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Article

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Chiral recognition studies of α-(nonafluoro-*tert*-butoxy)carboxylic acids by NMR spectroscopy

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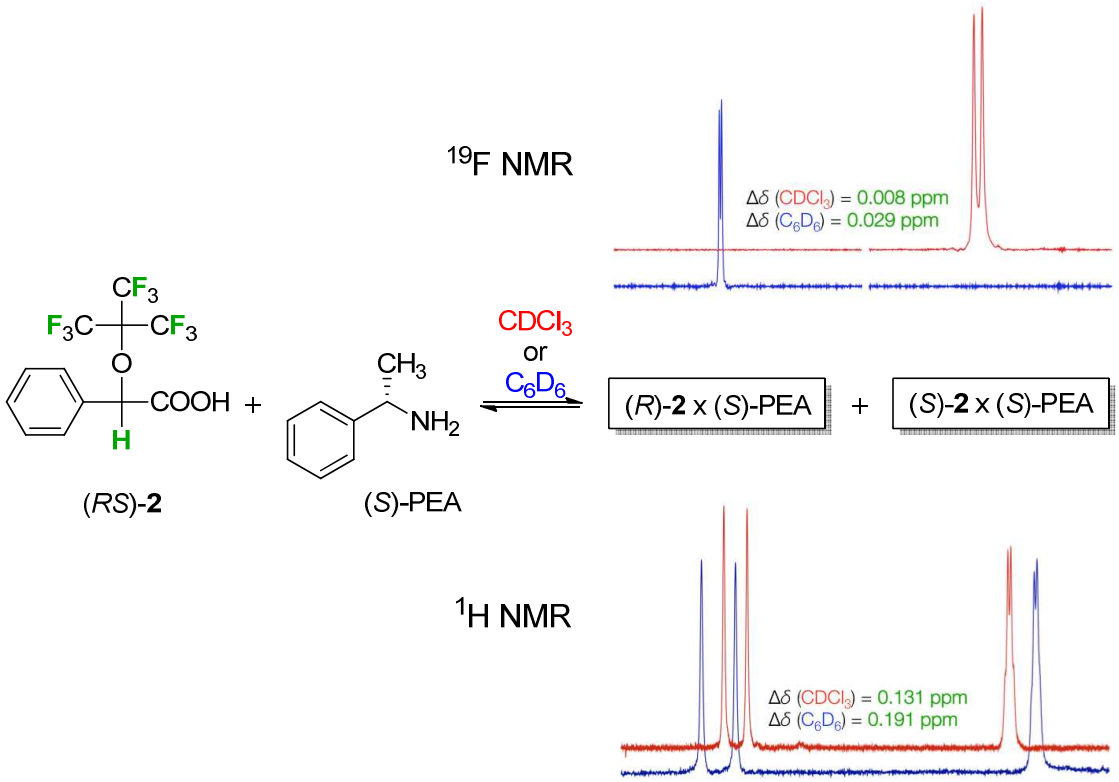


Abstract

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 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 5mM 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 to determine enantiomeric excess (*ee*) of chiral organic compounds.[1,2] With the application of CSAs, there is no need to modify covalently the analyte before the examination because there are only secondary interactions between the molecules in the solution (such as Coulombic and π-π interaction, hydrogen bonding). The formed diastereomeric complexes 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 atom or trifluoromethyl group.[5,6,7,8] The determination of *ee* with these fluorine-containing reagents is advantageous by ^{19}F NMR spectroscopy, since ^{19}F nuclei has 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.[9,10,11] Previously we reported the synthesis of three α-(nonafluoro-*tert*-butoxy)carboxylic acids, two of them in optically active form [(*R*)-**1**, (*RS*)-**2**, (*R*)-**3**] (Figure 1.).[12]

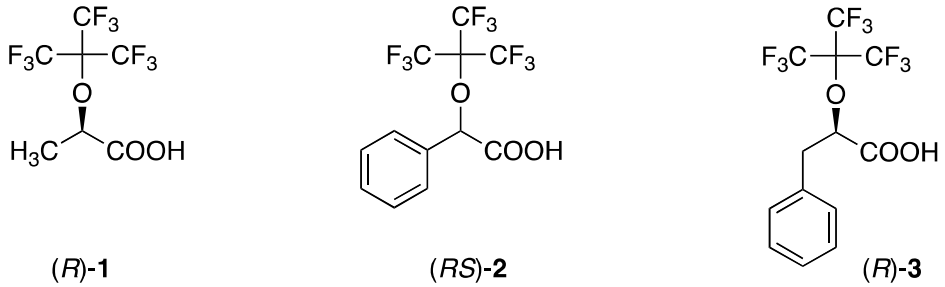


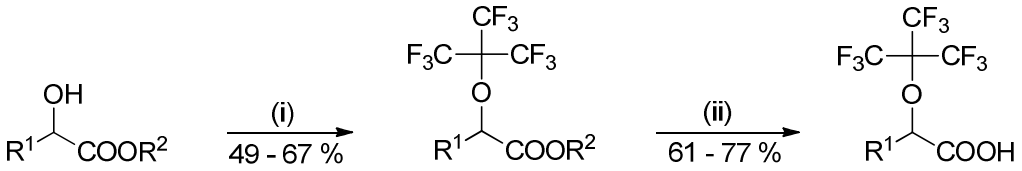
Figure 1. α-(Nonafluoro-*tert*-butoxy)carboxylic acids

The structural properties of these carboxylic acids are highly beneficial for their application as chiral solvating agents. They contain (i) an acidic functional group which 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, (iii) and in the case of (*RS*)-**2** and (*R*)-**3** an aromatic ring, which also helps to fix a stable conformation by π-π interaction. 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 above α-(nonafluoro-*tert*-butoxy)carboxylic acids.

Results and Discussion

Synthesis

The synthesis of α-(nonafluoro-*tert*-butoxy)carboxylic acids **1-3** was described in our preliminary work in detail.[12] It is worthy to note that, as expected, the stereospecific synthesis of caboxylic acids **1** and **3** resulted in the corresponding enantiomers, but similar methods yielded racemic product in the case of **2** (Scheme 1).

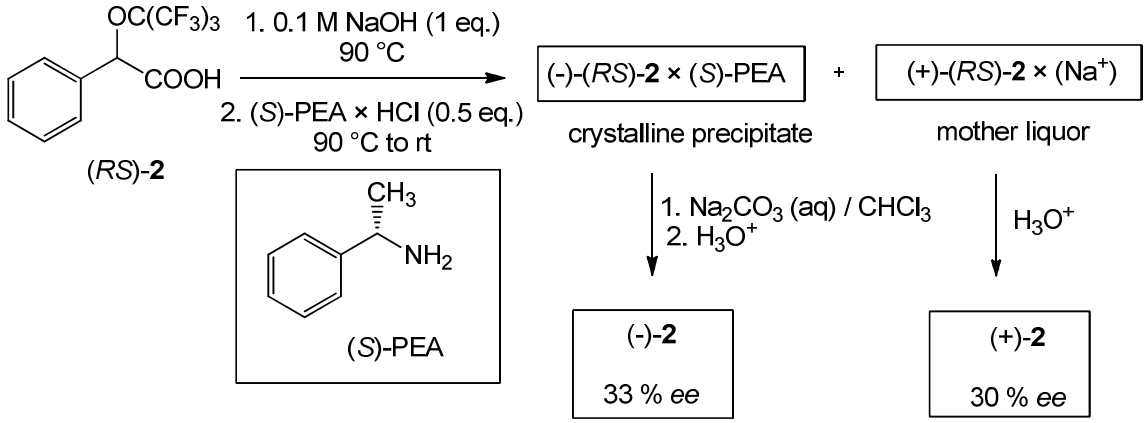


(*S*)-**4** : $R^1 = CH_3$, $R^2 = CH_2CH_3$ (*R*)-**7** : $R^1 = CH_3$, $R^2 = CH_2CH_3$ (*R*)-**1** : $R^1 = CH_3$
(*S*)-**5** : $R^1 = Ph$, $R^2 = CH_3$ (*RS*)-**8** : $R^1 = Ph$, $R^2 = CH_3$ (*RS*)-**2** : $R^1 = Ph$
(*S*)-**6** : $R^1 = Bn$, $R^2 = CH_3$ (*R*)-**9** : $R^1 = Bn$, $R^2 = CH_3$ (*R*)-**3** : $R^1 = Bn$

(i) : $(CF_3)_3COH$, DIAD, PPh_3, 0 °C to rt, Et_2O, 24 h
(ii) : NaOH, MeOH - CH_2Cl_2, rt, 24 h then HCl (aq)

Scheme 1. Syntheses of α-(nonafluoro-*tert*-butoxy)carboxylic acids 1-3

Because the application of **2** as 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 half equivalent of organic base (*S*)-phenylethylamine [(*S*)-PEA] as resolving agent in warm aqueous media (see Scheme 2). To one equivalent of racemic **2** one equivalent of NaOH and half equivalent of (*S*)-PEA × HCl were added. One of the diastereomeric salt separated in 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.



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

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 formed diastereomers are strictly fixed. Here, the typical difference of the chemical shifts in the two diastereomers is approximately 0.1 – 0.2 ppm in ^{1}H NMR and 0.3 – 0.7 ppm in ^{19}F NMR, respectively.[3,4] The second approach is using 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 (ii) the relative value of diastereomeric complex formation constants K_{RS} and $K_{SS,}$ i.e., the strength of interactions between the ion pairs, which depends primarily on the nature of the functional groups for a given molecule. Using this method have an advantage of

"easy" performance, by simply adding the reagent to a chiral compound in a small amount of deuterated solvent.

In our experiments the 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]

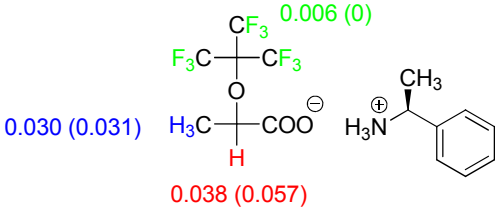
In these cases the recorded chemical shifts of the diastereomeric complexes are weighted averages of chemical shifts of the distinct protonation forms of the free and the protonated amine, according to their relative amounts. The integrals of the signals in ^{1}H and ^{19}F NMR spectra are proportional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

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 posses a great advantage. To enhance the ion pair formation between the CSA and the analyte, i.e. the differences in the chemical shifts between the diastereomers, the slightly polar $CDCl_3$ and the apolar C_6D_6 were used as solvents. Our preliminary experiments on the effect of acid : amine molar ratio revealed, that 1:1 stoichiometry provides the highest Δδ, thus this 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

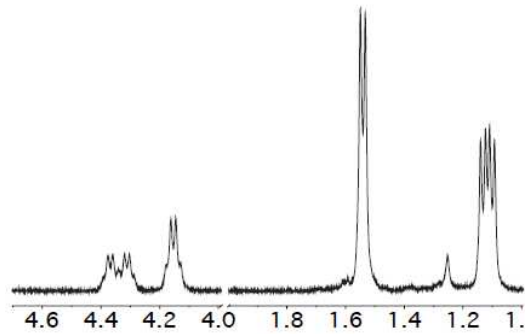
are summarized in Figure 2-4, where the differences in the chemical shifts (Δδ) and partial ^{1}H NMR spectra are given.

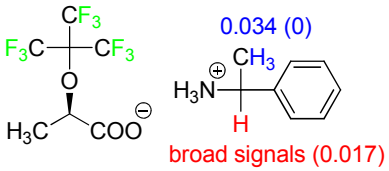
*(RS)-**1** × (S)-PEA and (R)-**1** × (RS)-PEA*

The racemic (*RS*)-**1** was analyzed with enantiopure (*S*)-PEA, while 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 concentration, using $CDCl_3$ as solvent. The diastereomeric salts formed between (*RS*)-**1** and (*S*)-PEA have chemical shift differences (Δδ) 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 CSA.[6,17] The signals of (*R*)-**1** × (*RS*)-PEA salt show broad signals for the 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 not baseline resolution was observed due to the multiplet resonances.

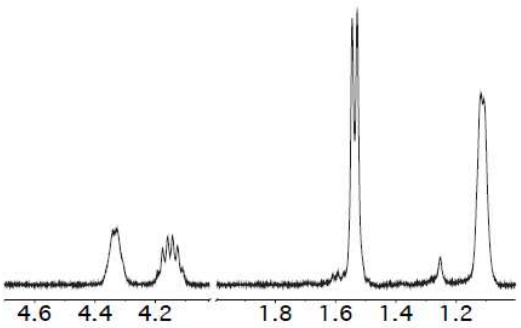


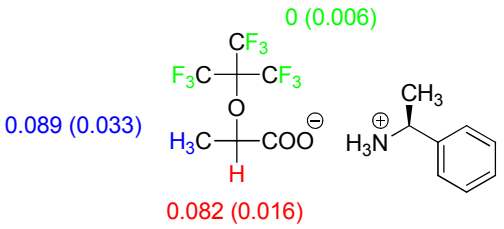
(*RS*)-**1** x (*S*)-PEA in $CDCl_3$



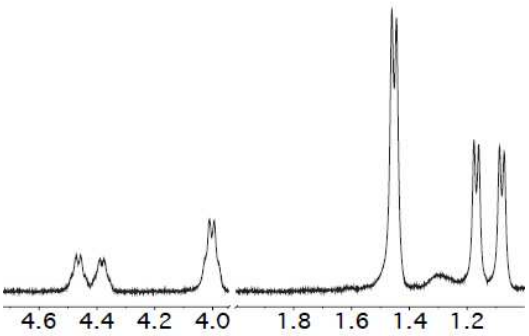


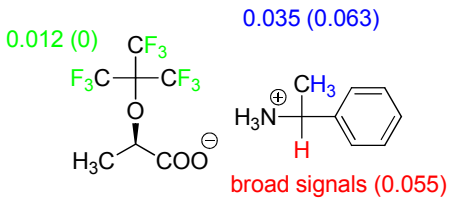
(*R*)-**1** x (*RS*)-PEA in $CDCl_3$





(*RS*)-**1** x (*S*)-PEA in C_6D_6





(*R*)-**1** x (*RS*)-PEA in C_6D_6

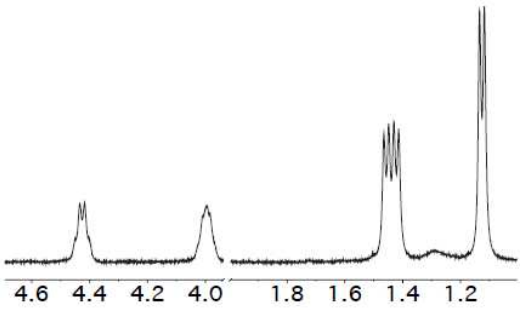


Figure 2. Chemical shift differences (blue: methyl protons, red: methine proton, green: fluorine atoms in ppm) and partial ^{1}H NMR spectra (400 MHz) for the diastereomeric salts of (*RS*)-1 × (*S*)-PEA and (*R*)-1 × (*RS*)-PEA in $CDCl_3$ and C_6D_6 when the concentration is 54 mM, data for 5 mM are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

In our second set of experiments C_6D_6 was used as solvent. In this case the 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 shown also in Figure 2. The measured Δδ of (*R*)-**1** × (*RS*)-PEA is 0.035 ppm for methyl protons, however the frequencies of methine group are not resolved in 54 mM concentration due to solubility problems. In this case applying lower concentration the signal separation is detectable; in 5mM solution the chemical shift difference is 0.055 ppm for the methine and 0.063 ppm for methyl protons. Even better chiral discrimination can be achieved using racemic fluorous acids. (*RS*)-**1** × (*S*)-PEA shows 0.082 ppm difference for the methine and 0.089 ppm 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.

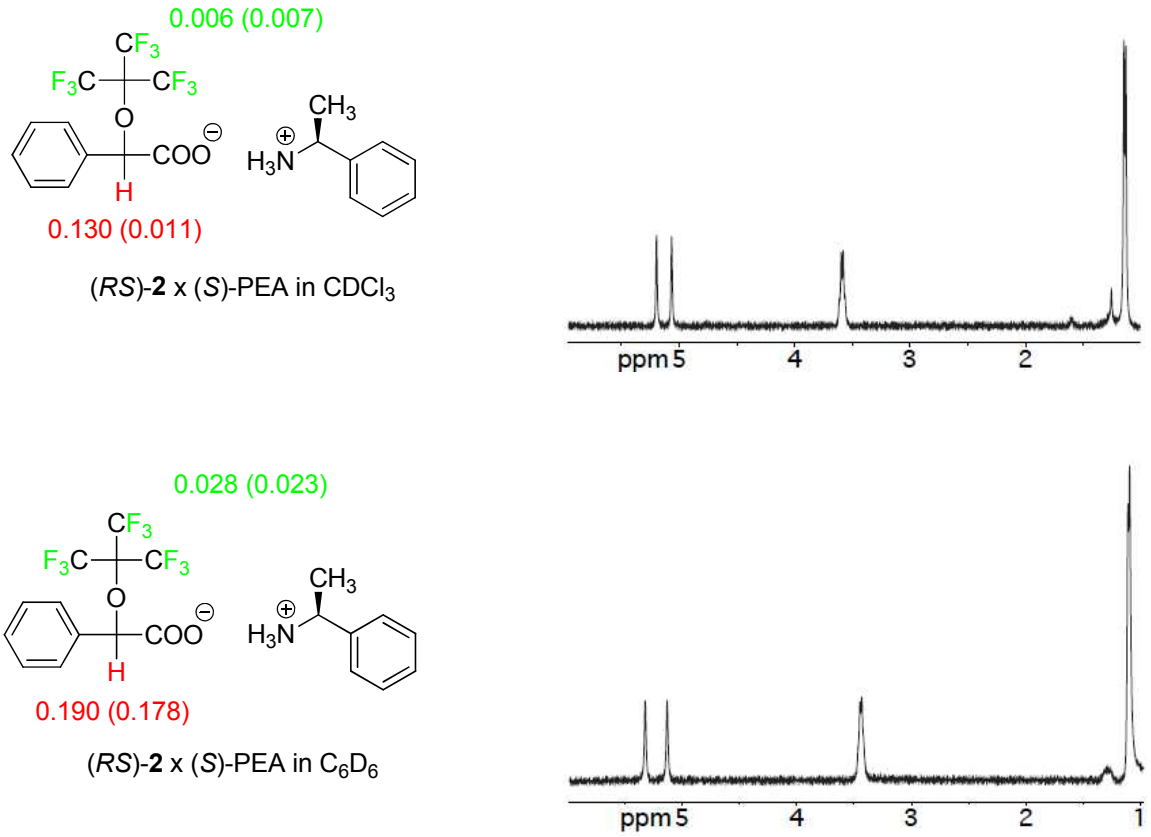


Figure 3. Chemical shift differences (red: methine proton, green: fluorine atoms in ppm) and partial ^{1}H NMR spectra (400 MHz) for the diastereomeric salt of (*RS*)-2 × (*S*)-PEA in $CDCl_3$ and C_6D_6 when the concentration is 54 mM, data for 5 mM are given in brackets

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 which 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 $CDCl_3$ 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 directly attached phenyl group to the chiral center resulting in a favorable π-π interaction between the aromatic groups. As expected, the integral ratio of the two separated methine peaks of (*RS*)-**2** is 1 : 1-while 1 : 2 for the enantiomerically enriched (33 % *ee*) compound (+)-**2**/(-)-**2**.

Similarly to $CDCl_3$ the highest Δδ=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 non-equivalence, which are comparable to the literature reported values for CDAs.

*(R)-**3** × (RS)-PEA*

In the case of (*R*)-**3** × (*RS*)-PEA Δδ of the methine protons of PEA is 0.019 ppm and 0.026 ppm for methyl protons (Figure 4) when $CDCl_3$ was used as solvent. It is worthy to note 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 racemic form in the salts with (*R*)-**1** and (*R*)-**3**, the methyl protons show larger Δδ, 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.

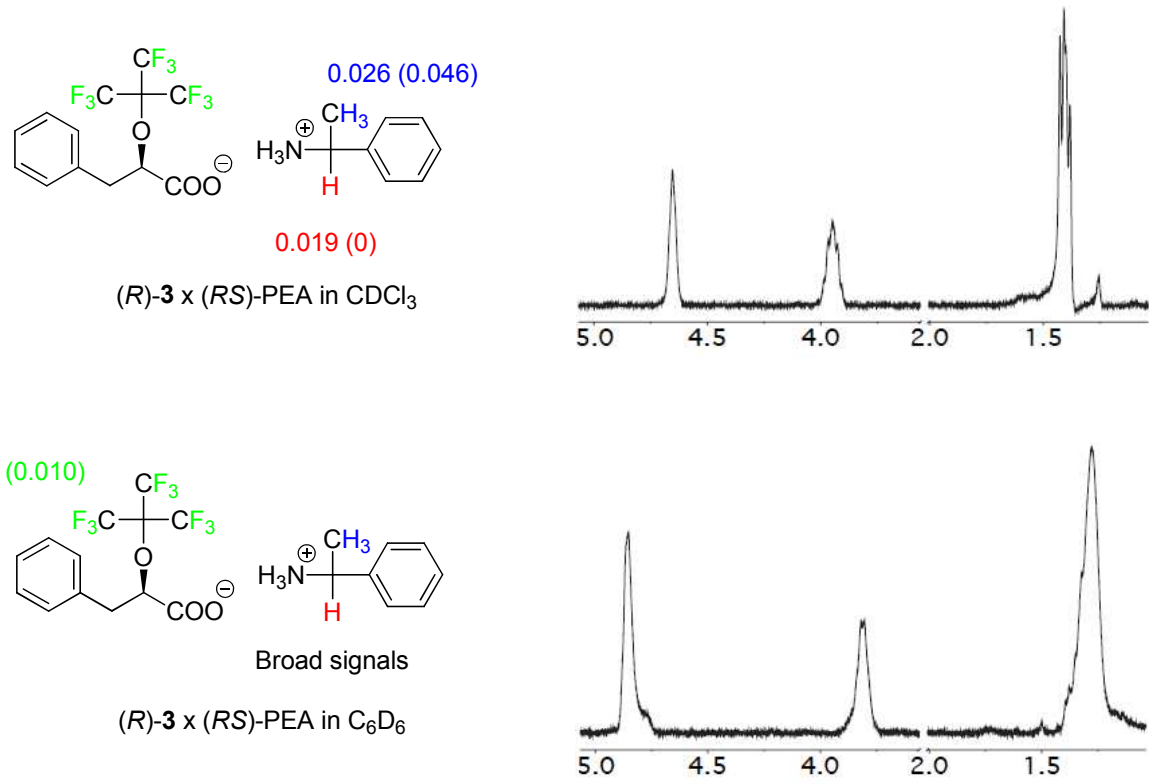


Figure 4. Chemical shift differences (blue: methyl protons, red: methine proton, green: fluorine atoms in ppm) and partial ^{1}H NMR spectra (400 MHz) for the diastereomeric salt of (*R*)-3 × (*RS*)-PEA in $CDCl_3$ and C_6D_6 when the concentration is 54 mM, data for 5 mM are given in brackets

^{19}F NMR measurements

^{1}H is the most commonly used nuclei for *ee* determination by NMR spectroscopy, since protons are present in almost all organic molecules and it has the highest sensitivity. However, analytical protocols for *ee* 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 to 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 ^{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 complement method to ^{1}H NMR, especially when studying pure compounds with crowded proton spectra or mixtures of compounds. Observing ^{19}F nuclei the spectra overlap is eliminated by the wider chemical shift range of ^{19}F signals and to the absence of signal multiplicities in standard proton decoupled spectra.[18]

Although in our cases fluorine atoms are further from the stereogenic center, ^{19}F NMR spectra also indicate the difference between the above diastereomeric salts. These Δδ values are also demonstrated in Figure 2-4.

The detected ^{19}F chemical shift differences show strong correlation with the ^{1}H NMR results. Accordingly, considerable Δδs were observed also 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), while the best resolution of the resonances was observed in the case of the carboxylic acid (*RS*)-**2** × (*S*)-PEA in C_6D_6 in 54 mM concentration (0.028 ppm, Figure 3 and 6).

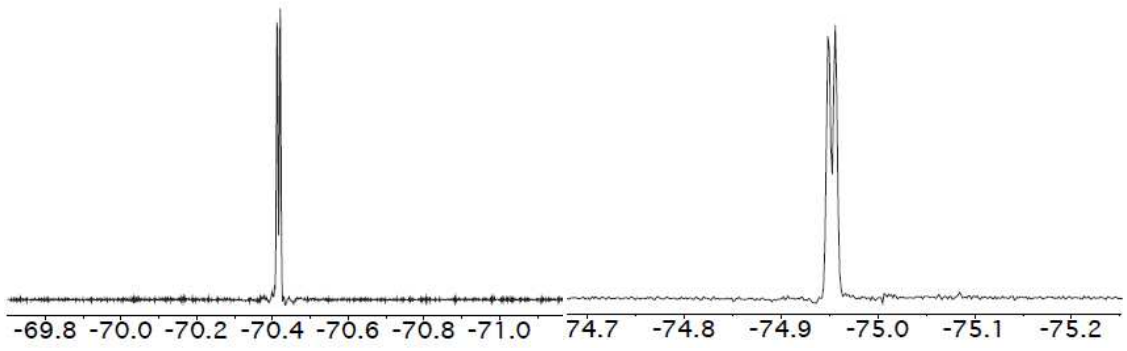


Figure 5. Partial ^{19}F NMR spectra (376.40 MHz) for the (*RS*)-1 × (*S*)-PEA salt in $CDCl_3$ in 54 mM (left) and in C_6D_6 in 5 mM (right)

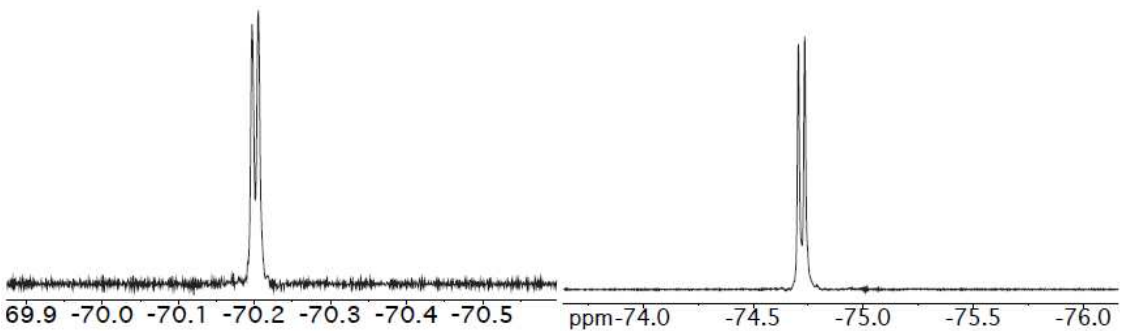


Figure 6. Partial ^{19}F NMR spectra (376.40 MHz) for the (*RS*)-2 × (*S*)-PEA salt in $CDCl_3$ in 54 mM (left) and in C_6D_6 in 54 mM (right)

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

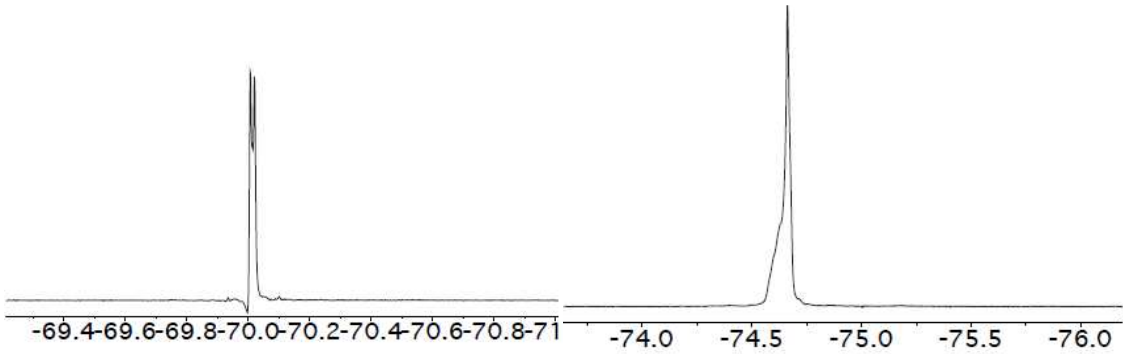
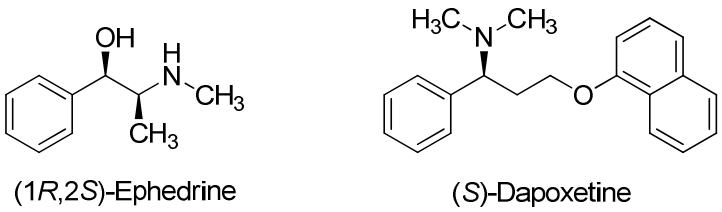


Figure 7. Partial ^{19}F NMR spectra (376.40 MHz) for the (*R*)-3 × (*RS*)-PEA salt in $CDCl_3$ in 54 mM (left) and in C_6D_6 in 54 mM (right)

For further exploration of the potential use of (*RS*)-**1** and (*RS*)-**2** as chiral discriminating agents we tested their applicability also with other known organic bases (1*R*,2*S*)-ephedrine (EPH) and (*S*)-dapoxetine [(*S*)-Dpx] (Figure 8). Ephedrine is a biologically active amine used as a drug of low toxicity for treating asthma.[19] It is available from

natural source in chiral form. The (*S*)-enantiomer of dapoxetine is also a drug with serotonine transporter inhibitory effect.[20,21]



(1*R*,2*S*)-Ephedrine (*S*)-Dapoxetine

Figure 8. Structure of (1*R*,2*S*)-Ephedrine and (*S*)-Dapoxetine

Both amines have 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 (*RS*)-**1** and (*RS*)-**2,** but no chemical shift differences between the enantiomers were observed, thus we could not differentiate them by ^{1}H NMR. In contrary, in their ^{19}F NMR spectra in 5 mM C_6D_6 solutions we observed two singlets, thus the diastereomeric salts formed become distinguishable under this condition. The Δδ in (*RS*)-**1** × EPH and (*RS*)-**2** × EPH are 0.008 ppm and 0.010 ppm, respectively (Figure 9). In order to prove the effective chiral recognition ability of (*RS*)-**2**, we tested it also with optically active dapoxetine using C_6D_6 as solvent. The ^{19}F NMR spectrum shows two singlet signals for the enantiomers with 0.014 ppm chemical shift difference (Figure 10).

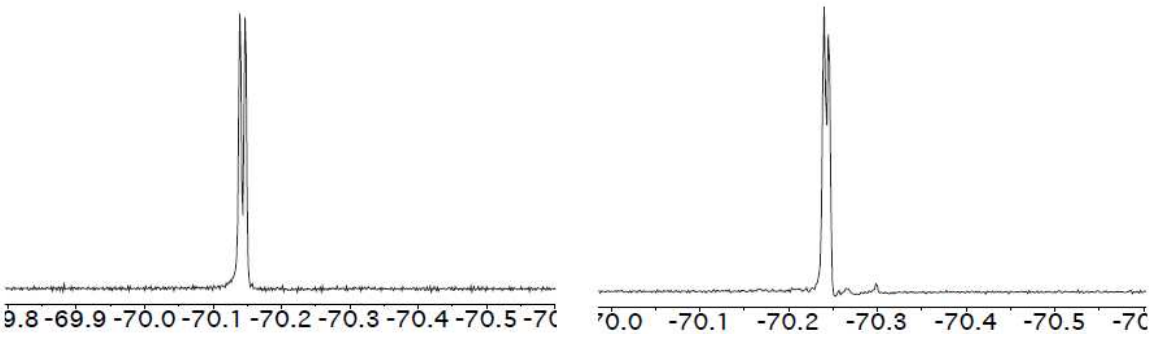


Figure 9. Partial ^{19}F NMR spectra (376.40 MHz) for the ephedrine salts in C_6D_6 in 5 mM; EPH × (*RS*)-1 (left) and EPH × (*RS*)-2 (right)

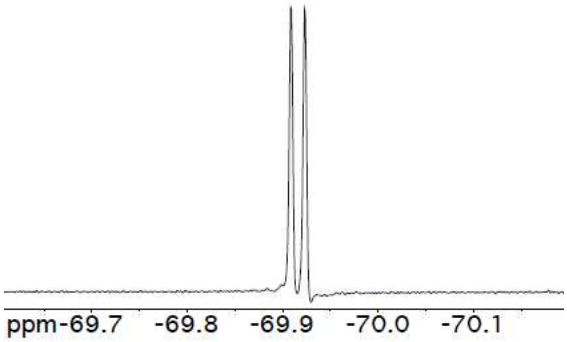


Figure 10. Partial ^{19}F NMR spectra (376.40 MHz) for the (*S*)-dapoxetine salt (*S*)-Dpx × (*RS*)-2 in C_6D_6 in 5 mM

ECD measurements

As a part of our above 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 show 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 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 of the benzene chromophore, respectively (Figure 11).

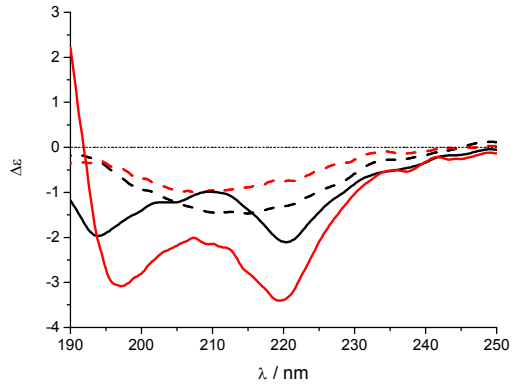


Figure 11. Far-UV ECD spectra of (*R*)-1 (dash) and (*R*)-3 (solid) in acetonitrile (black) and *iso*-octane (red)

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

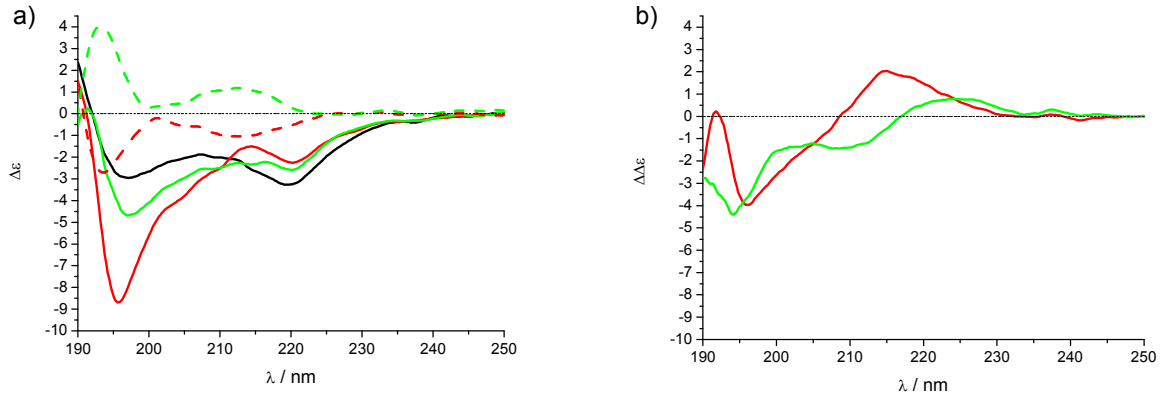


Figure 12. a) Far-UV ECD spectra of heterochiral (green solid) and homochiral (red solid) 1:1 complexes of (*R*)-3 (black) with (*S*)-PEA (green dash) and (*R*)-PEA (red dash) in isooctane. b) Difference spectra of the complexes, $\Delta(\Delta\varepsilon)=\Delta\varepsilon_{comp} - (\Delta\varepsilon_{(R)\text{-}3}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

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 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 correlations with the data received from NMR measurements (cf. Figure 6 and 9).

Figure 13 shows the recorded ECD spectra of the racemic mandelic acid derivative (*RS*)-**2** with (*S*)-PEA [ie. the sum of (*R*)-**2** × (*S*)-PEA and (*S*)-**2** × (*S*)-PEA] and (*R*)-PEA [ie. 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 curves indicates interactions between the racemic fluorous acid and the enantiomers of PEA.

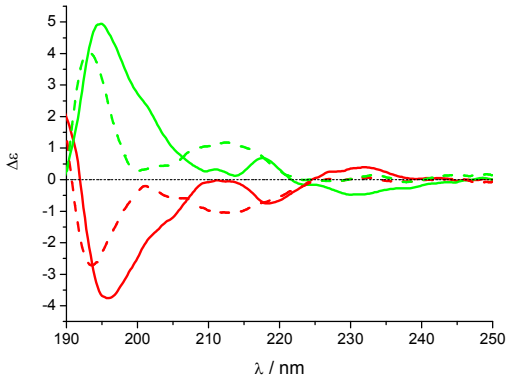


Figure 13. Far-UV ECD spectra of the complexes of (*RS*)-2 × (*S*)-PEA (green solid) and (*RS*)-2 × (*R*)-PEA (red solid) and (*S*)-PEA (green dash) and (*R*)-PEA (red dash) in isooctane

Conclusion

α-(Nonafluoro-*tert*-butoxy)carboxylic acids (**1**-**3**) show chiral recognition ability towards chiral amines in apolar solvents. Thus using optically active **1**-**3** as CSA a 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 time with the sample used for the identification of the product, just adding the optically active carboxylic acid as CSA. Observing the chemical shift difference of the protons close to the chiral centers in the diastereomeric salts by ^{1}H NMR spectroscopy was feasible. The measured Δδs for the methine protons are 0.017–0.190 ppm which values are comparable to those of the 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. Since these fluorine atoms are extremely sensitive towards their chemical environment, ^{19}F NMR spectroscopy offers great potential to determine *ee* of samples bearing complex ^{1}H NMR spectra. The measured ^{19}F NMR chemical shift differences were 0.006-0.028 ppm which values are also 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 acidic component both diastereomeric salts show significant ^{19}F NMR chemical shift differences 0.010 and 0.014 ppm in C_6D_6. Therefore, optically active α-(nonafluoro-*tert*-butoxy)carboxylic acids **1**-**3** are promising CSAs both in ^{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 the solution of (±)-**2** (1.00 g, 2.7 mmol) in 0.1 M NaOH (27 ml) was added the solution of (*S*)-PEA (0.164 g, 1.35 mmol) in 1 M HCl (1.35 ml) at 90 ºC. The mixture was allowed to stand for a night 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 the acid (-)-**2** 130 mg of the latter salt was suspended in 1 M HCl (pH ~ 2), the resulting white precipitate was filtered and dried over P_2O_5 to yield acid (-)-**2** {50 mg; $[\alpha]_{578}$ = -24° (c = 0.5, methanol), mp 104 – 106 °C}.

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

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 mmol, 0.027 mmol, 0.040 mmol, 0.054 mmol amine was added and measured the NMR spectra. As deuterated solvent $CDCl_3$ and C_6D_6 were used. All measurements were carried out at 298 K.

CD experiments

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

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Supporting Information. 2D NMR spectra for **1**, **2** and **3** and characterization data for diastereomeric salts. This material is available free of charge via the Internet at http://pubs.acs.org.

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