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Tandem crystallization strategies for resolution of 3,3,3-trifluorolactic acid [$CF_3CH(OH)COOH$] by chiral benzylamines

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Abstract

Resolution of *rac*-3,3,3-trifluorolactic acid by diastereomeric salt formation was reinvestigated. The use of (S)-1-phenylethylamine gives coprecipitation of two diastereomeric phases, **1** (S)-[$NH_3CH(CH_3)Ph$](S)-[$CF_3CH(OH)COO$] and **2** (S)-[$NH_3CH(CH_3)Ph$](R)-[$CF_3CH(OH)COO]\cdot H_2O$. Pure phase **1** may be obtained using molecular sieves as desiccants. Resolution by (S,S)-2-amino-1-phenylpropan-1,3-diol gives monoclinic (S,S)-[$NH_3CH(CH_2OH)CHOHPh$] (R)-[$CF_3CH(OH)$-COO] **3** with minor (S)-3,3,3-trifluorolactate contamination, which is precluded in the recrystallized orthorhombic form **4**. A new resolution using inexpensive phenylglycinol gives pure phase **5** (S)-[$NH_3CH(CH_2OH)Ph$] (S)-[$CF_3CH(OH)COO$] in 76% yield, 94% ee in a single step, in preference to its (S)-(R) diastereomer **6**. Overall efficient resolution for both enantiomers of the trifluorolactic acid (each ca. 70% yield, 99% ee) may be achieved by various two-step "tandem" crystallizations, involving direct addition of either water or a second base to the filtrate from the initial reaction.

KEYWORDS

diastereomeric salt formation, pyramidal disorder, resolution, solid solutions, tandem crystallization, trifluorolactic acid

1 | INTRODUCTION

3,3,3-Trifluorolactate has promise as a building block for synthesis of organofluorine compounds for use in medicine or optical and crystalline materials[1-3] or as a chiral derivatizing agent.[4] Its widespread use is restricted by the high cost of resolved 3,3,3-trifluorolactic acid in excess of US$ 600 per gram. This makes an inexpensive and efficient resolution of the racemic compound highly desirable. Figure 1 summarizes current approaches to enantiopure 3,3,3-trifluorolactic acids. Path A indicates that several chiral synthetic or enzymatic approaches have been employed,[5-8] but these are not commercially attractive. Classical optical resolution using diastereomeric salt formation (Path B) is a viable alternative,[9-14] especially if both enantiomers of the acid are desired.

A published resolution using (R,R)- or (S,S)-2-amino-1-phenylpropan-1,3-diol appears effective with 90% ee,[10] but the resolving agents are still quite expensive. More recent, but somewhat inconsistent, reports offered a possible resolution route via diastereomeric salt formation using inexpensive (R)- or (S)-α-methyl-benzylamine

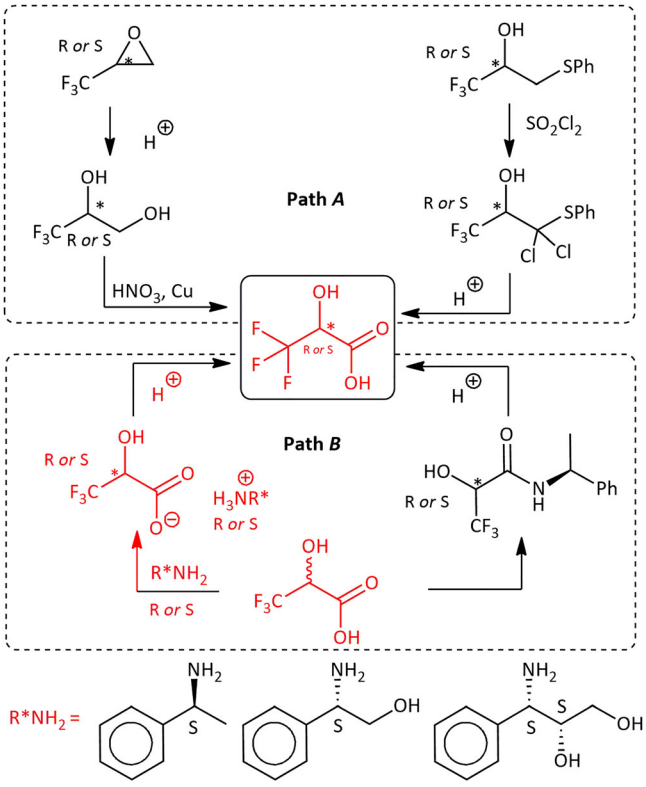


FIGURE 1 Approaches to the resolution of *rac*-$CF_3CH(OH)COOH$

(1-phenylethylamine),[13,14] the ammonium ion of which is a commonly used cation in such resolutions.[13,15] A patent source[13] claimed that each of enantiomer of 3,3,3-trifluorolactic acid could be isolated by switching between anhydrous and water-containing solvents in the diastereomeric salt recrystallizations. The absolute configurations were assigned by comparison with known samples on chiral GC, and up to 95.2% ee on the first run was reported. By contrast, a later publication from the same group[14] indicated only 68% ee for the (S)-3,3,3-trifluorolactic acid can be obtained with a similar protocol in the first crystallization step. No explanation for the modest % ee was given, and no crystal structure determinations were reported for either of the systems.[10,14]

We therefore decided to reinvestigate these to see whether conditions could be further optimized, deduce the reason for the low enantioselectivity for the 1-phenylethylamine case, and find an effective and inexpensive method for resolution of 3,3,3-trifluorolactic acid.

2 | MATERIALS AND METHODS

2.1 | General

Rac-3,3,3-trifluorolactic acid was prepared by literature method[12] via a base-hydrolysis of 3,3-dichlorotrifluoroacetone purchased from ABCR. Other reagents and solvents were obtained from Sigma-Aldrich or TCI chemicals at 99% reagent grade and used as received without further purification. Ethyl acetate used was dried with calcium hydride under N_2 atmosphere.

Intensity data for single crystal structures were measured at 100 K on a Rigaku Oxford Diffraction Superova diffractometer (Cu-Kα radiation, Atlas detector) with details as recently reported.[16] Structures were solved and refined using SHELXL[17] embedded in the Olex2 platform.[18,19] Experimental powder X-ray diffractograms were recorded on a Panalytical Xpert Pro and compared with those simulated using the Mercury software package.[20] These may be found in Supplementary Data S1.

2.2 | Crystallization of salts 1 and 2 using 1-phenylethylamine

A 9:1 ethyl acetate: hexane solution (2 mL) of *rac*-3,3,3-trifluorolactic acid (0.97 mmol, Fw 144.1, 140 mg) was added an equimolar requivalent of (S)-1-phenylethylamine (1 mmol, Fw 121.2, 128 μL) and heated at 60°C 2 hours following previous method.[12] Upon cooling the resulting colorless crystalline solids (174 mg, ca. 70% yield, 50% ee) were found by P-XRD and S-XRD to be a mixture of **1** (S)-$[NH_3CHMePh]$ (S)-$[CF_3CH(OH)COO]$ and **2** (S)-$[NH_3CHMePh]$ (R)-$[CF_3CH(OH)COO]\cdot H_2O$. Pure **1** and **2** can be isolated stepwise (see Section 2.5).

2.3 | Crystallization of salts 3 and 4 using 2-amino-1-phenylpropan-1,3-diol

Rac-3,3,3-trifluorolactic acid (0.97 mmol, Fw 144.1, 140 mg), (1S,2S)-2-amino-1-phenyl-1,3-propane-diol (1 mmol, Fw 167, 167 mg) heated (60°C, 2 h) in 2 mL ethyl acetate.[10] Colorless plates obtained on cooling (130 mg, Fw 311, 86% yield, 92% ee). P-XRD and S-XRD reveal that this is a mixture of polymorphic phase-types **3** (monoclinic) and **4** (orthorhombic) (S,S)-$[NH_3CH(CH_2OH)CHOHPh]$ (R)-$[CF_3CH(OH)COO]$. The S-XRD of **3** shows enantio contamination at the anion site. The product was recrystallizated in ethyl actate/hexane 9:1 in 40°C for 10 minutes. It is cooled for 3 hours and affords pure phase **4** (75% yield) with little or no enantio contamination (99% ee).

2.4 | Crystallization of salts 5 and 6 using phenylglycinol

Rac-3,3,3-trifluorolactic acid (0.97 mmol, Fw 144.0, 140 mg), (S)-phenylglycinol (0.55 mmol, Fw 138, 75 mg)

were heated (60°C, 2 h) in 2 mL ethyl acetate. Upon cooling, colorless plates of (S)-[$NH_3CH(CH_2OH)Ph$](S)-[$CF_3CH(OH)COO$] **5** (104 mg, Fw 281, 76% yield, 95% ee) obtained by filtration. Single recrystallization gives overall 70% yield with 99% ee. Combustion analysis for **5** $C_{11}H_{14}F_3NO_4$ calc. (found) C 46.98% (46.87) H 5.02% (5.12) N 4.98% (5.51).

Crystals of the diastereomeric salt **6** (S)-[$NH_3CH(CH_2OH)Ph$](R)-[$CF_3CH(OH)COO$] (86 mg, Fw 281, 63% yield) can be obtained by further addition of (S)-phenylglycinol (0.5 mmol. 70 mg) to the filtrate solution, crystals obtained after crystallization at room temperature for 8 hours. The product is contaminated ith salt **5**; therefore, its enantiomeric excess was not determined.

2.5 | Tandem resolution of *rac*-3,3,3-trifluorolactic acid using (S)-1-phenylethylamine

Equimolar amount of *rac*-3,3,3-trifluorolactic acid (7.0 g, 48.5 mmol) and (S)-1-phenylethylamine (6.4 mL, 50 mmol,) in 90 mL dry ethyl acetate (3 Å UOP molecular sieves) were refluxed for 2 hours under N_2 with flow extractor charged with freshly calcined 3 Å UOP molecular sieves for removal the traces of water. Solution was slowly cooled to 0°C in ice bath and left for 3 hours. Resulting colorless block crystals of **1** were filtered off (5.40 g, 84% yield, 92% ee).

A total of 7 mL of water was added to the filtrate, heated to full dissolution of precipitate, and slowly cooled down to ambient temperature. The platy white crystals of **2** settle out after 3 hours (2.91 g) and a further crop (2.65 g) overnight. Combined yield of salt **2** (S)-[$NH_3CHMePh$] (R)-[$CF_3CH(OH)COO$]·H_2O) was 5.56 g, 81% yield (96% ee).

2.6 | Tandem resolution of *rac*-3,3,3-trifluorolactic acid by sequential use of (S)-phenylglycinol and (S)-1-phenylethylamine

Rac-3,3,3-trifluorolactic acid (10.31 mmol, 1.485 g), (S)-phenylglycinol (5.4 mmol, 0.739 g) were heated (60°C, 2 hours) in 5.5 mL ethyl acetate. Upon cooling, colorless plates of **5** (S)-[$NH_3CH(CH_2OH)Ph$] (S)-[$CF_3CH(OH)COO$] (1.102 g, 76% yield, 94 % ee) were obtained by filtration. Then water (0.6 mL) and (S)-1-phenylethylamine (5.4 mmol, 0.657 g) were added to the mother liquor and crystals of **2** (S)-[$NH_3CHMePh$](R)-[$CF_3CH(OH)COO$]·H_2O (0.835 g, 58% yield, 95 % ee) after 5 hours and a further crop (170 mg) collected overnight to give a total yield of 69%.

2.7 | Determination of % ee by chiral chromatography

HPLC experiments were performed with a Thermo Scientific Dionex UltiMate 3000 instrument fitted with Phenomenex Lux 5 μm Amylose-1 LC chiral column (250 × 4.6 mm) running with normal phase 92 hexane: 8 i-propanol: 0.2 trifluoroacetic acid at 5°C. Injection volumes of 5 μL were used and run time 40 minutes. The typical retention times of *rac*-3,3,3-trifluorolactic acid were 21.4 and 23.1 minutes. These peaks were close but clearly resolved with $w_{1/2}$ ave of 1.0 minute (R = 1.6). Peaks were detected from UV absorption at 210 nm. The quantification of the racemate gave an acceptable ratio of 50.2: 49.8% based on peak area.

The % ee in salts came from (R)/(S) peak integrations after crude 3,3,3-trifluorolactic acid was obtained from dried organic extract, after salts treated with 50:50 ethyl acetate: 1 M HCl soln. to remove cation to aqueous phase.

3 | RESULTS

3.1 | Resolution 1: Reinvestigation using 1-phenylethylamine

In the previous report for the resolution of *rac*-3,3,3-trifluorolactic acid, an equimolar requivalent of (S)-1-phenylethylamine was added to a 9:1 ethyl acetate: hexane solution of the acid.[12] This was then heated at 60°C for 30 minutes and upon cooling afforded a solid in 75% yield with 68% ee. Three crystallizations were required to obtain a reasonably enantiopure sample. To examine the system in more detail, the reaction was duplicated on a mmol scale reaction in ethyl acetate. Solids collected were in ca. 70% yield, and these were ground and a powder X-ray pattern was recorded of the product mixture.

A single crystal structure determination of a specimen from the solid mixture showed the structure to be the (S)-(S) salt **1**, (S)-[$NH_3CHMePh$] (S)-[$CF_3CH(OH)COO$]. Details of this and other single crystal structure determinations are given in Table 1. The structure of an ion pair in **1** is shown in Figure 2.

Crystals of **1** are monoclinic, space group $P2_1$ and have two ion pairs per cell ($Z' = 1$, $Z = 2$) and a cell volume of 652.2Å^3 at 100 K. The structure refined to acceptably low (R)-indices and Flack parameter with a clean final electron density map (no difference peaks or holes >0.2 $e^-Å^{-3}$) consistent with a clean (S)-(S) cation-anion stereochemistry for the salt in the single crystal specimen. The structure itself was thus consistent with a more optimal resolution; hence, the phase purity of the solid product

TABLE 1 Crystal data summaries for **1-6**

Compound	1	2	3	4	5	6
Abbreviated Name	(S)-[$NH_3CHMePh$] (S)-[$CF_3CH(OH)COO$]	(S)-[$NH_3CHMePh$] (R)-[$CF_3CH(OH)COO$]·H_2O	(S,S)-[$NH_3CH(CH_2OH)CHOHPh$] (R)-[$CF_3CH(OH)COO$]	(S,S)-[$NH_3CH(CH_2OH)CHOHPh$] (R)-[$CF_3CH(OH)COO$]	(S)-[$NH_3CH(CH_2OH)Ph$] (S)-[$CF_3CH(OH)COO$]	(S)-[$NH_3CH(CH_2OH)Ph$] (R)-[$CF_3CH(OH)COO$]
Code/CSD number	1899879	1899880	1899881	1899882	1899883	1899884
Empirical formula	$C_{11}H_{14}F_3NO_3$	$C_{11}H_{16}F_3NO_4$	$C_{12}H_{16}F_3NO_5$	$C_{12}H_{16}F_3NO_5$	$C_{11}H_{14}F_3NO_4$	$C_{22}H_{28}F_6N_2O_8$
Formula weight	265.23	283.25	311.26	311.26	281.23	562.46
Temperature/K	104(6)	100(2)	100(2)	100(2)	100(2)	100(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_1$
a/Å	8.2984(3)	8.2456(4)	5.1286(2)	5.12662(13)	5.00584(13)	9.25040(18)
b/Å	6.5985(3)	5.8699(3)	9.9509(3)	9.9597(2)	8.83174(18)	5.11803(11)
c/Å	12.0458(5)	13.2059(9)	13.2398(5)	26.4076(9)	13.6782(4)	25.9488(5)
α/°	90.00	90.00	90.00	90.00	90.00	90.00
β/°	98.618(4)	91.876(6)	97.818(4)	90.00	98.511(3)	98.281(2)
γ/°	90.00	90.00	90.00	90.00	90.00	90.00
Volume/$Å^3$	652.15(5)	638.83(6)	669.40(4)	1348.37(6)	598.06(3)	1215.71(4)
Z, Z′	2, 1	2, 1	2,1	4, 1	2, 1	4, 2
ρ_{calc} g/cm^3	1.351	1.473	1.544	1.533	1.562	1.537
Radiation, μ/mm^{-1}	1.097	1.215	1.278	1.269	1.298	1.277
F(000)	276	296	324	648	292	584
Crystal size/mm^3	0.10 × 0.05 × 0.02	0.10 × 0.05 × 0.01	0.12 × 0.08 × 0.02	0.20 × 0.10 × 0.02	0.10 × 0.10 × 0.02	0.13 × 0.08 × 0.04
2Θ maximum/°	135	135	135	135	135	134
Index ranges	$-8 \le h \le 9$, $-7 \le k \le 7$, $-14 \le l \le 13$	$-9 \le h \le 9$, $-7 \le k \le 7$, $-15 \le l \le 15$	$-6 \le h \le 6$, $-11 \le k \le 11$, $-14 \le l \le 15$	$-4 \le h \le 6$, $-11 \le k \le 11$, $-31 \le l \le 27$	$-5 \le h \le 4$, $-10 \le k \le 10$, $-16 \le l \le 16$	$-11 \le h \le 9$, $-6 \le k \le 6$, $-30 \le l \le 30$
Total, indep. reflections (%)	3430, 2298	3699	4065, 2369	3624, 2394	3165, 2093	10450, 4210
Data quality indices (%)	R_{int} = 0.0247, R_{sig} = 0.0392	R_{int} = twin, R_{sig} = 0.0313	R_{int} = 0.0234, R_{sig} = 0.0327	R_{int} = 0.0219, R_{sig} = 0.0339	R_{int} = 0.0294, R_{sig} = 0.0387	R_{int} = 0.0263, R_{sig} = 0.0320
Data/restraints/parameters	2298/1/166	3699/1/198	2369/1/214	2394/0/214	2093/1/192	4210/1/383
Goodness-of-fit F^2	1.042	1.018	1.023	1.059	1.016	1.025
Final R indexes [$I \ge 2\sigma$ (I)]	R_1 = 0.0360, wR_2 = 0.0939	R_1 = 0.0305, wR_2 = 0.0756	R_1 = 0.0295, wR_2 = 0.0765	R_1 = 0.0277, wR_2 = 0.0677	R_1 = 0.0260, wR_2 = 0.0628	R_1 = 0.0284, wR_2 = 0.0689
Final R indexes [all data]	R_1 = 0.0378, wR_2 = 0.0955	R_1 = 0.0328, wR_2 = 0.0765	R_1 = 0.0306, wR_2 = 0.0775	R_1 = 0.0287, wR_2 = 0.0683	R_1 = 0.0280, wR_2 = 0.0639	R_1 = 0.0299, wR_2 = 0.0698
Diff. peak/hole e$Å^{-3}$	+0.19/−0.14	+0.32/−0.14	0.34/−0.18	+0.20/−0.20	+0.24/−0.14	+0.21/−0.15
Flack parameter	0.06(16)	−0.07(8)	−0.11(10)	−0.10(8)	0.04(9)	−0.05(7)

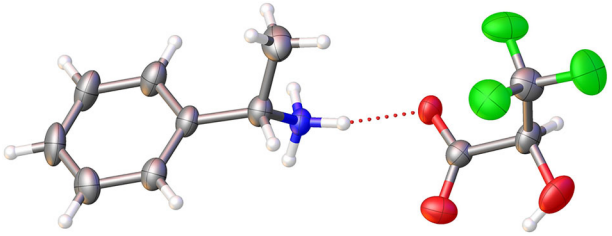


FIGURE 2 Ion pair from the crystal structure of **1** (S)-[$NH_3CHMePh$](S)-[$CF_3CH(OH)COO$]

was suspect. A simulation of the powder X-ray diffraction pattern from **1** showed that corresponding peaks were found prominently in the experimental p-XRD pattern of the bulk powder (Figure 3).

However, these were not exclusive, and many additional diffraction lines could not be indexed. This implied the presence of a second phase. After mounting of several specimens from the batch, a crystal with similar but distinctly different unit cell constants was identified.

The X-ray structure determination of this revealed it be the (S)-(R) salt **2** (S)-[$NH_3CHMePh$](R)-[$CF_3CH(OH)COO$]·H_2O which crystallized as a monohydrate. Structural details are given in Table 1, and the monoclinic unit cell metrics are indeed similar to **1**, and the space group is again $P2_1$. The unit cell volumes are identical within two standard deviations although the asymmetric unit now also contains a water of hydration (Figure 4).

The handedness in the structure is indicated by the (S)-configuration of the cation used in the reaction. This time, the initial (R)-value was not of high quality, the Flack parameter was of high uncertainty, and some residual electron density could be found near C2 the chiral carbon of the lactate. Finally, this was modelled

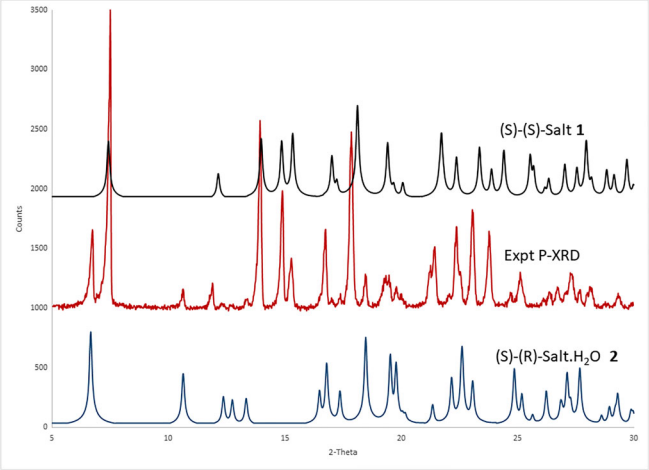


FIGURE 3 Powder XRD patterns indicating solid is a coprecipiatate of phases **1** and **2**

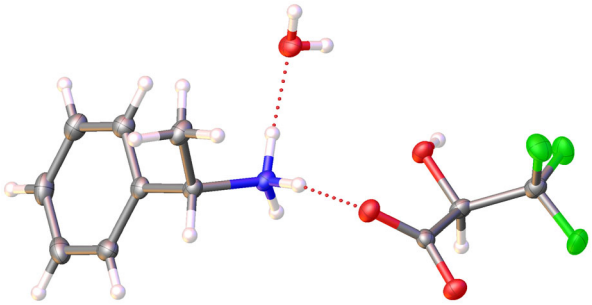


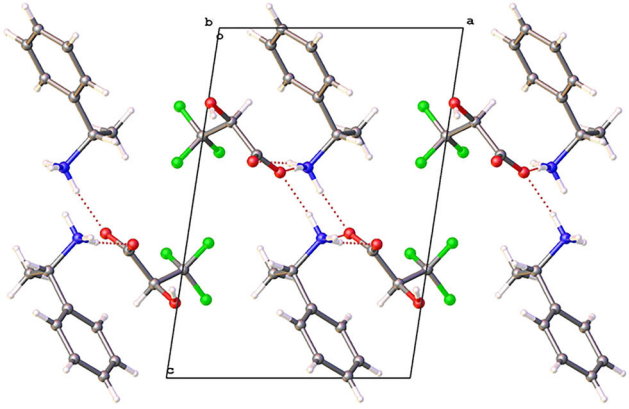
FIGURE 4 Asymmetric unit from the X-ray structure of **2** (S)-[$NH_3CHMePh$](R)-[$CF_3CH(OH)COO$]·H_2O

using the Olex2 X-ray software program with a split position for C2 with occupancies 93:7 corresponding to the (S)- and (R)-anion configurations, respectively.

This type of "pyramidal" disorder may be found where the chiral C centre is directly bonded by H.[21] Here, it is possible within the crystal, since it allows minimal positional disruption for the three main substituents at the chiral centre, namely, the carboxylate, the alcohol, and the CF_3 group. Closer examination of phases **1** and **2** shows that inspite of the cell similarities, the internal packing arrangements are quite unrelated, as shown in Figure 5.

The formation of a solvate has been identified by Fogassy et al as a factor that may favour one enantiomer in diastereomeric salt resolutions.[22,23] More recently, we have shown that the resolution of 1,2-diamonopropane by chiral spiroborate anion was facilitated by formation of a methanol solvate.[24] However, in this case, the possibility to form hydrate **2** apparently complicates the precipitation process.

It is likely that due to entropic factors,[25] upon cooling, anhydrous phase **1** is first formed at a higher temperature. Subsequently, **2**, which having a smaller volume with an extra water is more efficiently packed, is then favoured at lower temperatures closer to ambient. Resolutions solely favouring **1** might be possible by ensuring a higher temperature at which nucleation first occurs, as well as scrupulous removal of water, both of which will disfavour hydrate formation. Conversely, room temperature crystallizations from semi-aqueous solvent mixtures might afford pure **2**. However, pure phase **2** would still only offer less than 86% ee which was found even after removing of the minor (S)-anion. The addition of activated 3 Å molecular sieves to the reaction absorbed traces of water and resulted in successful formation of pure phase **1**. Subsequent addition of water to the filtrate then allowed for facile isolation of **2** with high enantiopurity. This showed that a successful resolution using 1-phenylethylamine was indeed possible.



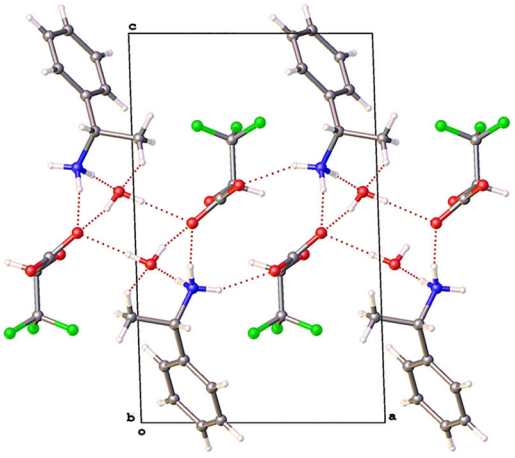


FIGURE 5 Packing diagrams for **1** (top) and **2** both viewed along [010] monoclinic b-axis, indicating the unrelatedness of their structures

3.2 | Resolution 2: Reinvestigation using 2-amino-1-phenylpropan-1,3-diol

Although more expensive than 1-phenylethylamine, Seebach et al reported several successful resolutions using the chiral (R,R)- and (S,S)-forms of 2-amino-1-phenylpropan-1,3-diol. These included 3-hydroxy-2-trifluoromethylpropionic acid,[26] as well as 3,3,3-trifluorolactic acid[10] for which an efficient resolution with >90% ee in the first crystallization step was claimed. No crystal structure of the product was determined in the original report. We therefore decided to reinvestigate the resolution of *rac*-3,3,3-trifluorolactic acid using the (S,S)-2-amino-1-phenylpropan-1,3-diol. A crystal structure determination of the main product phase **3** showed the salt to contain predominantly the (R)-3,3,3-trifluorolactic acid anion (Figure 6).

A particular ion pair can be identified in this structure with two intermolecular hydrogen bonds forming a $R^2_2(10)$ ring by Etter notation.[27] As might be

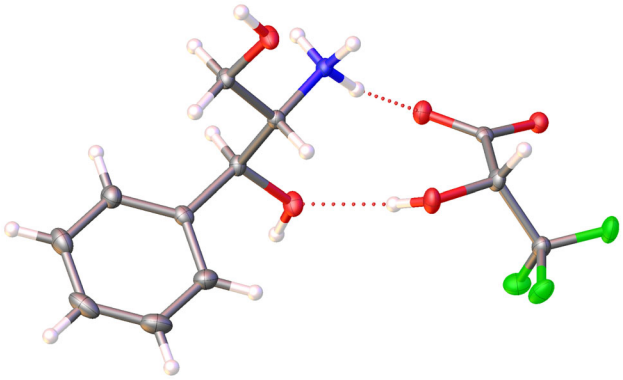


FIGURE 6 Ion pair in **3** (S,S)-[$NH_3CH(CH_2OH)CHOHPh$] (R)-[$CF_3CH(OH)COO$] with $R^2_2(10)$ motif (50% ellipsoids)

anticipated, a complex network of hydrogen bonds holds the crystals together since there are six H-bond donors per ion pair.

The P-XRD of the solid indicated reasonable phase purity, but there were a few minor additional peaks that could not be indexed to the unit cell of **3**. Our initial assumption was that the additional peaks might belong to the diastereomeric salt, as was the case for the α-methylbenzylammonium phases **1** and **2**. Successive recrystallizations with 90% recoveries were undertaken, but surprisingly, the resulting powder patterns (Figure 7) indicated that the contaminant peaks were reinforced. A crystal **4** from the recrystallized material was mounted and its unit cell found to be related but different to **3**. Compound **4** has an orthorhombic $P2_12_12_1$ rather than monoclinic $P2_1$ cell, with the a- and b-axes similar in both, but doubling of the longer c-axis from around 13 to 26 Å. Its single crystal structure revealed that **4** was a polymorphic form of **3** and the salt again

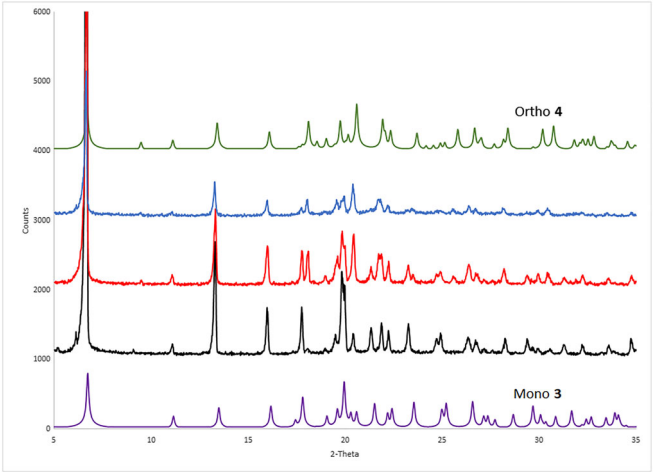


FIGURE 7 Experimental powder XRD patterns of crystallized solids (black, red, and blue) versus simulated from structures of polymorphs **3** and **4**

had $(S,S)^{+}(R)^{-}$ configurations. The relationship in packing between the two polymorphs is well illustrated in Figure 8, viewed along [100] direction in each structure. Phase **3** (top) shows packing in two cells along c-direction corresponding to a single doubled cell for **4** in which a second set of ions is rotated by 180° to form the screw axis along the doubled-c.

Notably, the H-bond network in the two structures is fully conserved, but they differ in the packing regions between Ph and CF_3 groups.

Since the additional diffraction peaks do not belong to a separate diastereomeric salt phase, the question is why is there only 90% ee in the product solids? Careful examination of the anion sites in **3** and **4** reveals that although both structures are of high quality, in **3,** there are ghost peaks of +0.34 and +0.19eÅ^{-3} near to the lactate chiral carbon suggesting the presence of the (S)-enantiomer of 3,3,3-trifluorolactate anion. The main extra peak is from the OH position and the weaker one an alternative C2 chiral carbon position for this minor (S)-component. The configurational swap can be achieved with little reorientation of the CF_3 and COO groups and switching of two OH—O hydrogen bonds of around 2.8 Å for the major component to a shorter OH—O of 2.6 Å for the minor one (Figure 9). It is of note that the monoclinic form which is slightly more efficiently packed is replaced by the orthorhombic one upon recrystallization, and this may be a subtle interplay of competing entropy and enthalpy factors in the two structures.

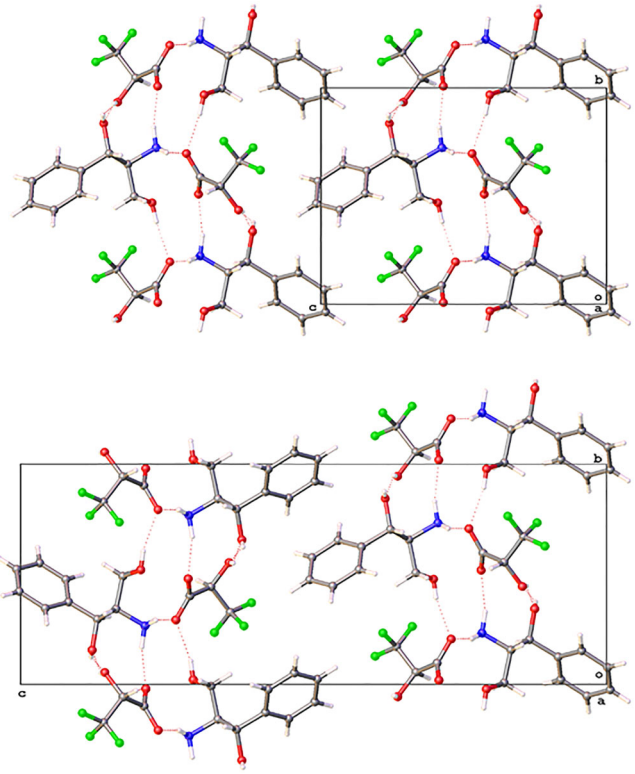


FIGURE 8 Polymorphic (S,S)-[$NH_3CH(CH_2OH)$-CHOHPh] (R)-[$CF_3CH(OH)COO$] **3** (monoclinic, top) and **4** (orthorhombic, bottom)

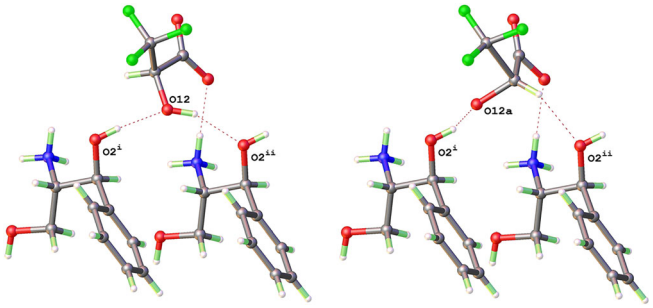


FIGURE 9 (R/S)-[$CF_3CH(OH)COO$] anion disorder model in 3.

3.3 | Resolution 3: New studies using phenylglycinol

The high crystallinity and tractable nature of the salts **1** and **2** led us to seek a subtle modification of the crystallizing cation, which would have different packing, but retain the compatibility with the 3,3,3-trifluorolactate anions. One option was to extend the methyl group to ethyl and the other to incorporate an alcohol group to make it CH_2OH.

Figure 9. (R/S)-[$CF_3CH(OH)COO$] anion disorder model in **3**

Free amine bases with both (R)- and (S)- forms for both options are commercially available. It was decided to investigate phenylglycinol system, since it was felt the alcohol group will place more constraints on packing and reduce likelihood of pyramidal disorder. That additional hydroxy groups can assist resolutions is well established.[28] Recently, we found that *rac*-phenylglycinol could be cleanly resolved by chiral spiroborate anions, whereas attempts for *rac*-1-phenylethylamine gave (R/S)-pyramidal disordered sites.[21] An attempt to resolve 3,3,3-trifluorolactic acid via diastereomeric salt crystallization was set up as previously, although this time using around 0.5 mmol (S)-phenylglycinol in place of 1.0 mmol (S)-1-phenylethylamine.

The ethyl acetate solution was heated at 60°C for 2 hours and cooled to ambient temperature. A crystalline solid **5** was isolated in 76% yield. A single crystal structure determination of the product showed it to be the (S)-(S) salt **5** (S)-[$NH_3CH(CH_2OH)Ph$](S)-[$CF_3CH(OH)COO$] (Figure 10).

This is also monoclinic $P2_1$ with some metrical similarities in cell constants to **1** and **2**. The addition of the alcohol functionality in the cation introduces an extra group that can serve as donor in forming a H-bond to

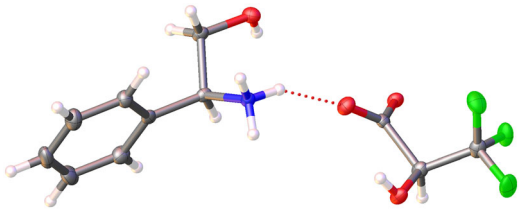


FIGURE 10 Ion pair in **5** (S)-[$NH_3CH(CH_2OH)Ph$] (S)-[$CF_3CH(OH)COO$] (50% ellipsoids)

the alcohol OH of the anion. Interestingly, the volume of the unit cell 598Å^3 is substantially contracted from that of **1** and **2**, implying a substantially improved packing efficiency than either α-methylbenzylammonium salt. This feature might indicate a clean resolution could be indicated.

Powder XRD of the isolated bulk solid showed that the only major crystalline peaks belonged to phase **5** (Figure 11). The enantiopurity in **5** was also supported by excellent R-value, Flack refinement, and low residual electron density features in the final difference map.

The structure of **5** entails four hydrogen bonds from the (S)-cation to four separate (S)-3,3,3-trifluorolactate anions, as well as an additional OH—O from the lactate alcohol to the cation —OH. The results from chiral chromatography supported the high 92% ee from this single crystallization step.

To further investigate the effective resolution in this case, we also attempted to crystallize the diastereomeric salt **6** (S)-[$NH_3CH(CH_2OH)Ph$] (R)-[$CF_3CH(OH)COO$] by adding the (S)-phenylglycinol to filtrate that is enantiomeric rich in (R)-$CF_3CHOHCOOH$. This crystallized with two ion pairs per asymmetric unit, which form an $R^4_3(10)$ hydrogen bonded ring as shown in Figure 12.

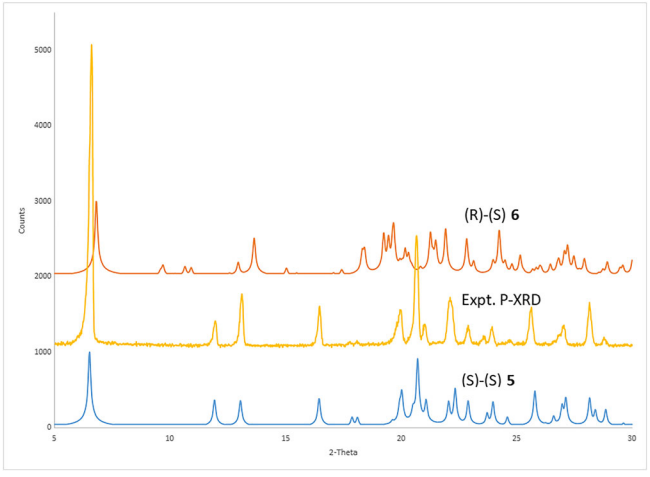


FIGURE 11 P-XRD patterns: Bulk powder (yellow, middle) matches simulated from (S)-(S) salt **5** (blue), not diastereomeric **6** (orange)

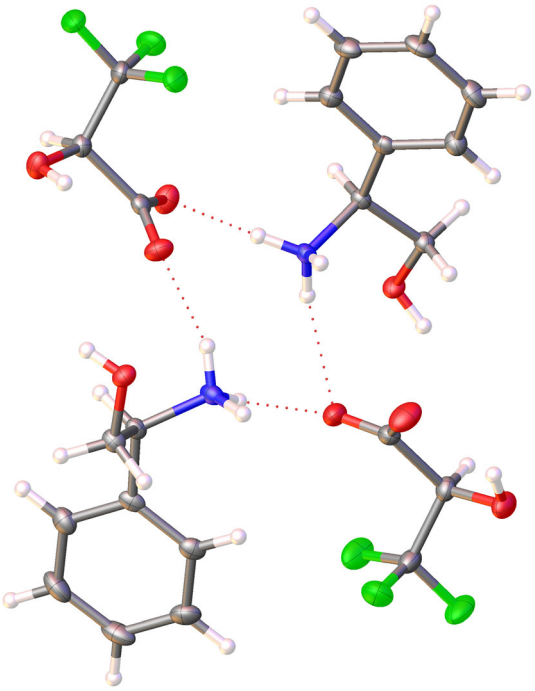


FIGURE 12 Asymmetric unit with Z′=2 for **6** (S)-[NH_3 $CH(CH_2OH)Ph$](R)-[$CF_3CH(OH)COO$] (50% ellipsoids)

The packing efficiency in this diastereomeric (S)-(R) salt is considerably lower than the (S)-(S) form **5**, the density of which is about 1.3% higher. This differentiation helps explain the preference for the (S)-(S) salt. The extended H-bond network in **5** could not readily allow for the type of pyramidal or OH/H type disorders that were found at the anion sites in compounds **2** and **3**, respectively.

4 | DISCUSSION

4.1 | Comparison of resolving agents for CF_3-lactate

Resolution via diastereomeric salt formation is a classical method[22,29] which is becoming somewhat neglected partly due to the development of new routes to efficient asymmetric syntheses with enantiomeric control such as organocatalysis.[30-32] However, the combined use of powder diffraction and modern single crystal X-ray structure determination can be of value in understanding the mechanism of resolution and in identifying the issues when such resolutions are not fully efficient.

The results from the resolution in the three systems studied (sections 2.2-2.4) is summarized graphically in Figure 13.

In the case of resolution of 3,3,3-trifluorolactic acid by (S)-1-phenylethylamine, the product solids were not pure

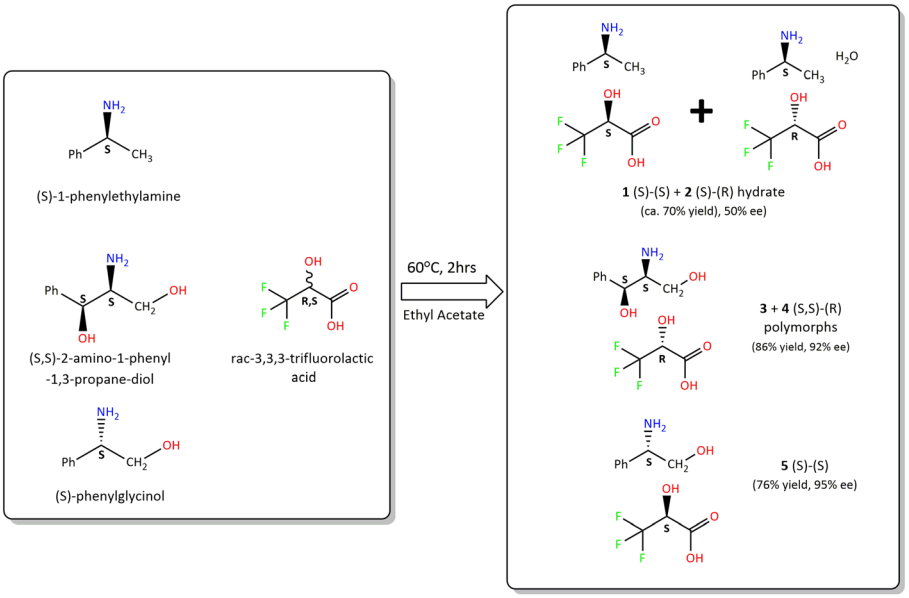


FIGURE 13 Summary of 3,3,3-trifluorolactic acid resolution outcomes using (S)-amines (1 mmol scale)

phase, and a mixture of **1** (S)-[$NH_3CHMePh$] (S)-[$CF_3CH(OH)COO$] and **2** (S)-[$NH_3CHMePh$] (R)-[$CF_3CH(OH)COO$]·H_2O was formed. The single crystal structures of each phase were determined from specimens taken from the same product batch. These revealed that whist *internally* the (S)-(S) salt was effectively enantiopure the same was not true for the hydrated phase **2**, which could be described as a diastereomeric solid solution. Such issues were noted as a source of potential problems in previous resolutions in which the enantiomers showed considerable shape similarity.[21] A similar example in which 1-phenylethylamine was involved was in the resolution of *rac*-malic acid.[33] The product salt was found to be predominantly (R)-[$NH_3CHMePh$] (S)-[Malate] which was contaminated by the (R)-anion in a single solid-solution phase.

Here, the S-XRD studies help explain the low resolution efficiency found in the previous study[14] and also indicate that isolation of pure phase **1** would be a better strategy than isolating pure phase **2**. Fortunately, suppression of **2** is fairly easily achieved by the introduction of 3 Å molecular sieves to thoroughly dessicate the reaction and allows production of pure phase **1** in acceptable yield.

The reinvestigation of the resolution of 3,3,3-trifluorolactic acid using 2-amino-1-phenyl-propan-1,3-diol supports the earlier findings[8] that an effective resolution can be achieved after two steps. The first crystallization afforded two phase types **3** and **4**; however, in this case, both were predominantly of the chirality (S,S)-[$NH_3CH(CH_2OH)CHOHPh$] (R)-[$CF_3CH(OH)COO$].

Phases **3** and **4** were found to be monoclinic and orthorhombic polymorphic arrangements respectively with preserved H-bonding patterns. These differ from each other by taking AAAA type translationally related molecular layers in the monoclinic form **3** and changing to an ABAB arrangement, with 180° rotation of alternate layers, in the orthorhombic form **4**. This effectively doubles the unit cell c-axis from 13 to 26 Å.

Detailed study of crystallization conditions might allow for one or other form to be obtained pure phase, but it is notable that again we find phase **3** has a slight enantio contamination by careful analysis of the single crystal structure. In this case, it is due to an H/OH positional disorder in the 3,3,3-trifluorolactate anion. In the predominant (R)- form, two OH—OH-bonds are found involving the lactate alcohol group as both donor and acceptor. When the H and OH positions are effectively switched, just one H-bond is formed, but this is shorter and thus energetically competitive. Further recrystallization to give higher enantiopurity appears to favour orthorhombic **4**.

In the case of (S)-phenylglycinol, a new alternative resolution system is presented. This benefits from having conditions affording a single phase product in good yield that is largely free of enantio contamination.

The cost and availability of both enantiomers of the resolving cations may also be a consideration and ultimately the use of (S)-phenylglycinol, at least for the first step may be the best overall approach. The detailed study of the structures of the product phases is valuable in giving insight into the mechism for resolution and in some cases how to improve its efficiency, but finally the

enantioexcess of isolated solids, or residual solutions needs to also be proved.

As shown in Table 2, the best strategies have been evaluated. Entry I gives our results for the classical method of Seebach et al[10] after one (Ia) or two steps (Ib). Entries II and III are tandem resolutions which may be slightly superior. Entry II involves two steps with the same (S)-1-phenylethylamine base which (S)-(S) salt **1** is first isolated under anhydrous conditions followed by the (S)-(R) hydrate **2** under aqueous conditions. Entry III which is also competitive is similar to II but uses (S)-phenylglycinol in the first step.

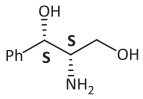
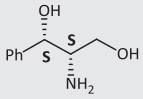
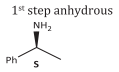
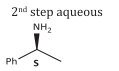
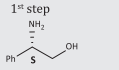
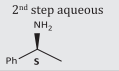
Optical methods such as circular dichroism are rather problematic for 3,3,3-trifluorolactic acid and derivatizations to afford spectroscopic handles are both time-consuming and have the potential for introducing either diastereomer ratio distortion or even additional racemization. The availability of new chiral HPLC chromatography columns (Lux 5 μm Amylose-1 LC Column 250 × 4.6 mm) able to withstand direct application of acids and bases is a useful development and herein we have attempted to prove that separation protocols for quantifying its % ee are possible.

First, the chromatography conditions for separation and detection of the isomers of *rac*-3,3,3-trifluorolactic acid were established using 92 hexane: 8 i-propanol as the eluting solvent with 0.2 eq. trifluoroacetic acid added to provide an acidic buffer for the 3,3,3-trifluorolactic acid and ensure its protonation. The UV detection at 210 nm was found to be sufficiently sensitive to give quantitation of the *rac* material with adequate separation (R = 1.6) and integrated values of 50.2% and 49.8% for the two enantiomeric peaks, which eluted at times 21.5 and 23.1 minutes (Figure 14).

The identification of the two peaks only came from the later screening of the 3,3,3-trifluorolactic acid from the resolved solids and is consistent with the first eluted peak being the (S)-isomer. The % ee in salts came from relative peak integrations obtained after dissolution of the salts with 50:50 ethyl acetate: 10% HCl mixtures.

The cations are segregated into the aqueous acid layer. After further extractions with ethyl acetate, the combined organic fractions were dried with Na_2SO_4 evaporated to dryness to give quantitative yield of the enriched 3,3,3-trifluorolactic acid.

TABLE 2 Summary of 3,3,3-trifluorolactic acid resolution on gram scale

	Amine	Configuration of Salt	Yield %	% ee TFLA
Ia		**3** (S,S)-(R)[a]	84	92
Ib		**4** (S,S)-(R)[b]	73	99
II	 1st step anhydrous	**1** (S)-(S)[c]	70	92
	 2nd step aqueous	**2** (S)-(R)·H_2O[d]	77	96
III	 1st step	**5** (S)-(S)[a]	76	94
	 2nd step aqueous	**2** (S)-(R)·H_2O[d]	69	95

[a]After precipitation from racemic acid.

[b]After 2nd crystallization of the salt from Entry Ia.

[c]From dry ethyl acetate.

[d]Addition of 12% water to the filtrate for crystallization.

4.2 | Resolution by tandem crystallization

The results from the three resolutions of 3,3,3-trifluorolactic acid indicate that all three benzyl- or aryl-amines could form the basis of an efficient resolution (Figure 12). The price and availability of both enantiomers of the amines studied can be an issue. In general, 1-phenylethylamine would be typically preferred, since the cost of both enantiomers is low.

However, in our studies, we have shown that unless some care is taken, both diastereomeric salts will precipitate in two separate phases. Fortunately, one of these is a hydrate, the nucleation of which can be suppressed using molecular sieves.

With these points in mind, several overall strategies of resolution by tandem (step-wise) crystallization that offer reasonable resolution efficiency with isolation of both enantiomers in acceptable yield and relatively simple

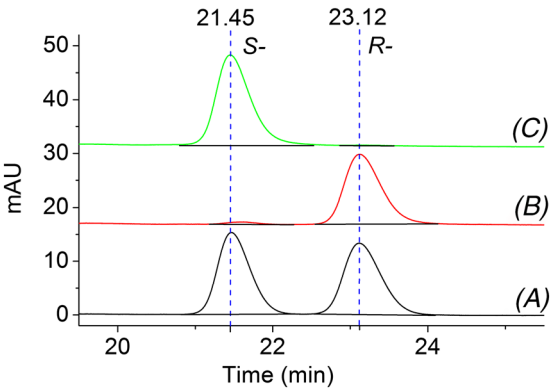


FIGURE 14 Chiral HPLC chromatograms showing separated eluted [$CF_3CHOHCOOH$] peaks for (A) racemic starting material, (B) (R)-acid from **3**, and (C) (S)-acid from **1**

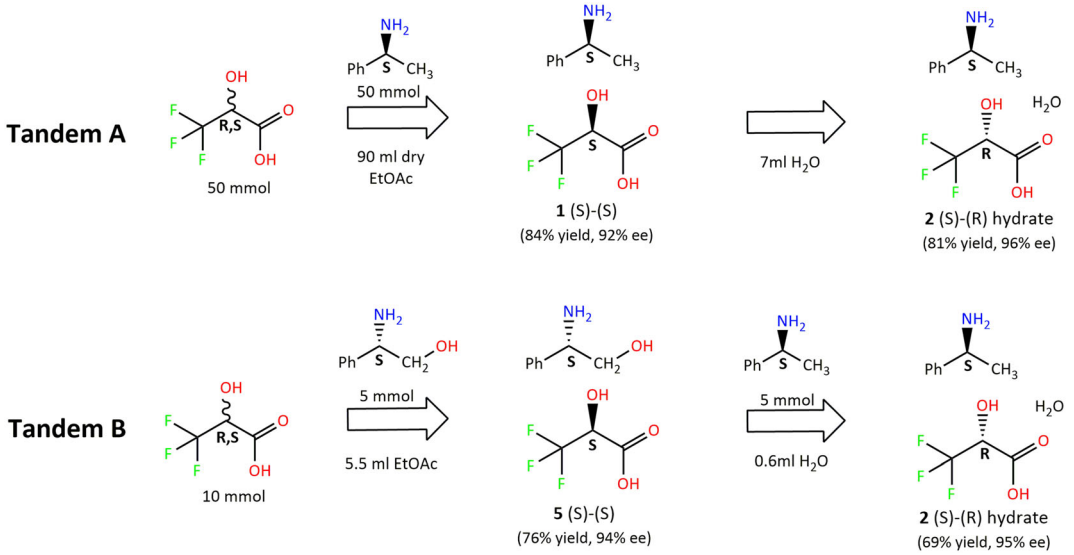


FIGURE 15 Two possible tandem strategies

work up can be devised and two of the better approaches are detailed in Table 2 and Methods A and B (Figure 15).

4.2.1 | Tandem Method A

This method requires the availability of just one enantiomer of 1-phenylethylamine. If this is (S)-1-phenylethylamine, then the first step should be carried out under anhydrous conditions (eg, 3 Å molecular sieves) using equimolar ratio of (S)-1-phenylethylamine to *rac*-3,3,3-trifluorolactic acid.

This can give 84% yield of the (S)-(S) salt **1** with 92% ee. This then requires a single recrystallization (at around 90% yield) to afford **1** with 99% ee. In Step 2, the filtrate can also then be readily worked up by simple addition of water to give 86% yield of the hydrated (S)-(R) salt **2** with high 96% ee.

The chiral 3,3,3-trifluorolactic acids can be released from these salts by addition of acid and organic phase extraction into ethyl acetate. However, it is suggested this may be carried out just prior to their further use, since the chiral acids themselves are highly hygroscopic and untractable solids. Hence, longer-term storage is better effected by leaving the enantiopure 3,3,3-trifluorolactate anions in their organic salt forms.

4.2.2 | Tandem Method B

Method A is relatively simple and inexpensive. Competitive alternative methods starting with (S)-phenylglycinol in Step 1 can also be devised. Reaction of 5 mmol eq. (S)-phenylglycinol with *rac*-3,3,3-trifluorolactic acid affords the (S)-(S) salt **5** in 76% isolated yield and 94% ee. A single high-yield recrystallization will produce this phase with >99% ee. The filtrate solution may then be readily treated with a further 5 mmol eq. of a second resolving base. In Method B, the (S) enantiomer of 1-phenylethylamine can be used to give a high yield and enantiopurity of the (S)-(R).H_2O salt **2** with the addition of water to the mixture in the second step. In this case, the anhydrous form of (S)-(S) salt **1** is strongly disfavoured as little (S)-3,3,3-trifluorolactate remains in solution.

4.2.3 | Other possible tandem methods

In theory, any chiral amines such as 2-amino-1-phenylpropan-1,3-diol that may form salts with 3,3,3-trifluorolactic acid can be used in Step 2. However, due to the high availability and low cost of 1-phenylethylamine, our suggested tandem methods show an obvious advantage against others.

4.2.4 | Summary of tandem resolutions

A key point in the tandem resolutions is that by switching to a second chiral amine for Step 2, the possibility of a lingering contamination through formation of racemic crystals containing ±enantiomers of both cation and anion is avoided. The further advantage of the phenylglycinol system is that only 0.5 eq. need be used in the first step (both of the other systems require 1.0 eq. of base to work effectively) allowing the other base to be directly added to the filtrate solution in the second step. Our work shows a tandem resolution method with 1-phenylethylamine because of its availability and cost.

In principle, however, any combination involving another amines that can form diastereomeric salts with 3,3,3-trifluorolactic acid (not limited to mentioned resolution) could also be successful.

5 | CONCLUSION

Under suitable conditions, effective resolution of 3,3,3-trifluorolactic acid can be carried out by all the three benzylammonium ion systems studied. The resolution using 1-phenylethylamine was reinvestigated, and the modest % ee obtained previously[14] was explained by the fact that two diastereomeric phases coprecipitate, as indicated by p-XRD patterns of the product solids. The (S)-(S) salt **1** predominates in the mixture but is contaminated by the (S)-(R) hydrate **2**. This can be suppressed using dry conditions.

The more expensive (S,S)-2-amino-1-phenyl-propan-1,3-diol, use of which was originally reported by Seebach,[10] is indeed quite effective and gives solids with 90% ee. These are actually polymorphic, and the monoclinic form **3** allows some diastereomeric contamination at the anion site. Recrystallization affords a cleaner orthorhombic form **4**. Finally, another alternative may be offered by use of (S)-phenylglycinol as resolving base. This affords a single-phase product (S)-(S) salt **5** with no diastereomeric contamination via solid solution. The (S)-(R) salt **6** prepared from the separate chiral components is found to have less efficient crystal packing, explaining its higher solubility, and hence the selective precipitation of **5**.

Based on effective resolutions by all the three arylamine systems, tandem strategies for isolation of both enantiomers of 3,3,3-trifluorolactic acid with 99% ee and approximately 70% isolated yields can readily be devised. These involve either addition of water or addition of a second aliquot of base to the filtrate from the original resolution and minimal work up.

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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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