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Chiral Recognition Studies of α-(Nonafluoro-*tert*-butoxy)carboxylic Acids by NMR Spectroscopy

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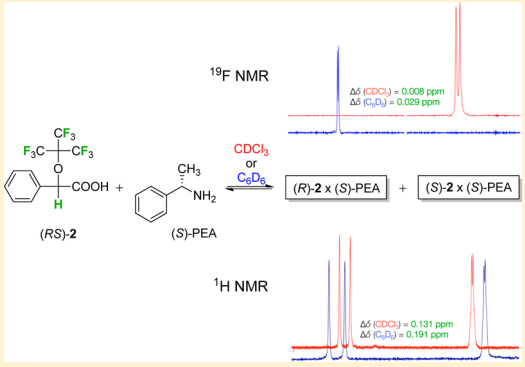
Supporting Information

ABSTRACT: Three chiral α-(nonafluoro-*tert*-butoxy)carboxylic acids (*R*)-**1**, (*RS*)-**2**, (*R*)-**3** were synthesized to examine their application as chiral solvating agents with amines. As a model compound, first (*S*)- and/or (*RS*)-α-phenylethylamine was used, and their diastereomeric salts were investigated by ^{1}H and ^{19}F NMR and ECD spectroscopy. The NMR spectroscopic studies were carried out at room temperature using the slightly polar $CDCl_3$ and apolar C_6D_6 as solvents in 5 mM and 54 mM concentrations. The difference of the chemical shifts (Δδ) in the diastereomeric complexes is comparable with other, well-known chiral derivatizing and solvating agents (e.g., Mosher's acid, Pirkle's alcohol). Diastereomeric salts of racemic acids (*RS*)-**1** and (*RS*)-**2** with biologically active amines (1*R*,2*S*)-ephedrine and (*S*)-dapoxetine were also investigated by ^{19}F NMR spectroscopy.



INTRODUCTION

Chiral solvating agents (CSAs) are powerful reagents used for determining enantiomeric excess (ee) of chiral organic compounds.[1,2] With the application of CSAs, there is no need to covalently modify an analyte prior to the examination because there are only secondary interactions between the molecules in the solution (such as Coulombic and π−π interactions, hydrogen bonding). The diastereomeric complexes formed are distinguishable by spectroscopic methods (NMR, ECD); therefore, the enantiomeric composition of the sample can be determined.[3,4]

To date, numerous chiral discriminating agents are available. Among them, several contain fluorine atoms or trifluoromethyl groups.[5−8] The determination of ee with these fluorine-containing reagents is advantageous by ^{19}F NMR spectroscopy because ^{19}F nuclei have favorable nuclear properties, and there are no or minimal overlapping peaks in the recorded ^{19}F NMR spectra of the diastereomeric complexes.

Synthesis and utilization of nonafluoro-*tert*-butoxy group-containing chiral molecules are still limited.[9−11] Previously, we reported the synthesis of three α-(nonafluoro-*tert*-butoxy)-carboxylic acids, two of which are in the optically active form [(*R*)-**1**, (*RS*)-**2**, (*R*)-**3**] (Figure 1).[12]

The structural properties of these carboxylic acids are highly beneficial for their application as chiral solvating agents. They contain (i) an acidic functional group that is responsible for the interaction between the chiral reagent and the analyte, (ii) a bulky hydrophobic $OC(CF_3)_3$ moiety, which possesses a significant steric hindrance on one side of the stereogenic center and decreases the rotational movements around the chiral center, and (iii) in the case of (*RS*)-**2** and (*R*)-**3**, an aromatic ring, which also helps to fix a stable conformation by π−π interactions. The simple structures of these compounds are coupled with simple spectral properties; consequently, there are only a few signals belonging to the acids in their ^{1}H NMR spectra. Additionally, ^{19}F NMR spectra have only one strong singlet related to the nine chemically equivalent fluorine atoms. In this paper, we present an extended experimental study on the enantiomeric discrimination ability of the listed α-(nonafluoro-*tert*-butoxy)carboxylic acids.

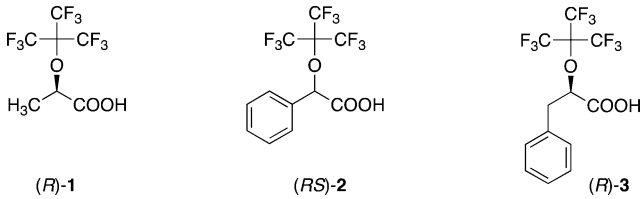


Figure 1. α-(Nonafluoro-*tert*-butoxy)carboxylic acids.

RESULTS AND DISCUSSION

Synthesis. The synthesis of α-(nonafluoro-*tert*-butoxy)-carboxylic acids **1**−**3** was described in detail in our preliminary

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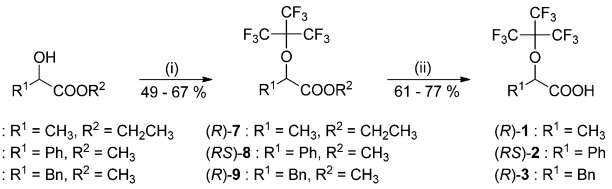
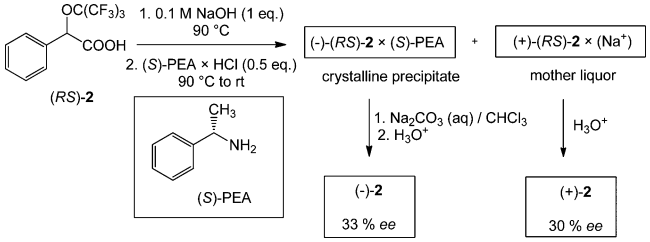
work.[12] It is worth noting that, as expected, the stereospecific synthesis of carboxylic acids **1** and **3** resulted in the corresponding enantiomers, but similar methods yielded a racemic product in **2** (Scheme 1).

Scheme 1. Syntheses of α-(Nonafluoro-*tert*-butoxy)carboxylic Acids 1−3



Because the application of **2** as a chiral agent is possible in its enantiomerically pure form, we tried to carry out its optical resolution. Testing several methods, we obtained the best result by using 0.5 equiv of the organic base (*S*)-phenylethylamine [(*S*)-PEA] as a resolving agent in warm aqueous media (see Scheme 2). To one equiv of racemic **2** were added 1 equiv of

Scheme 2. Resolution Experiments of (*RS*)-2 with (*S*)-PEA



NaOH and 0.5 equiv of (*S*)-PEA × HCl. One of the diastereomeric salts separated in its crystalline form, from which (−)-**2** was regenerated by aqueous Na_2CO_3 solution. This method provided enantiomerically enriched carboxylic acid (−)-**2** {ee: 33%, $[\alpha]_{578}$ −24° (*c* 0.5, methanol)}. The other enantiomer was prepared from the mother liquor by acidification in 30% ee {$[\alpha]_{578}$ +14° (*c* 0.5, methanol)}. Unfortunately, our further efforts to obtain optically pure **2** from these enantiomer mixtures failed. The efficiency of resolution was analyzed by ^{1}H NMR spectroscopy.

NMR Measurements. There are two main approaches to determine ee by NMR spectroscopy.[1,2] First, chiral-derivatizing agents (CDAs) are covalently bonded to the analyte; therefore, the structure of the diastereomers formed are strictly fixed. Here, the typical difference in the chemical shifts of the two diastereomers is approximately 0.1−0.2 ppm in ^{1}H NMR and 0.3−0.7 ppm in ^{19}F NMR.[3,4] The second approach uses chiral solvating agents for this purpose. These reagents form diastereomeric complexes with the dissolved enantiomers via rapid reversible equilibrium in a competition with the bulk solvent. This equilibrium is faster than the time scale of the NMR measurement; thus, there is one set of peaks for each diastereomeric complex.[13,14] The observed chemical shift anisochrony (~0.05 ppm in ^{1}H NMR)[13] is the result of: (i) the relative position of magnetically anisotropic groups (e.g., aryl, carbonyl) of the low energy conformers in the solution, and (ii) the relative value of diastereomeric complex formation constants K_{RS} and K_{SS} (i.e., the strength of the interactions between the ion pairs), which depend primarily on the nature of the functional groups for a given molecule. Using this method has the advantage of an "easy" performance by simply adding the reagent to a chiral compound in a small amount of deuterated solvent.

In our experiments, diastereomeric salt formation was investigated between fluorous carboxylic acids **1**−**3** and α-phenylethylamine (PEA) and characterized by ^{1}H and ^{19}F NMR spectroscopy. PEA has been widely used by others as a model substrate for enantioselective recognition studies.[15,16]

In these cases, the recorded chemical shifts of the diastereomeric complexes are weighted averages of chemical shifts of the distinct protonation forms of the free and protonated amine according to their relative amounts. The integrals of the signals in ^{1}H and ^{19}F NMR spectra are proportional to the amounts of the enantiomers; therefore, enantiomeric composition of the sample can be determined simply.

In our study, the first attempt was to observe the enantiorecognition phenomena on the ^{1}H nuclei followed by the ^{19}F NMR measurements. In several cases, when the enantiodifferentiation is inhibited by overlapping peaks, or if the ^{1}H NMR spectra are rather complex to interpret without spectral simulations, ^{19}F NMR experiments possess a significant advantage. To enhance the ion pair formation between the CSA and the analyte (i.e., the difference in the chemical shifts between the diastereomers), we used slightly polar $CDCl_3$ and apolar C_6D_6 as solvents. Our preliminary experiments on the effect of the acid:amine molar ratio revealed that a 1:1 stoichiometry provides the highest Δδ; thus, a 1:1 ratio was applied. NMR measurements were carried out on samples in two different concentrations of the diastereomeric salts (54 and 5 mM) in both solvents. ^{1}H and ^{19}F NMR spectra were recorded at room temperature immediately after mixing. The results are summarized in Figures 2−4, where the differences in the chemical shifts (Δδ) and partial ^{1}H NMR spectra are given.

(RS)-1 × (S)-PEA and (R)-1 × (RS)-PEA. Racemic (*RS*)-**1** was analyzed with enantiopure (*S*)-PEA, and optically active lactic acid derivative (*R*)-**1** was tested with racemic amine (*RS*)-PEA. In the first set of experiments, we recorded the ^{1}H NMR spectra in 54 mM using $CDCl_3$ as the solvent. The diastereomeric salts formed between (*RS*)-**1** and (*S*)-PEA have chemical shift differences (Δδ) of 0.038 ppm for the methine protons (quartets, 4.3−4.5 ppm) and 0.030 ppm for the methyl protons (doublets, 1.0−1.2 ppm) of (*RS*)-**1** (Figure 2). These values are close to those given in the literature (e.g., 0.05 ppm) using Pirkle's alcohol as the CSA.[6,17] The signals of the (*R*)-**1** × (*RS*)-PEA salt show broad signals for methine (quartets, 4.1−4.2 ppm) and 0.034 ppm for the methyl hydrogen atoms (doublets, 1.4−1.6 ppm) of (*RS*)-PEA. Our results indicate that chiral discrimination by NMR between **1** and PEA is possible to detect if one of the two compounds is enantiomerically pure. The measured Δδs are significant in both cases, but baseline resolution was not observed due to the multiplet resonances.

In our second set of experiments, C_6D_6 was used as the solvent. In this case, formation of the tight ion pairs is more favorable (larger K values); thus, the average chemical shifts are further away from those recorded for the pure carboxylic acid and the free amine. Our results show that the differences between the signals in the diastereomeric salts (Δδ) are more explicit in this apolar solvent. These data are also shown in

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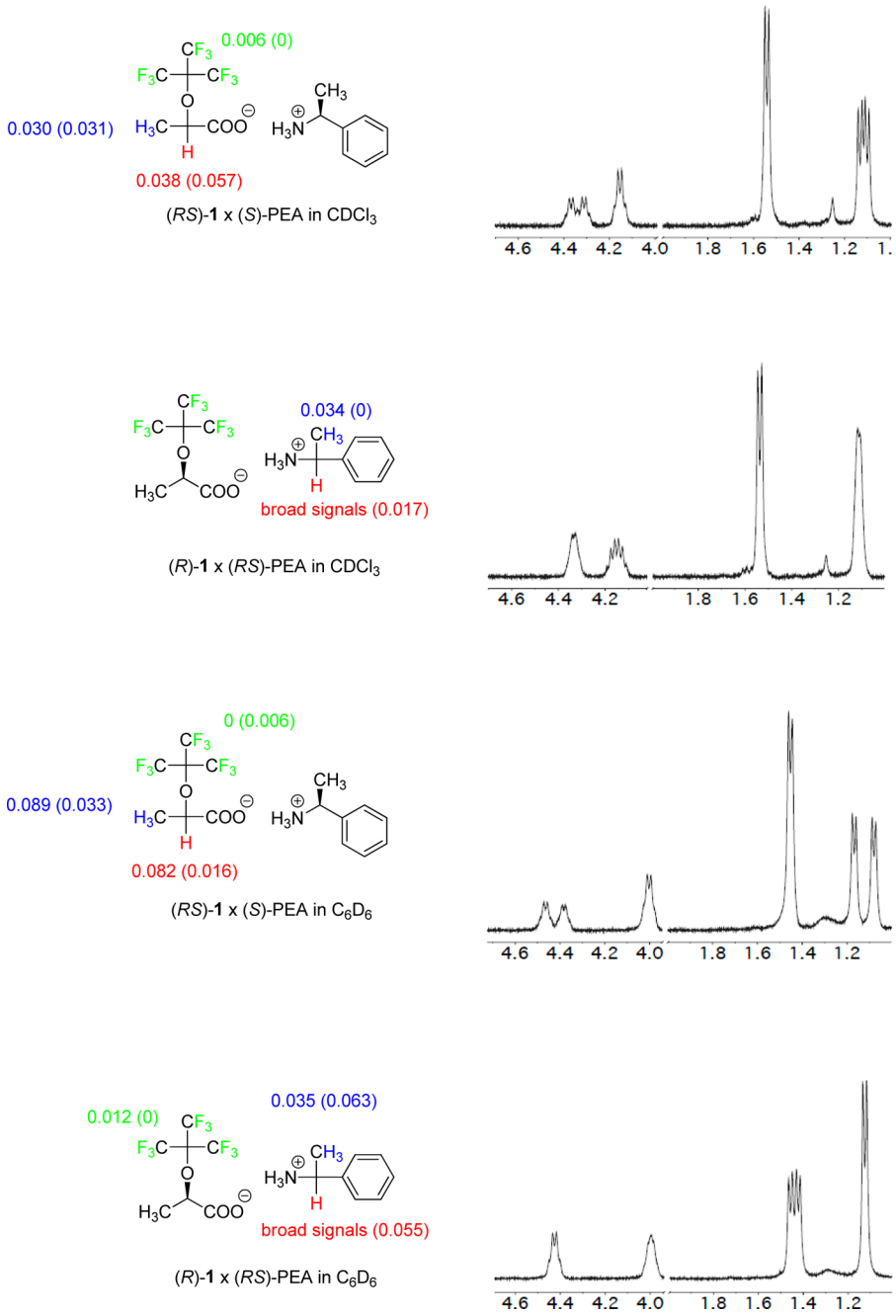

Figure 2. Chemical shift differences (blue, methyl protons; red, methine proton; green, fluorine atoms in ppm) and partial ^{1}H NMR spectra (400 MHz) for the diastereomeric salts of (*RS*)-**1** × (*S*)-PEA and (*R*)-**1** × (*RS*)-PEA in $CDCl_3$ and C_6D_6 when the concentration is 54 mM; data for 5 mM are given in brackets.

Figure 2. The measured $\Delta\delta$ of (*R*)-**1** × (*RS*)-PEA is 0.035 ppm for methyl protons; however, the frequencies of methine groups are not resolved at the 54 mM concentration due to solubility problems. In this case, applying a lower concentration results in the detection of signal separation; in a 5 mM solution, the chemical shift difference is 0.055 ppm for methine and 0.063 ppm for methyl protons. Even better chiral discrimination can be achieved using racemic fluorous acids. (*RS*)-**1** × (*S*)-PEA shows a 0.082 ppm difference for the methine and 0.089 ppm difference for methyl hydrogens.

*(RS)-**2** × (S)-PEA.* Chemical shift differences and partial ^{1}H NMR spectra for the salt of racemic mandelic acid derivative (*RS*)-**2** and optically active (*S*)-PEA are shown in Figure 3.

The signals in the ^{1}H NMR spectrum of (*RS*)-**2** × (*S*)-PEA, which belong to the methine protons of carboxylic acid **2**, appear as two sharp fully baseline separated singlets that do not overlap with other peaks (Figure 3). It is remarkable that this salt shows the highest $\Delta\delta$ = 0.130 ppm (at 5−5.3 ppm) in the $CDCl_3$ solvent, which is comparable to those reported for chiral derivatizing agents. The shifts of the resonances of this latter salt are much larger than those in the spectrum of fluorous lactic acid salt [(*RS*)-**1** × (*S*)-PEA], denoting a strong association between the ion pairs in the phenyl group-containing compound [(*RS*)-**2**]. This salt probably has a relatively rigid structure due to the phenyl group directly attached to the chiral center, resulting in a favorable π−π

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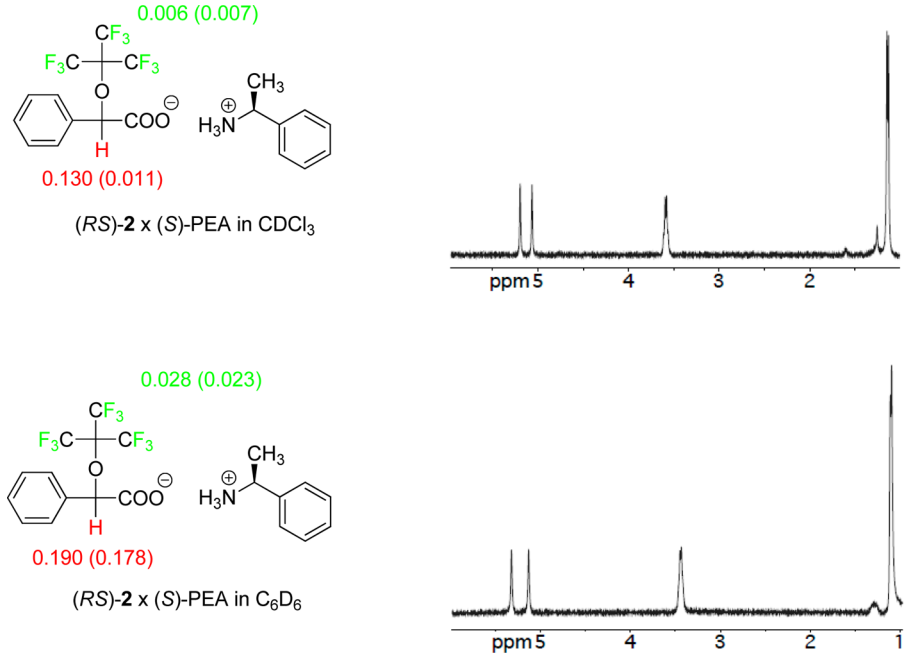

Figure 3. Chemical shift differences (red, methine proton; green, fluorine atoms in ppm) and partial ^{1}H NMR spectra (400 MHz) for the diastereomeric salt of (*RS*)-**2** × (*S*)-PEA in $CDCl_3$ and C_6D_6 when the concentration is 54 mM; data for 5 mM are given in brackets.

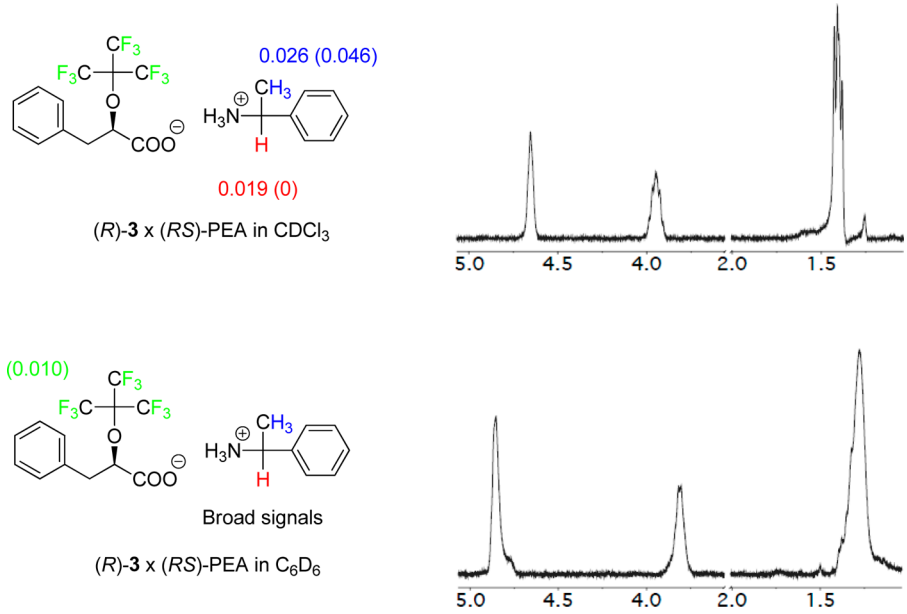

Figure 4. Chemical shift differences (blue, methyl protons; red, methine proton; green, fluorine atoms in ppm) and partial ^{1}H NMR spectra (400 MHz) for the diastereomeric salt of (*R*)-**3** × (*RS*)-PEA in $CDCl_3$ and C_6D_6 when the concentration is 54 mM; data for 5 mM are given in brackets.

interaction between the aromatic groups. As expected, the integral ratio of the two separated methine peaks of (*RS*)-**2** is 1:1, whereas it is 1:2 for the enantiomerically enriched (33% ee) compound (+)-**2**/(−)-**2**.

Similarly to $CDCl_3$, the highest $\Delta\delta$ = 0.190 ppm was detected in C_6D_6 for methine protons of (*RS*)-**2** × (*S*)-PEA. The signals of racemic fluorous carboxylic acids (*RS*)-**1** and (*RS*)-**2** show large chemical shift nonequivalences, which are comparable to the literature reported values for CDAs.

(R)-3 × (RS)-PEA. In the case of (*R*)-**3** × (*RS*)-PEA, $\Delta\delta$ is 0.019 for the methine protons of PEA and 0.026 ppm for methyl protons (Figure 4) when $CDCl_3$ was used as the solvent. It is worth noting that the spectra of this salt show broad, strongly overlapping signals, which can be attributed to the conformational flexibility of the formed diastereomeric complex. It should also be noted that when PEA is in its racemic form in the salts with (*R*)-**1** and (*R*)-**3**, the methyl protons show larger $\Delta\delta$ compared to the methine protons, although they are further from the chiral center. Unfortunately, the (*R*)-**3** × (*RS*)-PEA salt has low solubility in C_6D_6, resulting in broad signals; therefore, the diastereomers are not distinguishable.

^{19}F NMR measurements. ^{1}H is the most commonly used nuclei for ee determination by NMR spectroscopy because protons are present in almost all organic molecules, and it has the highest sensitivity. However, analytical protocols for ee

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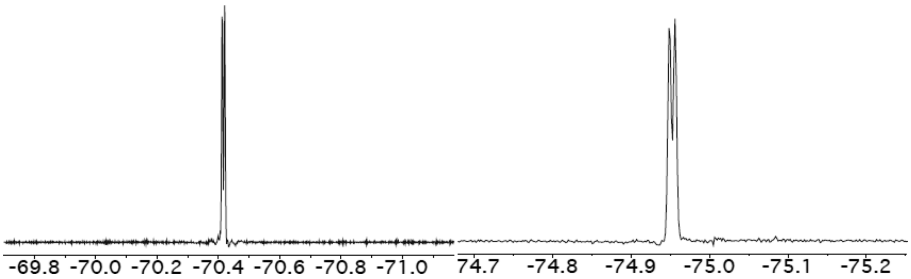

Figure 5. Partial ^{19}F NMR spectra (376.40 MHz) for the (*RS*)-**1** × (*S*)-PEA salt in $CDCl_3$ at 54 mM (left) and in C_6D_6 at 5 mM (right).

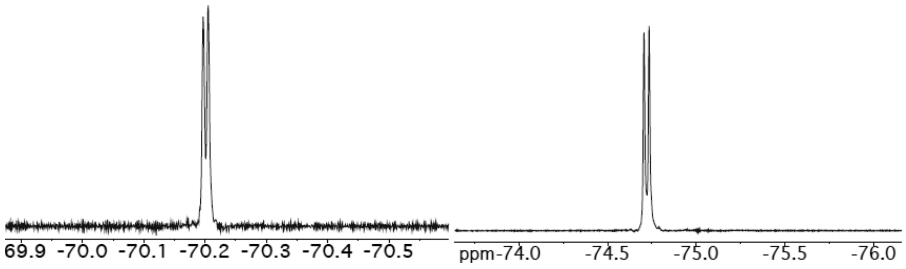

Figure 6. Partial ^{19}F NMR spectra (376.40 MHz) for the (*RS*)-**2** × (*S*)-PEA salt in $CDCl_3$ at 54 mM (left) and in C_6D_6 at 54 mM (right).

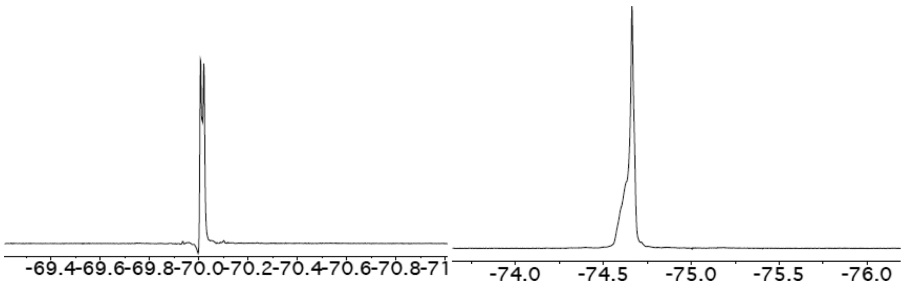

Figure 7. Partial ^{19}F NMR spectra (376.40 MHz) for the (*R*)-**3** × (*RS*)-PEA salt in $CDCl_3$ in 54 mM (left) and in C_6D_6 in 54 mM (right).

determination relying on ^{1}H NMR spectroscopy suffer from several disadvantages, namely, the narrow spectral window (low chemical shift dispersion in the range of 0−12 ppm) and the signal multiplicities due to ^{1}H−^{1}H coupling, which can inflict severe overlapping peaks. The range of fluorine chemical shifts and the sensitivity of ^{19}F NMR to emphasize the details of the local environment are higher than for ^{1}H NMR. At the same time, the singlet nature of the signals in standard ^{1}H decoupled experiments makes ^{19}F NMR a powerful alternative or complementary method to ^{1}H NMR, especially when studying pure compounds with crowded proton spectra or mixtures of compounds. Observing ^{19}F nuclei, the spectral overlap is eliminated by the wider chemical shift range of ^{19}F signals and by the absence of signal multiplicities in standard proton decoupled spectra.[18]

However, in our cases where the fluorine atoms are further from the stereogenic center, ^{19}F NMR spectra also indicate the difference between the diastereomeric salts above. These $\Delta\delta$ values are also demonstrated in Figures 2−4.

The detected ^{19}F chemical shift differences show strong correlation with the ^{1}H NMR results. Accordingly, considerable $\Delta\delta$s were also observed for both (*RS*)-**1** × (*S*)-PEA (0.006, 5 mM) and (*R*)-**1** × (*RS*)-PEA salts (0.012 ppm, 54 mM; Figure 2 and 5), and the best resolution of the resonances was observed in the case of the carboxylic acid (*RS*)-**2** × (*S*)-PEA in C_6D_6 at 54 mM concentration (0.028 ppm, Figures 3 and 6).

The complexes of the benzylic derivative (*R*)-**3** × (*RS*)-PEA are not distinguishable by ^{19}F NMR spectroscopy using routine conditions (Figures 4 and 7). However, measuring in a cold solution, conformational movements may be reduced, and thus, broad signals can be eliminated. Unfortunately, the low solubility of the above salts at lower temperatures hinders the application of this technique.

For further exploration of the potential use of (*RS*)-**1** and (*RS*)-**2** as chiral discriminating agents, we also tested their applicability with other known organic bases (1*R*,2*S*)-ephedrine (EPH) and (*S*)-dapoxetine [(*S*)-dpx] (Figure 8). Ephedrine is a

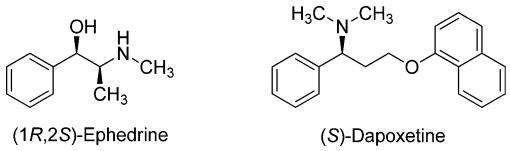

Figure 8. Structure of (1*R*,2*S*)-ephedrine and (*S*)-dapoxetine.

biologically active amine used as a drug with low toxicity for treating asthma.[19] It is available from a natural source in its chiral form. The (*S*)-enantiomer of dapoxetine is also a drug with a serotonine transporter inhibitory effect.[20,21]

Both amines have a complex structure; thus, their NMR spectra are more difficult to analyze than that of PEA. First, we recorded the ^{1}H NMR spectra of the diastereomeric complexes of ephedrine (EPH) as a potential CSA with the racemic acids

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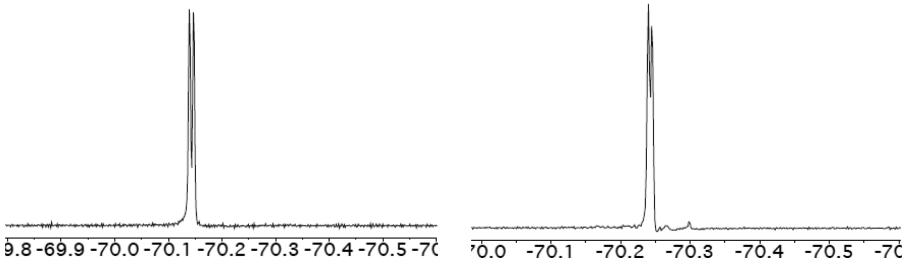

Figure 9. Partial ^{19}F NMR spectra (376.40 MHz) for the ephedrine salts in C_6D_6 at 5 mM; EPH × (*RS*)-**1** (left) and EPH × (*RS*)-**2** (right).

(*RS*)-**1** and (*RS*)-**2**; however, no chemical shift differences between the enantiomers were observed. Thus, we could not differentiate them by ^{1}H NMR. On the contrary, in their ^{19}F NMR spectra in 5 mM C_6D_6 solutions, we observed two singlets; thus, the diastereomeric salts formed became distinguishable under these conditions. The $\Delta\delta$ in (*RS*)-**1** × EPH and (*RS*)-**2** × EPH are 0.008 and 0.010 ppm, respectively (Figure 9). To prove the effective chiral recognition ability of (*RS*)-**2**, we also tested it with optically active dapoxetine using C_6D_6 as the solvent. The ^{19}F NMR spectrum shows two singlet signals for the enantiomers with 0.014 ppm chemical shift difference (Figure 10).

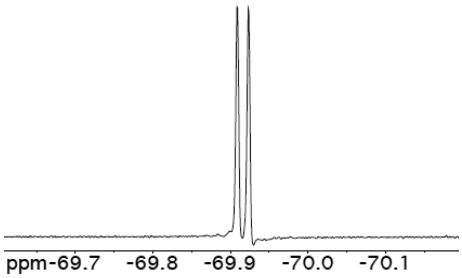

Figure 10. Partial ^{19}F NMR spectra (376.40 MHz) for the (*S*)-dapoxetine salt (*S*)-Dpx × (*RS*)-**2** in C_6D_6 at 5 mM.

ECD Measurements. As a part of our studies, we investigated the complex formation of (*R*)-**1**, (*RS*)-**2**, and (*R*)-**3** by far-UV ECD spectroscopy (190−250 nm). First, we recorded the ECD spectra of (*R*)-**1** and (*R*)-**3**, and their complexes, with (*R*)- and (*S*)-PEA. The spectrum of the lactic acid derivative (*R*)-**1** has a broad negative band in both acetonitrile and isooctane (Figure 11), and its 1:1 complex with one of the enantiomers of PEA shows only a very weak effect in this region (data not shown).

In the case of the aromatic (*R*)-**3**, the spectrum is more intensive. The explanation of the ECD spectra of the benzene chromophore is well-known and has been discussed in detail.[22] Thus, we can conclude that in this region the bands near 197 and 220 nm correspond to the ^1B_b and ^1L_a transitions, respectively, of the benzene chromophore (Figure 11).

The complex formation of the phenyllactic acid derivative (*R*)-**3** with the enantiomers of PEA is more effective in isooctane than in acetonitrile; thus, we discuss these results in the former solvent (Figure 12).

By using difference spectra [$\Delta(\Delta\varepsilon) = \Delta\varepsilon_{comp} - (\Delta\varepsilon_{(R)\text{-}3} + \Delta\varepsilon_{PEA})$], we are able to compare the discriminating efficiency. Figure 12b clearly shows that the spectra of the complexes are not only a simple sum of the enantiomers of **3** and PEA but also that there is an interaction between them. This effect is located in the region of the ^1L_a transition (205−222 nm) rather than ^1B_b. These results are in correlation with the data received from NMR measurements (c.f., Figures 6 and 9).

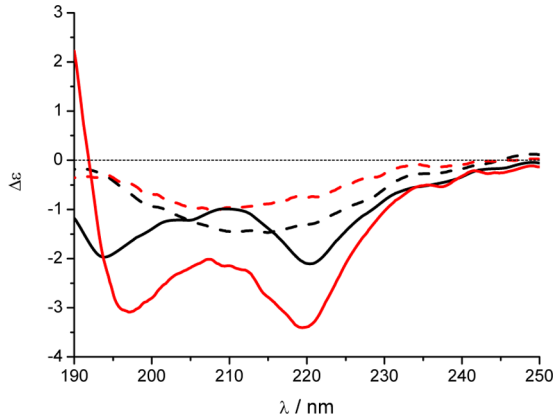

Figure 11. Far-UV ECD spectra of (*R*)-**1** (dash) and (*R*)-**3** (solid) in acetonitrile (black) and isooctane (red).

Figure 13 shows the recorded ECD spectra of the racemic mandelic acid derivative (*RS*)-**2** with (*S*)-PEA [i.e., the sum of (*R*)-**2** × (*S*)-PEA and (*S*)-**2** × (*S*)-PEA] and (*R*)-PEA [i.e., the sum of (*R*)-**2** × (*R*)-PEA and (*S*)-**2** × (*R*)-PEA], (*S*)- and (*R*)-PEA are also indicated. As can be seen, the 1:1 complexes with the enantiomers of PEA show mirror image ECD spectra. The change of intensity and the shape of the curves indicate interactions between the racemic fluorous acid and the enantiomers of PEA.

■ CONCLUSION

α-(Nonafluoro-*tert*-butoxy)carboxylic acids **1**−**3** show chiral recognition ability toward chiral amines in apolar solvents. Thus, using optically active **1**−**3** as CSAs for simple determination of enantiomeric excess (ee) of chiral amines can be achieved by NMR spectroscopy. This method is fast, accurate, and requires only small amounts of sample and reagent. The analysis of the enantiomeric ratio can be executed within a short period of time with the sample used for the identification of the product by just adding the optically active carboxylic acid as the CSA. Thus, observing the chemical shift difference of the protons close to the chiral centers in the diastereomeric salts by ^{1}H NMR spectroscopy is feasible. The measured $\Delta\delta$s for the methine protons are 0.017−0.190 ppm, which are values comparable to the values of known chiral derivatizing and solvating agents.[3] Concurrently, these fluorous carboxylic acids contain nine chemically equivalent fluorine atoms, which have only one strong singlet in ^{19}F NMR. Because these fluorine atoms are extremely sensitive toward their chemical environment, ^{19}F NMR spectroscopy offers great potential for determining the ee of the samples bearing complex ^{1}H NMR spectra. The measured ^{19}F NMR chemical shift

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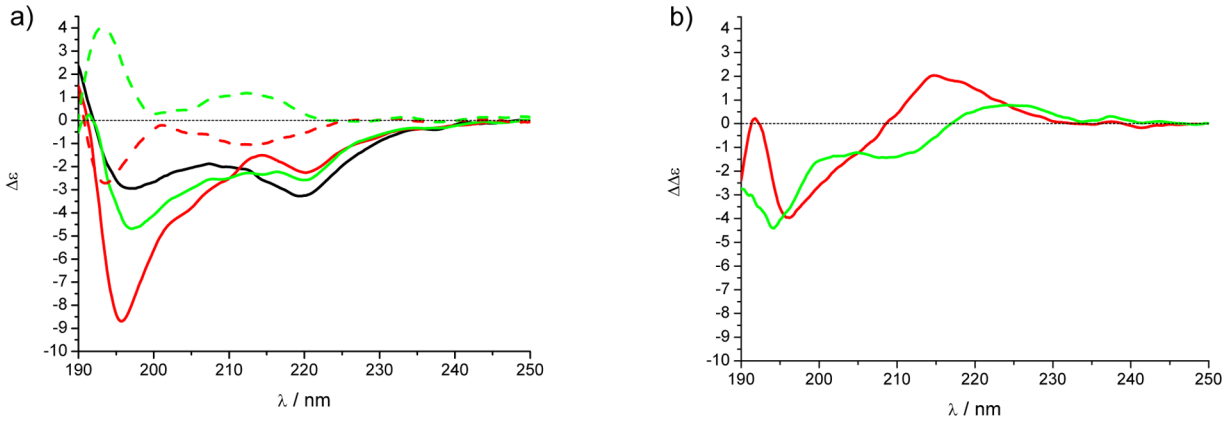

Figure 12. (a) Far-UV ECD spectra of heterochiral (green solid) and homochiral (red solid) 1:1 complexes of (*R*)-**3** (black) with (*S*)-PEA (green dash) and (*R*)-PEA (red dash) in isooctane. (b) Difference spectra of the complexes, $\Delta(\Delta\varepsilon) = \Delta\varepsilon_{comp} - (\Delta\varepsilon_{(R)\text{-}3} + \Delta\varepsilon_{PEA})$ for (*R*)-**3** and (*R*)-PEA (red curve), and (*R*)-**3** and (*S*)-PEA (green curve).

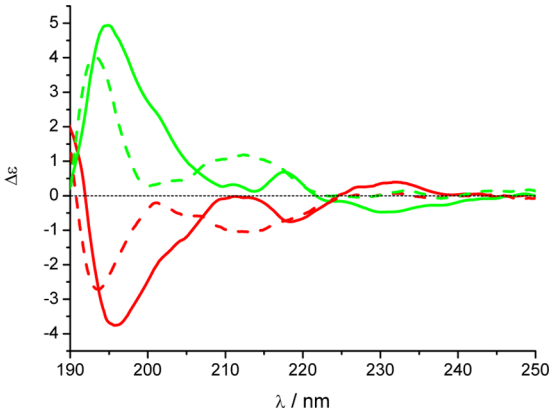

Figure 13. Far-UV ECD spectra of the complexes of (*RS*)-**2** × (*S*)-PEA (green solid), (*RS*)-**2** × (*R*)-PEA (red solid), (*S*)-PEA (green dash), and (*R*)-PEA (red dash) in isooctane.

differences were 0.006−0.028 ppm, which are values comparable to those of known chiral solvating agents.[6] In addition, **1**−**3** were tested using (1*R*,2*S*)-ephedrine and (*S*)-dapoxetine as amines. Employing (*RS*)-**2** as an acidic component, both diastereomeric salts show significant ^{19}F NMR chemical shift differences of 0.010 and 0.014 ppm in C_6D_6. Therefore, optically active *α*-(nonafluoro-*tert*-butoxy)carboxylic acids **1**−**3** are promising CSAs in both ^{1}H and ^{19}F NMR spectroscopy.

■ EXPERIMENTAL SECTION

Resolution Experiments. *Resolution of (RS)-2-Phenyl-2-[1,1-bis(trifluoromethyl)-2,2,2-trifluoroethoxy]acetic Acid [(±)-**2**].* To a solution of (±)-**2** (1.00 g, 2.7 mmol) in 0.1 M NaOH (27 mL) was added a solution of (*S*)-PEA (0.164 g, 1.35 mmol) in 1 M HCl (1.35 mL) at 90 °C. The mixture was allowed to stand overnight at rt and filtered to give the diastereomeric salt with (−) rotation {0.75 g, mp 110−135 °C, $[\alpha]_{578}$ −17° (*c* 0.5, DMF)}. To liberate acid (−)-**2**, 130 mg of the latter salt was suspended in 1 M HCl (pH ∼2), and the resulting white precipitate was filtered and dried over P_2O_5 to yield acid (−)-**2** {50 mg; mp 104−106 °C, $[\alpha]_{578}$ −24° (*c* 0.5, methanol)}.

The clear aqueous filtrate of the (+) salt was acidified with 1 M HCl to pH ∼2, and precipitated acid (+)-**1** was filtered off and dried to give partially resolved acid (+)-**1** {180 mg; mp 104.5−108 °C, $[\alpha]_{578}$ +14° (*c* 0.5, methanol)}.

NMR Experiments. NMR sample solutions were made as follows: 0.027 mmol carboxylic acid was dissolved in 600 μL of deuterated solvent. After ^{1}H and ^{19}F NMR measurements, 0.014, 0.027, 0.040, and 0.054 mmol amine were added, and the NMR spectra were measured using deuterated solvent $CDCl_3$ and C_6D_6. All measurements were carried out at 298 K.

ECD Experiments. ECD spectra were recorded at room temperature using a 0.1 cm cell for measurements between 190 and 250 nm. Acetonitrile and 2,2,4-trimethylpentane (isooctane) were used as solvents, and the concentration was 25 μM.

■ ASSOCIATED CONTENT

Supporting Information

Two-dimensional NMR spectra for **1**, **2**, and **3**, and characterization data for diastereomeric salts. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00706.

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Notes

The authors declare no competing financial interest.

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