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Solvent dependency though not solvate formation in the derivative–derivative resolution of *N*-formylphenylalanine

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Abstract—The efficiency of the resolution of *N*-formylphenylalanine was remarkably improved using (*S*)-(+)-2-benzylaminobutanol resolving agent in acetone. The efficiency of the resolution strongly depended on the quality of the solvent. Nevertheless, solvate formation did not occur during the process. The nature of the solvent-dependence was studied. The solid-melt binary phase diagram of the diastereomeric salts formed during the resolution by (*S*)-(+)-2-benzylaminobutanol was measured and discussed. It was recognized that the (*S*)-(+)-benzylaminobutanol (*S*)-(+)-*N*-formylphenylalanine salt exists in two polymorphic modifications.
The effect of structurally related chiral and achiral auxiliary reagents in the above resolution was also studied. Thus, (*S*)-(+)-2-benzylaminobutanol was applied together with an (*R*)-(+)-1-phenylethylamine auxiliary resolving agent and benzylamine was used as a half-equivalent achiral basic reagent in a Pope–Peachey type resolution of *N*-formylphenylalanine by (*S*)-(+)-2-benzylaminobutanol. The results are compared to those obtained by the structurally related (*R*)-(+)-1-phenylethylamine chiral auxiliary.

1. Introduction

Molecular structural similarities between a racemate and a resolving agent enhance chiral recognition by promoting the formation of multi-point interactions. During chiral recognition, homochiral and heterochiral associations (e.g., diastereoisomeric complexes, salts, etc.) are formed, which have different stabilities. Beyond the interactions between two molecules, the effect of structurally related compounds is also manifested on a higher supramolecular level, during the formation of crystal nuclei and the crystal growth. The structural similarity between the members of a family of resolving agents makes the solid solution formation common within a family.[1] The beneficial effect of the simultaneous use of several structurally related resolving agents has[2,3] been studied in Dutch resolution experiments.[3] This phenomenon is found to be the result of crystal nucleation inhibition effects between the members of a family of resolving agents.[4,5] The interaction of structurally similar molecules is expressed as a kinetic factor during the crystallization of the diastereomeric salts, which can potentially be utilized to improve the results of the resolution.

In our attempt to study more extensively the interactions between structurally related molecules in resolutions, racemic *N*-formylphenylalanine (FPhA) was chosen as a model compound (Fig. 1). In several previous communications,[6] we dealt with the applicability of structurally related resolving agents and auxiliary reagents in the resolution of FPhA. Separation methods of FPhA enantiomers were worked out for several benzylamine-derivative resolving

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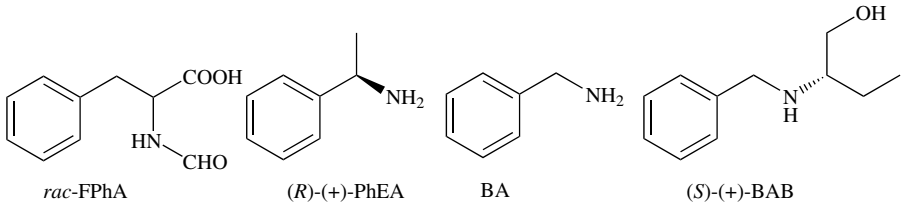

Figure 1. Molecular structures of the racemate and of the structurally related agents used in this study.

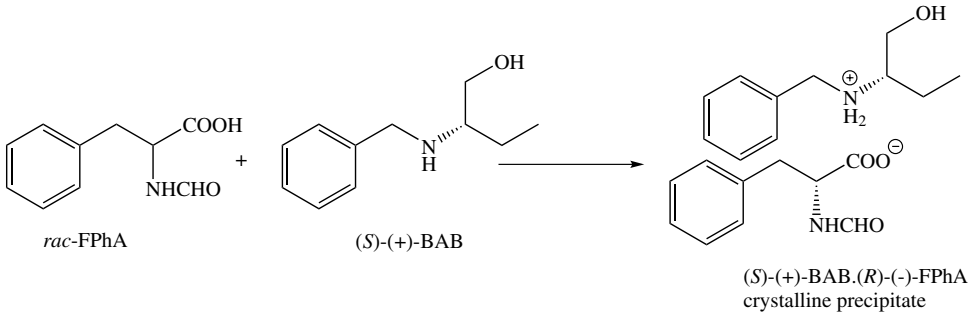

Figure 2. Resolution of racemic FPhA with (*S*)-(+)-BAB resolving agent.

agents. The results obtained with the different resolving agents were compared as a function of the molecular structures.

Herein we report on the structural similarity using the secondary amine type benzylamine-derivative: 2-benzylaminobutanol (BAB) as a resolving agent.[1] We intended to study the effects of larger structural differences among the racemate and the chiral and achiral auxiliaries (BA, Fig. 1) compared to the previously investigated agents. The substantial difference among the structures of the new resolving agent (BAB) and the previously used compounds is that the stereogenic carbon atom is placed on the other side of the nitrogen atom and not in the benzylamine moiety.

For comparison, the joint effects of (*R*)-(+)-1-phenylethylamine [(*R*)-(+)-PhEA] and benzylamine (BA, Fig. 1) have also been investigated in different solvents.

2. Results and discussion

2.1. Resolution of racemic *N*-formylphenylalanine (FPhA) with (*S*)-(+)-2-benzylaminobutanol [(*S*)-(+)-BAB] in water

At an early stage of the method development, we used water as a solvent in a similar way to the previously studied resolutions of racemic FPhA. In water, using (*R*)-(+)-PhEA as resolving agent, high enantiomeric excess could be achieved[7] (racemate: resolving agent 1:1 ratio: ee = 95%, yield = 44%, $F = 0.42$; half equivalent ratio: ee = 74%, yield = 46%, $F = 0.34$).

Under similar conditions, in aqueous solution, the efficiency of (*S*)-(+)-BAB was much smaller (ee: 27%, $F = 0.18$). In this case the diastereomeric salt that contained an excess of the (*R*)-(−)-FPhA enantiomer (Fig. 2) precipitated. Using half an equivalent of resolving agent, the result could be slightly improved upon (ee: 53%, $F = 0.22$) but these results were far behind those attained with PhEA ($F = 0.42$). Furthermore, the efficiency could not be improved upon in water solvent. Consequently, in aqueous solution, the minor structural similarity of the resolving agent causes a negative effect on the chiral separation.

2.2. Binary phase diagram of the (*S*)-(+)-benzylaminobutanol (*R*)-(−)-*N*-formylphenylalanine [(*S*)-(+)-BAB·(*R*)-(−)-FPhA] and (*S*)-(+)-benzylaminobutanol (*S*)-(+)-*N*-formylphenylalanine [(*S*)-(+)-BAB·(*S*)-(+)-FPhA] diastereomeric salt mixture

In order to gain a deeper insight into the details of the chiral recognition process, we determined the binary phase diagram[8,9] of the (*S*)-(+)-BAB·(*R*)-(−)-FPhA and (*S*)-(+)-BAB·(*S*)-(+)-FPhA diastereoisomeric salts (Fig. 3). The eutectic composition was found at 0.33 (*S*)-(+)-BAB·(*R*)-(−)-FPhA/(*S*)-(+)-BAB·(*S*)-(+)-FPhA ratio, the eutectic temperature is 371 K. The calculated expected efficiency on the basis of the data of the phase diagram is F_{calc}[†] = 0.51.[9] As was mentioned before, the experimentally determined F parameters of both resolutions in water (using an equivalent and half equivalent of resolving agent) have fallen far behind this value and could not be further optimized.

2.3. Resolution of racemic *N*-formylphenylalanine (FPhA) with (*S*)-(+)-2-benzylaminobutanol [(*S*)-(+)-BAB] in acetone

In order to improve the results and attain the efficiency that was predicted by the phase diagram the solvent of the

[†] $F_{calc} = \frac{1-2x_{eu}}{1-x_{eu}}$; x_{eu}: eutectic composition (molar ratio).

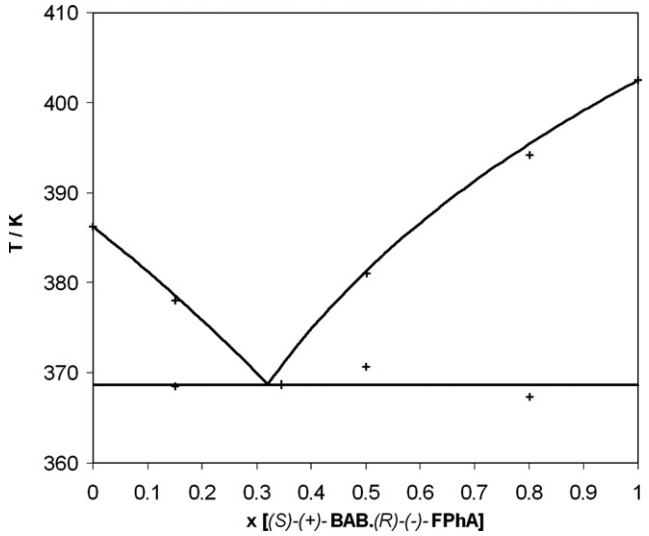

Figure 3. Binary phase diagram of the diastereomeric salt mixture.

diastereoisomeric salt formation was changed. By working in acetone with a 1:1 molar ratio, a remarkable enantiomer separation was achieved (Table 1). The (*S*)-(+)-BAB·(*R*)-(−)-FPhA diastereomeric salt precipitated, from which (*R*)-(−)-FPhA could be recovered with 83% ee and with considerably high efficiency ($F = 0.73$); this was much better than the results achieved with the previously used structurally related resolving agents.

Table 1. Comparison of the resolution results of FPhA with (*S*)-(+)-BAB in water and acetone

Solvent	Molar ratio racemate: resolving agent	ee[a] (%)	*Y*[b] (%)	*F*[c]	Time of crystallization
Water	1:1	27	66	0.18	12 days
Water	1:0.5	53	42	0.22	2 days
Acetone	1:1	83	88	0.73	15 h
Acetone	1:1	49	93	0.4	3 h
Acetone	1:0.5:0.5 Et_3N	51	42	0.21	

[a] Enantiomeric excess based on specific rotation.
[b] Yield.
[c] Fogassy-parameter characterizing the efficiency of the resolution; $F = \text{ee} \times Y$.[10]

Since the efficiency of the resolution in acetone was significantly higher (Table 1, 0.73, line 3) than the calculated value on the basis of the thermodynamic data (0.51), we were able to establish that acetone has an additional effect, which improves the results in an extent to exceed the thermodynamically determined state of the binary system investigated. Presumably, acetone, an achiral solvent, selectively interacts with the diastereomeric molecule-associates during the crystal formation. As a result of this interaction the chiral recognition processes are influenced and improved upon.

Rationalization of the observed phenomena can be done if the possible hemiaminal forming reaction of acetone with the resolving agent is taken into consideration (Fig. 4). Even this equilibrium reaction is slightly shifted into the (*S*)-BABHA direction, the latter compound exists in solution as a structurally similar resolving agent related to (*S*)-BAB. In other words, a special type of 'Dutch-resolution'[3] was accomplished by in situ formation of the relative of the original resolving agent. Presumably, (*S*)-BAB·(*R*)-FPhA is the less soluble salt within the equilibrium system while the other enantiomer stays in the solution mainly as an (*S*)-BABHA·(*S*)-FPhA salt or at least a strong acetone solvate of the (*S*)-BAB·(*S*)-FPhA salt exists in the solution while the crystalline diastereoisomeric salt does not contain any solvate. Thus, we have a different system in the thermodynamic equilibrium of the reaction mixture, than we have measured during the determination of the binary phase diagram mixing the separately prepared, solid, unsolvated diastereoisomeric salts in different ratios.

Using this theory we can explain the increase of the characteristic parameters of the (*S*)-BAB·(*R*)-FPhA salt precipitated after 3 h (ee: 49%, *F*: 0.46) and 15 h (ee: 83%, *F*: 0.73), respectively.

When (*R*)-(+)-PhEA resolving agent was used in acetone, significant enantiomer separation could not be achieved.

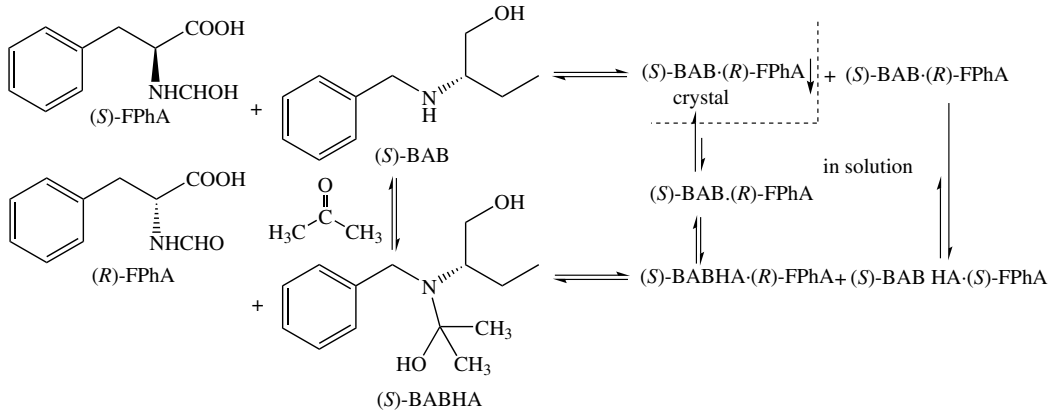

Figure 4. A possible explanation of improving effect of acetone.

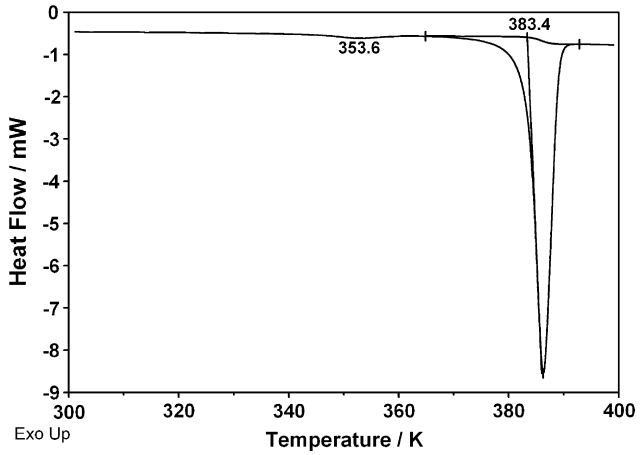

Figure 5. DSC curve of the (*S*)-(+)-BAB·(*S*)-(+)-FPhA diastereomer that shows the reversible polymorphic phase transition at 353.6 K and the melting of the salt.

2.4. Polymorphism of the more soluble (*S*)-(+)-BAB·(*S*)-(+)-FPhA diastereomer

We have also observed that the more soluble (*S*)-(+)-BAB·(*S*)-(+)-FPhA diastereomer has two polymorphic modifications in an enantiotopic relationship. The equilibrium temperature is 353.6 K (Fig. 5). The polymorphic phase transition is reversible, at room temperature the less stable modification transforms back to the stable form in a few hours and the polymorphic transition of the sample can be observed again by DSC. When polymorphism occurs in a given system, then the probability that kinetic effects could be expressed is increased, since the number of possible crystallization routes is increased.[11,12]

2.5. Dutch resolution of *N*-formylphenylalanine using (*S*)-(+)-2-benzylaminobutanol and (*R*)-(+)-1-phenylethylamine resolving agents

In water, using a mixture of (*S*)-(+)-BAB and (*R*)-(+)-PhEA resolving agents in a 1:1 ratio, (*R*)-(+)-1-phenylethylammonium (*R*)-(−)-*N*-formylphenylalaninate [(*R*)-(+)-PhEA·(*R*)-(−)-FPhA] was precipitated in low diastereomeric excess and low efficiency. The presence of (*S*)-(+)-BAB decreased the efficiency when compared to what could be achieved with pure (*R*)-(+)-PhEA resolving agent. Consequently the structural similarity of the two resolving agents was lower than needed for a favourable interaction.

When the above mentioned resolving agent mixture was used, now in acetone (5% water), the precipitating diastereomer changed to (*S*)-(+)-BAB·(*R*)-(−)-FPhA and the efficiency of the resolution was satisfactory (ee 81%, $F = 0.41$) but it was much smaller than the efficiency of the resolution with the pure (*S*)-(+)-BAB (Table 2). The change in the precipitating diastereomer caused by the change of solvent is noteworthy. The crystalline phases did not combine with each other as they do in regular Dutch resolution experiments, but competition was observed between them.

It had been formerly demonstrated that in aqueous solvent, the formation of (*R*)-(+)-PhEA. (*R*)-(−)-FPhA crystalline phase has a kinetic advantage.[13] In acetone, the precipitation of (*S*)-(+)-BAB·(*R*)-(−)-FPhA could be promoted by the selective interactions of the diastereoisomeric salts with the acetone solvent.

Table 2. Results of the resolutions of FPhA with (*S*)-(+)-BAB using (*R*)-(+)-PhEA as chiral additive

Solvent	Molar ratio	ee (%)	*Y* (%)	*F*
Water	FPhA:(*S*)-BAB:(*R*)-PhEA 1:0.5:0.5	28	21	0.06
Acetone (5% water)	FPhA:(*S*)-BAB:(*R*)-PhEA 1:0.5:0.5	81	51	0.41

2.6. Resolution of *N*-formylphenylalanine with (*S*)-(+)-2-benzylaminobutanol using benzylamine achiral additive

When half of the resolving agent (*S*)-(+)-BAB was replaced with achiral benzylamine (BA), (*R*)-(−)-FPhA·(*S*)-(+)-BAB precipitated from the acetone solution, with almost zero diastereomeric excess (ee 2%, $F = 0.01$, Table 3). In other words, BA achiral additive ruins the resolution with (*S*)-(+)-BAB. The effect of (*R*)-(+)-PhEA and BA on the resolution with (*S*)-(+)-BAB resolving agent is remarkably different despite their high structural similarity.

When the (*R*)-(+)-PhEA resolving agent was applied together with the BA additive in a 1:1 ratio, the results were similar to that obtained during the resolution with half an equivalent of (*R*)-(+)-PhEA resolving agent.[14] In the precipitated diastereoisomeric salt, the BA/(*R*)-(+)-PhEA ratio was approximately 1:4; presumably the similar molecular structures of the two agents made solid solution formation possible. The presence of the achiral BA hardly influences the chiral recognition phenomena when the structural differences between the resolving agent and the additive are slight. This is what we would expect whilst BA can replace (*R*)-(+)-PhEA in its molecular interactions but cannot express a chiral effect.

2.7. Complex solid–liquid equilibrium of the *N*-formylphenylalanine enantiomers

A binary phase diagram of the mixture of *N*-formylphenylalanine enantiomers was also constructed on the basis of thermoanalytical data (Fig. 6).[15] At room temperature, a conglomerate form seemed to be stable. At higher temperatures, an unstable racemic compound formed and then it transformed into a stable racemic compound form that melts at 167 °C (Table 4).

Table 3. Comparison of the resolutions using BA achiral additive with (*S*)-(+)-BAB and (*R*)-(+)-PhEA resolving agents

Solvent	Resolving agent	Molar ratio (racemate:resolving agent:additive)	ee (%)	*Y* (%)	*F*
Water	(*R*)-(+)-PhEA	1:0.5:0.5	75	35	0.26
Acetone (5% water)	(*S*)-(+)-BAB	1:0.5:0.5	2	59	0.01

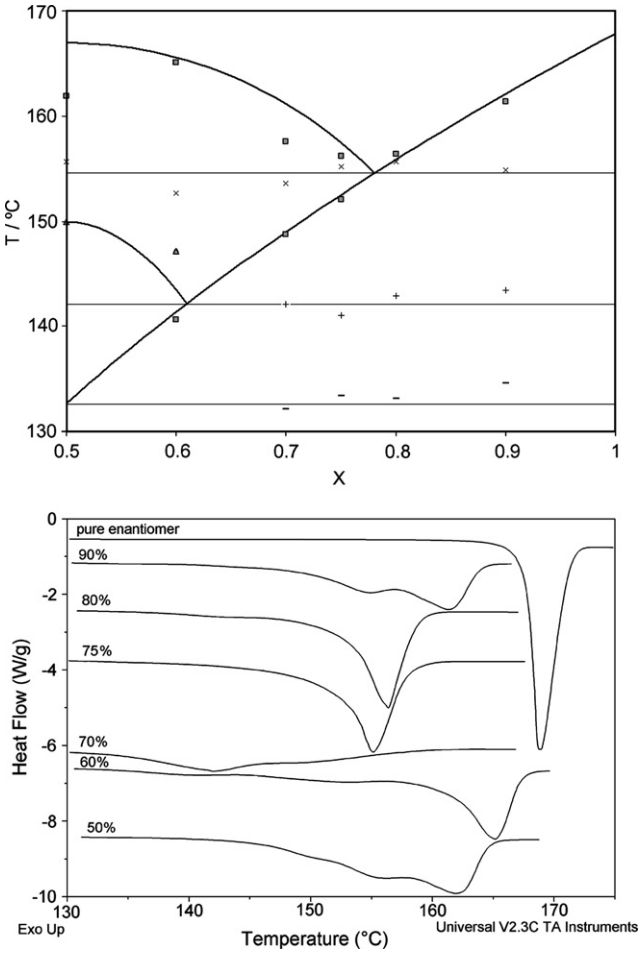

Figure 6. Binary phase diagram and DSC curves of the *N*-formylphenylalanine enantiomeric mixtures.

In order to find a good purification method for FPhA enantiomeric mixtures, three types of enantiomeric enrichment experiments were accomplished in our laboratory: fractional crystallization, parietal hydrochloride salt formation and recrystallization from water. The results are summarized in Table 5.

It can be seen from the experimental data that the FPhA enantiomeric mixtures can be purified until reaching the eutectic composition, however further purification is only possible with another derivative or using a chiral agent (repeated resolution).

Table 4. Characteristic data of the conglomerate and racemic forms of FPhA enantiomeric mixtures

	Conglomerate	Racemic compound **1**	Racemic compound **2**
Eutectic composition (*R*/*S*)	0.50	0.61	0.78
Enantiomeric excess (%)	0	22	56
Eutectic temperature (°C)	132.6	142.1	154.6

Table 5. Results of enantiomeric enrichment experiments

	Enantiomeric excess		
	ee_0[a] (%)	ee_1[a] (%)	ee_2[a] (%)
Fractional crystallization	49.6	19.3	75.0
Neutral solution/HCl	73.4	70.8	68.0
Recrystallization from water	75.0	73.4	74.5

[a] ee_0, ee_1 and ee_2: ee values of the starting material, the first isolated and the second isolated fraction, respectively.

3. Conclusions

A detailed investigation of the resolution of *N*-formylphenylalanine with (*S*)-*N*-benzylaminobutanol in water and in acetone has allowed us to develop a new method for the enantiomer separation of FPhA. The efficiency of the resolution, carried out with (*S*)-BAB in acetone, was significantly higher ($F = 0.73$) than that described in the literature method [(*R*)-PhEA resolving agent, $F = 0.42$][14] and higher than the calculated value ($F = 0.51$) of the resolvability expected on the basis of thermoanalytical data. The success was attributed to a special effect of the solvent (acetone) which can form a hemiaminal derivative of (*S*)-BAB resulting in an in situ formation of a relative resolving agent ((*S*)-BABHA) in the reaction mixture. Time-dependent experiments confirmed our hypothesis: prolonged crystallization time caused the best separation when it was long enough to achieve the diffusion-controlled equilibrium of the proposed multicomponent equilibrium system. In addition, two polymorphic forms of the more soluble diastereoisomeric salt ((*S*)-BAB-(*S*)-FPhA) were detected.

The structural similarity of (*S*)-*N*-benzylaminobutanol was not enough to make it able to cooperate with another structurally related benzylamine-derivative resolving agent [(*R*)-PhEA]. Instead, a competition was observed between the salts of the two resolving agents and the efficiency of the resolution, using the mixture of the resolving agents, was worse than it was with the use of the individual compounds.

The achiral benzylamine additive did not influence the chiral recognition process when its molecular structure was close to that of the resolving agent. In the case of (*S*)-*N*-benzylaminobutanol where the structural differences were more expressed, the negative effect of benzylamine on the enantiomer separation was significant.

Thermoanalytical investigations of FPhA enantiomeric mixtures showed a temperature-dependent conglomerate versus racemate formation. The presence of the thermodynamically more stable racemate strictly determines the efficiency of the enantiomeric enrichment processes: the ee cannot improve above the eutectic composition by these methods.

4. Experimental

Chemicals were products of Aldrich. Optical rotations were determined on a Perkin Elmer 241 polarimeter. DSC

measurements were performed by TA Instruments DSC 2920 in the 290–420 K temperature range with 5 K min^{-1} heating rate. Samples were placed in a hermetically sealed pan, the measuring cell was purged with 60 ml min^{-1} nitrogen gas.

4.1. Resolution of *N*-formylphenylalanine by (*S*)-(+)-2-benzylaminobutanol (1:1) in water

A mixture of racemic FPhA (1.93 g, 10.0 mmol) and (*S*)-(+)-BAB (1.8 g, 10.9 mmol) was dissolved in water (5 cm^3) under heating. After 12 days, the (*S*)-(+)-BAB·(*R*)-(−)-FPhA salt precipitated. This was filtered out and washed with water (2×0.3 cm^3), after which it was reacted with concd HCl (2 cm^3) in water (6 cm^3). The precipitated (*R*)-(−)-FPhA was filtered off and washed with water (2×0.5 cm^3). The process yielded 0.64 g of (*R*)-(−)-FPhA (66%) $[\alpha]_D^{20} = -19.3$ (*c* 2, ethanol).

The mother liquor of the diastereomeric salt was acidified with concd HCl (2 cm^3), the precipitated (*S*)-(+)-FPhA was filtered off and washed with water (2×0.5 cm^3), the mass of the dried product was 1.0 g. $[\alpha]_D^{20} = +12.5$ (*c* 2, ethanol).

4.2. Resolution of *N*-formylphenylalanine by (*S*)-(+)-2-benzylaminobutanol (1:1) in acetone

(a) A mixture of racemic FPhA (19.3 g, 0.1 mol) and (*S*)-(+)-BAB (17.9 g, 0.1 mol) was dissolved in hot acetone (10 cm^3). After one night (15 h), the (*S*)-(+)-BAB·(*R*)-(−)-FPhA diastereomer salt precipitate was filtrated and washed with acetone (2×1 cm^3). It was reacted with concd HCl (2×1 cm^3) in water (5 cm^3). The precipitated (*R*)-(−)-FPhA was filtered and washed by water (2×0.5 cm^3). The process yielded 0.85 g (*R*)-(−)-FPhA (88.0%) $[\alpha]_D^{20} = -62.3$ (*c* 2, ethanol), ee: 83.0%.
The mother liquor of the diastereomeric salt was evaporated and acidified with concd HCl (3 cm^3). The precipitated (*S*) -(+)-FPhA was filtered and washed by water (2×0.5 cm^3), the mass of the dried product was 0.95 g, (98%), $[\alpha]_D^{20} = +58.1$ (*c* 2, ethanol).

(b) The work is similar to that described before, but the diastereomer salt precipitate was filtrated after 3 h. The process yielded 0.90 g (*R*)-(−)-FPhA (93.3%) $[\alpha]_D^{20} = -36.8$ (*c* 2, ethanol), ee: 49.1%. The mass of the dried (*S*)-(+)-FPhA separated from mother liquor was 0.66 g, (68.5%), $[\alpha]_D^{20} = +41.8$ (*c* 2, ethanol).

4.3. Resolution of *N*-formylphenylalanine by (*S*)-(+)-2-benzylaminobutanol and (*R*)-(+)-1-phenylethylamine (1:0.5:0.5) in water

Racemic-**1** (1.93 g, 10.0 mmol), (*S*)-(+)-**3** (0.67 g, 5.5 mmol) and (*R*)-(+)-**2** (0.9 g, 5.5 mmol) were dissolved in water (5 cm^3). After 2 days the diastereomeric salt precipitated. It was filtrated and washed with water (2×0.3 cm^3). Then it was treated with concd HCl (2 cm^3) in water (5 cm^3) to give 0.2 g (*R*)-(−)-**1**, $[\alpha]_D^{20} = -20.8$ (*c* 2, ethanol).

The mother liquor was acidified with concd HCl (2 cm^3) and the precipitate filtrated to give 1.3 g (*S*)-(+)-**1**, $[\alpha]_D^{20} = +4.9$ (*c* 2, ethanol).

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