR.

## 2 | MATERIALS AND METHODS

### 2.1 | General

Amino acid esters acid salts were prepared according to the literature procedure.[8] Deuterated solvents were purchased from the Cambridge Isotope Laboratories, Inc. and used without further purifications. Unless noted otherwise, all reagents and solvents were obtained from commercial suppliers and used without further purifications. NMR spectra were recorded with the Bruker Ascend 400 spectrometer (400 MHz for $^{1}H$, 100 MHz for $^{13}C$, and 376 MHz for $^{19}F$) by using tetramethylsilane (TMS) ($\delta = 0$ ppm) as an internal standard for $^{1}H$ NMR, and $CDCl_3$ ($\delta = 77$ ppm) for carbon-13 ($^{13}C$) NMR.

### 2.2 | Quantitative analysis

Amino acid ester acid salt (0.03 mmol) and TEA (1.5 eq, 4.6 μL) were suspended in $CDCl_3$ (0.3 mL). 5-Fluoro-2-formylphenylboronic acid (**1c**) (1.1 eq), (*S*)-BINOL (1.5 eq), 4A molecular sieves, and $CDCl_3$ (0.7 mL) were added. The solution was stirred for 10 minutes and then analyzed by $^{19}F$ NMR spectroscopy

## 3 | RESULTS AND DISCUSSION

### 3.1 | Effects of fluorinated Benzaldehydes

Initially, we tested several fluorinated benzaldehydes **1a-c** as the $^{19}F$ NMR chiral reporter in James' method (Figure 1). Thus, a reaction of (±)-1-phenylethylamine (**2a**), (*S*)-BINOL, and aldehyde **1a-c** in $CDCl_3$ was performed at room temperature for 10 minutes, and then $^{1}H$ and $^{19}F$ NMR were measured. When 3-fluoro-2-formylphenylboronic acid (**1a**) was used, two signals were obtained on the $^{19}F$ NMR spectrum. The same reactions by use of optically pure (*S*)- and (*R*)-**2a** revealed that these two peaks are (*S*,*R*)-**3aa** and (*S*,*S*)-**3aa**, and the difference in these.

$^{19}F$ NMR shifts ($\Delta\delta$) is 0.16 ppm (Figure 1a). A benzaldehyde bearing fluorine atom at C4-position **1b**, interestingly afforded only one signal for the corresponding diastereomer on the $^{19}F$ NMR spectrum, although two diastereomers were detected on its $^{1}H$ NMR (Figure 1-b). 5-fluoro-2-formylphenylboronic acid (**1c**) was found as a good chiral $^{19}F$ NMR reporter as well as **1a** from the view point of peak separation (Figure 1c). Furthermore, the assembly proceeded nicely to afford a 93% yield of **3ca**, whereas the yields of **3aa** (28%) and **3ba** (33%) were much lower, presumably because of the steric hindrance and/or electronic effects. Therefore, we selected **1c** as a $^{19}F$ NMR chiral reporter in this work.

### 3.2 | Optimization of analytical conditions

With $^{19}F$ NMR reporter **1c**, we then optimized the reaction and measurement conditions for chiral quantitative analysis of amino acid esters by $^{19}F$ NMR. First, molar ratio and several additives were tested, and the results are summarized in Table 1. Thus, $^{1}H$ and $^{19}F$ NMR spectra of the reaction mixture of (±)-phenylalanine methyl ester (**2b**) with **1c** and (*S*)-BINOL in $CDCl_3$, with or without additives, were measured. When **2b** with an equal molar amount of **1c** and (*S*)-BINOL were mixed and reacted, two signals appeared on the $^{19}F$ NMR spectrum with an integral ratio of 1:1.40 (entry 1). These two signals were confirmed as the corresponding diastereomeric imine (*S*,*R*)- and (*S*,*S*)-**3cb** by the reaction using optically pure (*R*)- and (*S*)-**2b**. In this case, the starting amino acid ester **2b** remained and **3cb** was obtained in only 77% yield. The apparent disproportionation of the diastereomer ratio of **3cb** was considered to be due to the kinetic resolution. Various reaction conditions were tested in order to increase the chemical yield of **3cb**. Although the reaction was performed in toluene-$d_8$ and $CD_2Cl_2$ to afford **3cb** in 73% and 58% yield, respectively, the diastereomer ratios of **3cb** were not improved (entries 2 and 3). While amino acid ester **2b** still remained when the reaction was carried out in toluene-$d_8$, an almost full consumption of **2b** was observed by use of $CD_2Cl_2$. However, the imine that was generated by the reaction of **1c** and **2b** without (*S*)-BINOL was afforded as a by-product, which was presumably troublesome in the quantitative chiral analysis. Increasing the amount of aldehyde **1c** (1.1 eq) and (*S*)-BINOL (1.2 eq) affected these two values to afford **3cb** in an 88% yield with a 1:1.14 diastereomer ratio (entry 4). Use of a further excess amount of (*S*)-BINOL (1.5 eq) improved the diastereomer ratio up to 1:1.09 (entries 5 and 6). Because the present analysis is performed on $^{19}F$ NMR spectra, it was considered that the addition of organic amines such as TEA would not prevent the quantification so much. Indeed, the addition of TEA effectively improved the conversion (entries 9 and 10), and the best diastereomer ratio (1;1.05) was obtained when the reaction of **2b** with 1.1 eq of **1c** and 1.5 eq of (*S*)-BINOL was performed in $CDCl_3$, in the presence of MS4A and TEA (0.5 eq) (entry 10).

Because amino acid esters were generally prepared as acid salts by use of chlorination reagents, such as $SOCl_2$,[8] it is preferred that the enantiomeric excesses are determined directly by use of these salts. Thus, the use of phenylalanine hydrochloride (**2b·HCl**) was examined (Table 2). In James' previous report,[5b] amino acid ester hydrochloride was preliminarily treated with $Cs_2CO_3$, and then the insoluble inorganic species were removed by filtration. They also reported that the use of

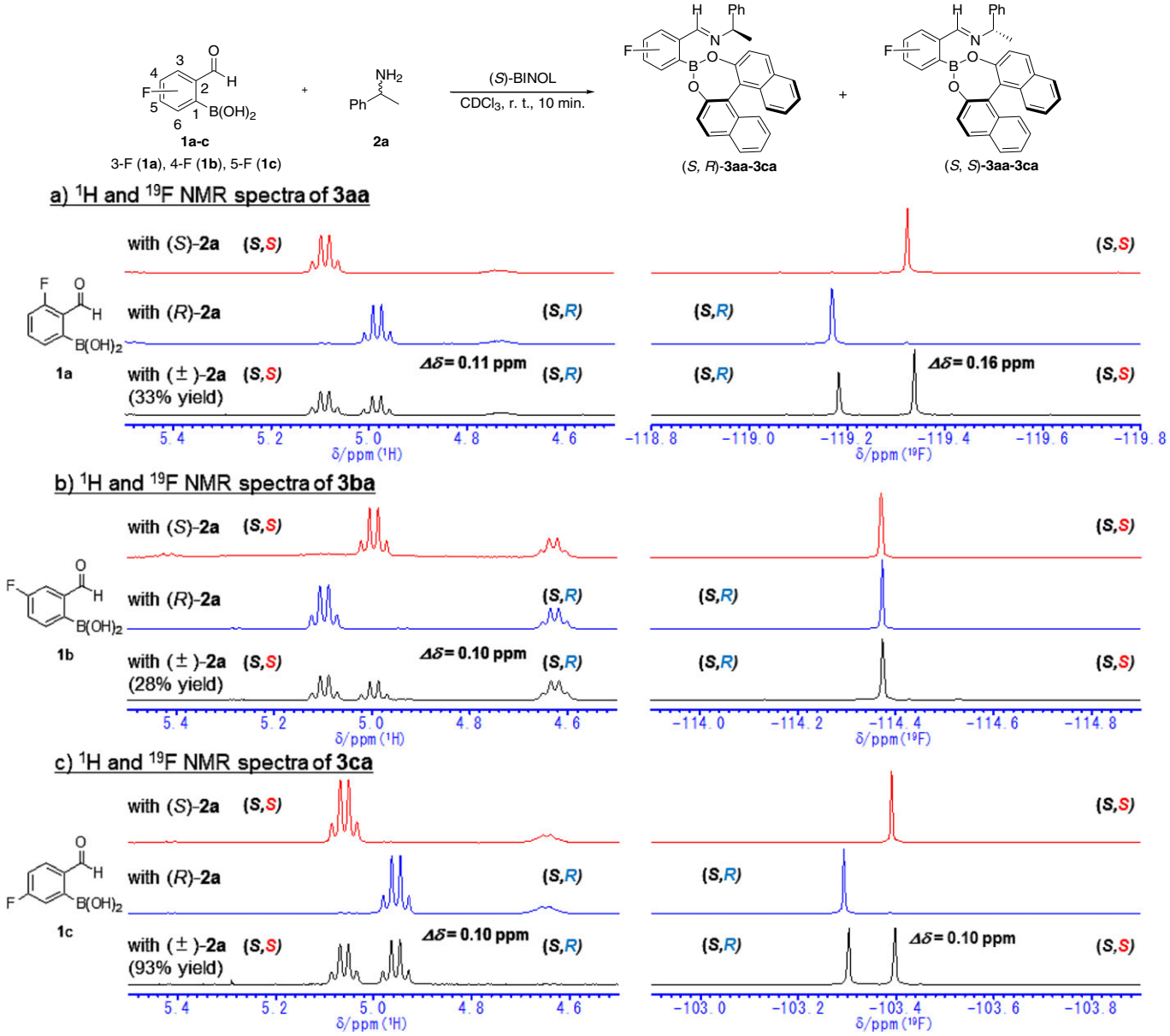


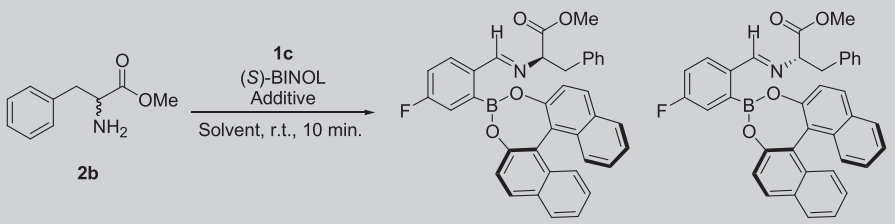

**FIGURE 1** Effect of fluorinated benzaldehydes **1a-c** and nuclear magnetic resonance (NMR) spectra

a slightly excess amount of $Cs_2CO_3$ sometimes caused the problematic racemization of amino acid esters and that this racemization could be suppressed by using $K_2CO_3$ instead of $Cs_2CO_3$. Therefore, we started from the use of these dicarbonates as a base. When **2b·HCl** was treated with **1c** and (*S*)-BINOL in the presence of MS4A and a 1.1 equivalent of $K_2CO_3$, an apparent disproportionation of the diastereomer ratio was observed (entry 1). A similar result was obtained with $Cs_2CO_3$ (entry 2). The disproportionation was considered to be caused by a low chemical yield of **3cb** (less than 63% yield). On the other hand, the use of TEA was also effective in the quantitative analysis of amino acid salt. Thus, the reaction was carried out in the presence of a 1.1 equivalent of TEA to afford **3cb** in an 89% yield with a better diastereomer ratio (1:1.18, entry 3). Increasing the amount of TEA and (*S*)-BINOL to 1.5 eq obtained **3cb** in an almost quantitative yield with a sufficient diastereomer ratio (1:1.06, entry 4).

## 3.3 | Scope of amino acid esters

Various amino acid ester salts (**2b-n·HX**) were tested under the optimized analytical conditions, and the results are summarized in Table 3 (Experimental details and the NMR spectra are provided in Supporting Information). As shown in entries 2 and 3, (±)-phenylalanine benzyl ester *p*-toluenesulfonic acid (PTSA) salt (**2c·PTSA**) and its allyl ester (**2d**) also showed good separation of the $^{19}F$ NMR signals and a good diastereomer ratio (1:1.06 and 1:1.04,

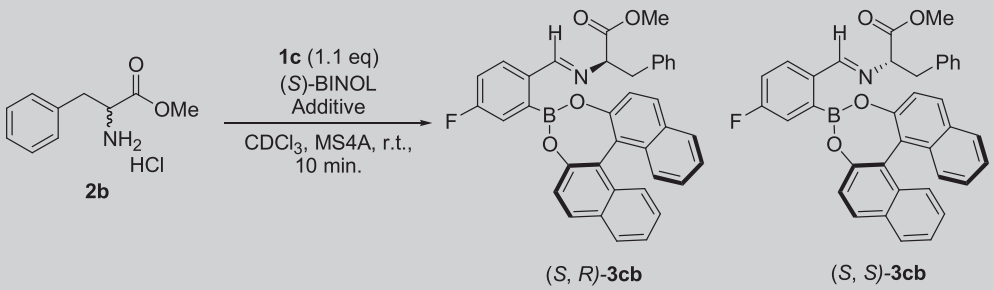
**TABLE 1** Optimization of analytical conditions for phenylalanine methyl ester (**2b**)[a]




| Entry | 1c (eq) | (S)-BINOL (eq) | Solvent | Additive | Dr (*S,R*: *S,S*) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | 1.0 | 1.0 | $CDCl_3$ | – | 1:1.40 | 77 |
| 2 | 1.0 | 1.0 | Toluene-$d_8$ | – | 1:1.95 | 73 |
| 3 | 1.0 | 1.0 | $CD_2Cl_2$ | – | 1:1.14 | 58 |
| 4 | 1.1 | 1.2 | $CDCl_3$ | – | 1:1.18 | 88 |
| 5 | 1.1 | 1.5 | $CDCl_3$ | – | 1:1.24 | 92 |
| 6 | 1.1 | 2.0 | $CDCl_3$ | – | 1:1.09 | 88 |
| 7 | 1.1 | 1.2 | $CDCl_3$ | MS4A | 1:1.13 | 88 |
| 8 | 1.1 | 1.5 | $CDCl_3$ | MS4A | 1:1.16 | 72 |
| 9 | 1.1 | 1.2 | $CDCl_3$ | MS4A<br>TEA (0.5 eq) | 1:1.13 | >99 |
| 10 | 1.1 | 1.5 | $CDCl_3$ | MS4A<br>TEA (0.5 eq) | 1:1.05 | >99 |

[a]Reaction conditions: phenylalanine methyl ester (**2b**) was treated with **1c** and (*S*)-BINOL in the presence of given additives in solvent at room temperature for 10 min. The reaction mixture was analyzed by $^1H$ and $^{19}F$ NMR.

**TABLE 2** Optimization of analytical conditions for phenylalanine methyl ester hydrochloride (**2b•HCl**)[a]

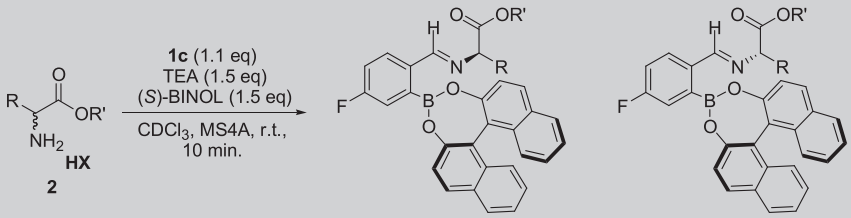


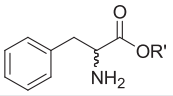
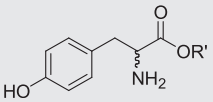
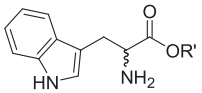
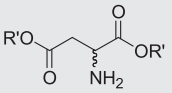
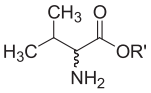
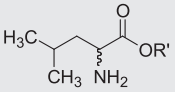
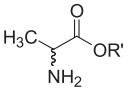
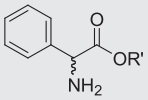

| Entry | (S)-BINOL (eq) | Additive (eq) | Dr (*S,R*: *S,S*) | Yield (%) |
|---|---|---|---|---|
| 1 | 1.2 | $K_2CO_3$ (1.1) | 1:1.79 | 45 |
| 2 | 1.2 | $Cs_2CO_3$ (1.1) | 1:1.55 | 63 |
| 3 | 1.2 | TEA (1.1) | 1:1.18 | 89 |
| 4 | 1.5 | TEA (1.5) | 1:1.06 | >99 |

[a]Reaction conditions: phenylalanine methyl ester hydrochloride (**2b·HCl**) was treated with **1c** (1.1 eq) and (*S*)-BINOL in the presence of additive and MS4A in $CDCl_3$ at room temperature for 10 min. The reaction mixture was analyzed by $^1H$ and $^{19}F$ NMR.

respectively). Tyrosine methyl ester hydrochloride (**2e·HCl**) and tryptophan methyl ester hydrochloride (**2f·HCl**) were also successfully separated to afford the corresponding imines **3ce** and **3cf** with a 1:1.07 and 1:1.07 diastereomer ratio, respectively (entries 4 and 5). Compared with these arylalanine derivatives, small Δδ values were obtained with the other amino acid esters. For example, a Δδ value of the corresponding diastereomers **3cg** derived from aspartic acid methyl ester hydrochloride (**2g·HCl**) was only 0.12 ppm (entry 6).

**TABLE 3** Scope of amino acid esters[a]




| Entry | Amino acid ester 2 | | HX | $^{19}$F NMR shift Δδ | Dr (*S*,*R*: *S*,*S*) |
|---|---|---|---|---|---|
| 1 |  | R′ = me (**2b**) | HCl | 0.36 | 1:1.06 |
| 2 | | R′ = Bn (**2c**) | PTSA | 0.41 | 1:1.06 |
| 3[b] | | R′ = Allyl (**2d**) | – | 0.39 | 1:1.04 |
| 4 |  | R′ = me (**2e**) | HCl | 0.35 | 1:1.07 |
| 5 |  | R′ = me (**2f**) | HCl | 0.34 | 1:1.07 |
| 6 |  | R′ = me (**2g**) | HCl | 0.12 | 1:1.08 |
| 7 |  | R′ = me (**2h**) | HCl | 0.04 | 1:1.07 |
| 8 |  | R′ = me (**2i**) | HCl | 0.08 | 1:1.08 |
| 9 |  | R′ = me (**2j**) | HCl | 0.01 | n.d.[d] |
| 10[c] | | R′ = me (**2j**) | HCl | 0.07 | 1:1.04 |
| 11 | | R′ = Bn (**2k**) | PTSA | 0.06 | 1:1.05 |
| 12 |  | R′ = me (**2l**) | HCl | 0.03 | n.d.[d] |
| 13[c] | | R′ = me (**2l**) | HCl | 0.00 | n.d.[d] |
| 14 | | R′ = Bn (**2m**) | PTSA | 0.03 | 1:1.01 |
| 15[b] | | R′ = Allyl (**2n**) | – | n.d.[e] | n.d.[d] |

[a]Reaction conditions: amino acid derivatives **2·HX** was treated with **1c** (1.1 eq.) and (*S*)-BINOL (1.5 eq) in the presence of TEA (1.5 eq) and MS4A in $CDCl_3$ at room temperature for 10 min. The reaction mixture was analyzed by $^1$H and $^{19}$F NMR.

[b]TEA (0.5 eq) was used.

[c]$CD_2Cl_2$ was used instead of $CDCl_3$.

[d]Not determined.

[e]Not distinguished.

Further decreasing Δδ was obtained with valine (**2h·HCl**) and with leucine (**2i·HCl**) derivatives (entries 7 and 8). Although, only 0.01 ppm differences in $^{19}$F chemical shifts of the corresponding diastereomeric imines derived from (±)-alanine methyl ester hydrochloride (**2j·HCl**) were observed when $CDCl_3$ was used as a solvent (entry 9), the use of $CD_2Cl_2$ instead of $CDCl_3$ slightly improved the Δδ value (0.07 ppm) and enabled us to determine the diastereomer ratio (1:1.06, entry 10). Fortunately, $^{19}$F NMR signals of the corresponding diastereomers of alanine benzyl ester PTSA salt (**2k·PTSA**) appeared with Δδ = 0.06 and dr = 1:1.05 even in $CDCl_3$ (entry 11). Phenylglycine methyl ester hydrochloride (**2l·HCl**) did not obtain a good Δδ value in both $CDCl_3$ and in $CD_2Cl_2$, and the diastereomer ratios were not determined (entries 12 and 13). Use of its benzyl ester PTSA salt **2m·PTSA** afforded almost the same Δδ as in $CDCl_3$ (0.03 ppm); however, the diastereomer ratio could be determined because of the sharpness of the signals (entry 14). $^{19}$F shifts of the

diastereomers derived from phenylglycine allyl ester (**2n**) were not discriminated at all (entry 15).

### 3.4 | Quantitative chiral analysis of amino acid esters

Various ee of **2e·HCl** (75, 50, 20, 0, −20, −50, and −75% ee) were prepared. The ee values were determined by both chiral HPLC and the present $^{19}$F NMR method and the correlation of these ee values are shown in Figure 2

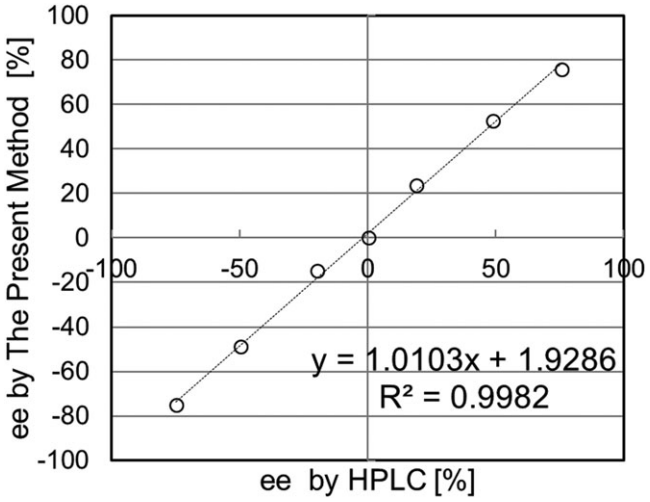



**FIGURE 2** Comparison of ee values of tyeosine methyl ester hydrochloride (**2e·HCl**) between HPLC and the present method

(Experimental details and the NMR spectra are provided in Supporting Information), suggesting that the present $^{19}$F NMR method resulted in the highly quantitative chiral analysis.

A mixed solution of D- and L-amino acid methyl esters was analyzed. Thus, a mixed solution of 20% ee of L-phenylalanine methyl ester hydrochloride (**2b·HCl**), 80% ee of D-**2f·HCl**, and racemic **2k·PTSA** was prepared and treated with **1c** and (*S*)-BINOL under the optimized conditions. As a result of the $^{19}$F NMR analysis, ee values of **L-2b**, **D-2f**, and **2k** were determined in 17.9%, 82.2%, and almost racemate (1.0% ee), respectively (Figure 3; Experimental details and the NMR spectra are provided in Supporting Information). This result suggested that enantio-purities of multiple amino acid esters could be analyzed at one time.

## 4 | CONCLUSION

We have investigated the quantitative chiral analysis of amino acid derivatives through the James–Bull method, in which TEA was found to be effective for the reaction conversion without significant loss of enantiomeric excess. The operation is very easy, and the accuracy of the quantification is sufficient. ee values of a mixture of alanine benzyl ester, tryptophan methyl ester, and phenylalanine methyl ester could be simultaneously determined through our present method.

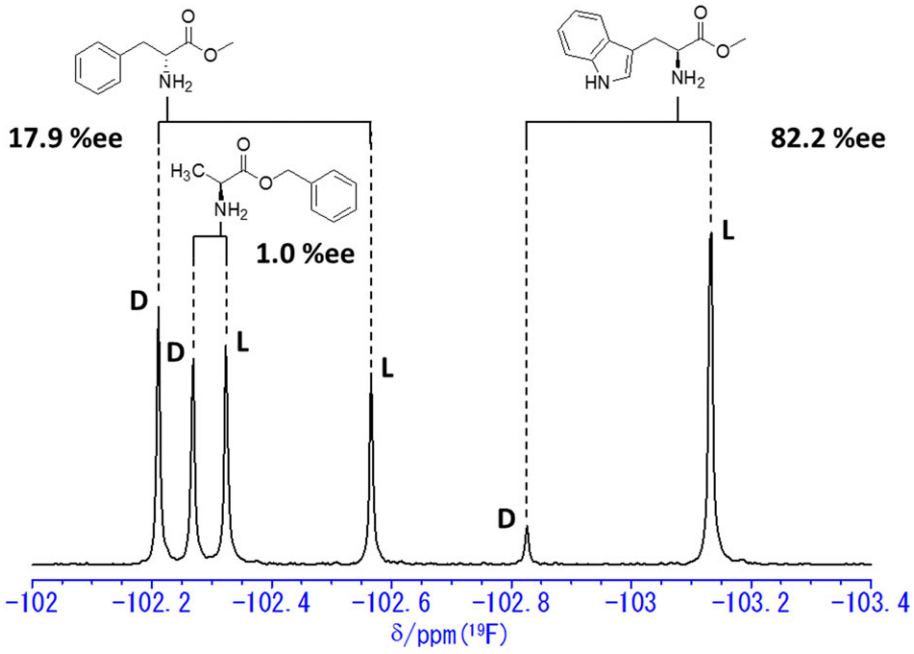



**FIGURE 3** $^{19}$F NMR spectrum of a mixed solution of L-phenylalanine methyl ester hydrochloride (**2b·HCl**, 20% ee), D-tryptophan methyl ester hydrochloride (**2f·HCl**, 80% ee), and DL-alanine benzyl ester PTSA salt (**2k·PTSA**)

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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