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The influence of molecular structure and crystallization time on the efficiency of diastereoisomeric salt forming resolutions

Emese Pálovics [a], József Schindler [a], Ferenc Faigl [a,b], Elemér Fogassy [b,*]

[a] *Research Group for Organic Chemical Technology, Hungarian Academy of Sciences, Hungary*
[b] *Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, H-1521 Budapest, PO Box 91, Hungary*

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ABSTRACT

Reciprocal resolutions between compounds (racemates and enantiomers) with similar structures have been examined. Amongst structurally similar compounds (so called relative structures) several *N*-acyl amino acids and amino acid esters were investigated. A part of the resolving agent or the racemic compound could be replaced by an achiral compound with a relative structure and an additive could occasionally improve significantly the efficiency of the resolution. Both the kinetic and the thermodynamic controls were observed as governing factors of the reciprocal resolutions.

1. Introduction

Since Pasteur,[1] the most widespread and well-known method used in both research and industrial practice for the separation of enantiomers is based upon fractional crystallization of diastereoisomeric salts. The known procedures have been compiled and reported on in several books[2–4] and reviews.[5–7] During this period of time, several important observations and recognitions improved the techniques used by structural chemists, several of which caused a change of attitude, such as the Marckwald rule[8] or the recognition of Pope and Peachey:[9] the application of half an equivalent of resolving agent together with half an equivalent of an achiral reagent, which has the same chemical character as the resolving agent, for the resolution of an equivalent amount of racemate. In this case, the diastereoisomeric salts have to be separated from the achiral salts of the enantiomers by fractional crystallization instead of crystallization of a mixture of diastereoisomeric salts; thus the efficiency of the resolution could be improved. Another essential recognition is the 'Dutch resolution'[10] which uses a mixture of resolving agents and may give better results than those observed when the resolving agents are used individually.

An extension of the 'Dutch resolution' is when equimolar amounts of structurally related resolving agents are used as nuclear inhibitors.[11]

Sakai[12] recognized that the configuration of the major enantiomer in the diastereoisomeric salt depends on the dielectric constant (ε) of the solvent used and hence developed the so-called 'dielectrically controlled resolution' (DCR) for the separation of both enantiomers of α-amino-ε-caprolactam. This finding is in good agreement with our earlier observations in the cases of the resolutions of 1-phenylglycine derivatives with tartaric acid.[13] During that time, we developed a quantitative approach to the efficiency of the resolutions and the equations containing the empirical factor of solvent polarity (E_T correlates with ε) as a strongly influencing parameter of the chiral discrimination processes.[13,14] Sakai also recognized a correlation between the relative molecular length of the resolving agent to the racemic compound and the resolvability.[15]

The resolution of several racemic amino acids was accomplished with derivatives of their own enantiomers (benzoyl-**PhA**, **FoPhA**/**PhGA**) or with a structurally similar chiral amine (e.g., **PhEA**). Therefore, we were interested in reciprocal resolutions where the derivatives of amino acids with either acidic or basic character could be used both as racemic compounds and in optically active form as resolving agents, respectively. It should be mentioned that these amino acid derivatives have a characteristic structural relationship between certain limits.

The compounds used were the N-acylated or esterified derivatives of phenylglycine **PhG** and phenylalanine **PhA**. These compounds were treated as structurally similar derivatives of 1-phenylethylamine **PhEA** and 1-phenyl-isopropylamine **A**, respectively. We also investigated the influence of structurally similar achiral compounds, benzylamine **BA** and phenoxyacetic acid **POAA**, on the efficiencies of reciprocal resolutions (see Scheme 1).

2. Results and discussion

2.1. The resolution of *N*-acyl amino acids with structurally similar bases

First the racemic *N*-acyl amino acids were resolved with optically active esters **PhGMe**, **PhAMe**, amide **PhGA**, and the

* Corresponding author.
E-mail address: efogassy@mail.bme.hu (E. Fogassy).

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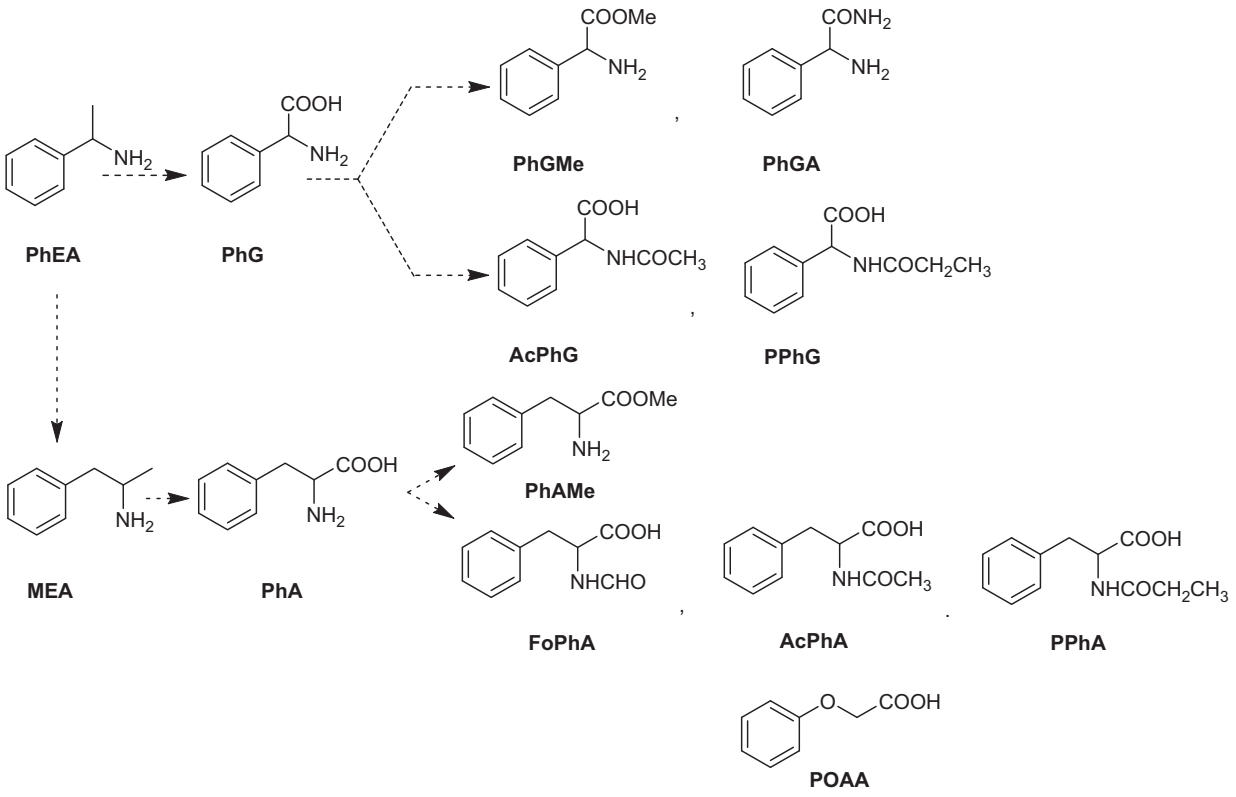


Scheme 1. A 'Family tree' of the structurally similar model compounds.

structurally similar bases **PhEA**, and its derivative **MEA**, in aqueous solution (Table 1).

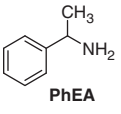
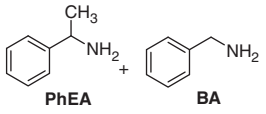
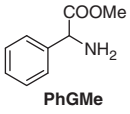
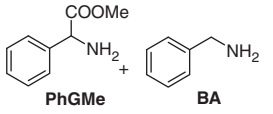
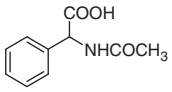
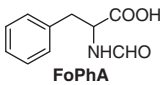
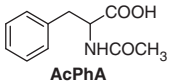
Based on the results shown in Table 1, it can be seen that the optically active methyl esters of the amino acids **PhGMe**, **PhAMe**

Table 1
Results of resolutions of racemic *N*-acyl amino acids with structurally similar derivatives

Racemic compounds	Resolving agents														
	PhGMe			PhAMe			PhGA			PhEA			MEA		
	oy[a]	*Y*[b]	*F*[c]	oy[a]	*Y*[b]	*F*[c]	oy[a]	*Y*[b]	*F*[c]	oy[a]	*Y*[b]	*F*[c]	oy[a]	*Y*[b]	*F*[c]
AcPhG	29.8	134	0.40	96.1	56.0	0.54									
PPhG	68.5	34.5	0.24				62.5	18.0	0.11						
FoPhA	71.9	54.0	0.39							90.8	44.0	0.40			
AcPhA	55.0	47.6	0.26	92.8	61.1	0.57	74.5	58.1	0.43	5.0	102	0.05	71.8	26.4	0.19
PPhA	33.5	85.5	0.29				63.3	76.0	0.48						

[a] Optical yield; the maximum optical rotations of the *N*-acyl amino acids are known so we expect that the optical yield will be very close to the enantiomeric excess (ee).
[b] Yield refers to one of the enantiomers in the racemate.
[c] $F = \text{oy} * Y$.

Table 2
Results of the resolutions of racemic *N*-acyl amino acids with **PhEA**, **PhGMe** and with their mixtures with **BA**

Racemic compounds	Resolving agents											
	 **PhEA**			 **PhEA** **BA**			 **PhGMe**			 **PhGMe** **BA**		
	oy[a]	Y[b]	F[c]	oy[a]	Y[b]	F[c]	oy[a]	Y[b]	F[c]	oy[a]	Y[b]	F[c]
 **AcPhG**				26.2	45.3	0.12	29.8	134	0.40	85.1	64.2	0.55
 **FoPhA**	90.8	44.0	0.40	71.2	34.2	0.24	71.9	54.0	0.39	71.1	42.0	0.30
 **AcPhA**	5.0	100	0.05	25.0	64.0	0.16	55.0	47.6	0.26	95.0	19.0	0.18

[a] Optical yield; the maximum optical rotations of the *N*-acyl amino acids are known hence we expect that the optical yield will be very close to the enantiomeric excess (ee).
[b] Yield refers to one of the enantiomers in the racemate.
[c] $F = \text{oy} * Y$.

are suitable resolving agents for every racemic compound. Phenylglycine amide **PhGA** differentiated between the enantiomers of three compounds.

Consequently each racemic *N*-acetyl amino acid could be resolved with structurally similar resolving agents, especially optically active **PhAMe**, which gave good results with **AcPhG** and **AcPhA**. It is noteworthy that **PhEA** could properly discriminate between the **FoPhA** enantiomers. Therefore, the effect of different additives was examined in order to achieve reasonable efficiencies of resolution with **PhEA**.

2.2. Resolution using a mixture of resolving agents and compounds with a related structure

It is known that using the conditions of a 'Dutch resolution' may improve the efficiency of a resolution related to the resolution carried out with a simple resolving agent, and in several cases the addition of another or several (structurally similar) resolving agents to the original one, which was unable to differentiate between the enantiomers, may induce efficient chiral discrimination. We supposed that if a part (half) of **PhEA** was replaced by an analogous, but achiral compound, benzylamine (**BA**), it could improve the chiral discriminating effect of **PhEA** for some racemic model compounds. The resolutions of **AcPhG**, **FoPhA** and **AcPhA** using a mixture of **PhGMe** and **BA** were accomplished and the results were compared to the results of the enantiomer separations attempted by **PhEA** alone (Table 2).

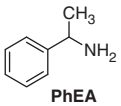
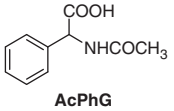
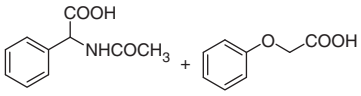
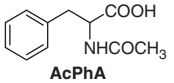
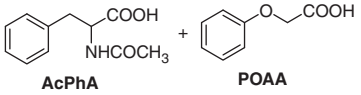
The experimental data show that **BA** had a slightly positive effect in the cases of resolutions of **AcPhG** and **AcPhA** with **PhEA**+**BA**. In the third case, this resolving agent mixture decreased the efficiency of resolution. Good results were also achieved with the **PhGMe**+**BA** combination. The enantiomeric excess increased significantly when **AcPhG** and **AcPhA** were resolved with the aforementioned mixture of amines (29.8%→85.1% and 55.0%→95.0%, respectively).

2.3. Resolution of a mixture of racemic compounds and their analogs

In a special combination of 'Dutch resolution' the structurally similar racemic compounds were mixed before diastereoisomeric salt formation. It turned out that several compounds, which could not be resolved into it their enantiomers with certain resolving agents, could be separated into the pure enantiomers when a structurally similar racemate was added into the reaction mixture before crystallization of the diastereoisomers.[10]

Starting from the aforementioned observation, two compounds were selected (**AcPhG** and **AcPhA**), which did not give enantiomer separation with optically active **PhEA**. The effects of the addition of a structurally similar achiral compound (phenoxyacetic acid, **POAA**[†]) not be resolved into it their enantiomers with certain resolving agents, could be separated into the pure enantiomers when a structurally similar racemate was added into the reaction mixture before crystallization of the diastereoisomers.[10]

Table 3
Resolution of racemic **AcPhG**, **AcPhA** and their mixtures with **POAA**

Racemic compounds/+ the achiral additive	Resolving agent  **PhEA**		
	oy[a]	Y[b]	F[c]
 **AcPhG**			
 **AcPhG** **POAA**	31.0	97.9	0.30
 **AcPhA**	5.0	102	0.05
 **AcPhA** **POAA**	87.5	61.5	0.54

[a] Optical yield; the maximum optical rotations of the *N*-acyl amino acids are known so we expect that the optical yield will be very close to the enantiomeric excess (ee).
[b] Yield, refers to one of the enantiomers in the racemate.
[c] $F = \text{ee} * Y$.

[†] The 3-phenylpropionic acid would be an better choice than the phenoxyacetic acid, but experimentally the efficiency of the resolution was improved just in a small amount (10%). On the other hand, applying the **POAA** this result becomes predominant.

to racemic compounds were then investigated. The results are summarized in Table 3.

On the basis of the aforementioned experimental facts, we presumed that the presence of **POAA** in an equivalent amount with the racemic compound would make the conditions of the crystallization of a diastereoisomeric salt favourable.

2.4. The influence of the time of the crystallization

Recently, we described[16] that in certain cases, the duration of crystallization has a strict role in determination of the efficiency of the resolution. It was observed that during the crystallization of **FoPhA*****PhEA** diastereoisomeric salts, the initially high enantiomeric excess (90.8%) diminished when the filtration of the precipitated salt was carried out after a longer standing. This kinetic control was verified by the different rates of crystallization of the two diastereomers,[17] i.e., a large difference was observed in the kind of crystal growth of the diastereomers. The crystals of the faster crystallizing diastereoisomer grew independently from the direction (every side of the nucleus), while the other diastereoisomer formed only linear crystals (Table 4a).

Thus, the racemic *N*-acyl amino acids could be successfully resolved by bases with a similar structure, although, the most efficient resolutions could be achieved using their *N*-acetyl derivatives.

As a result, the possibility of reciprocal resolution was examined. A racemic mixture of the base, applied earlier as a resolving agent **PhEA**, was resolved with the enantiomers of *N*-acyl amino acids (**FoPhA** and **AcPhA**). We were particularly interested in the crystallization time dependence of the efficiencies of the reciprocal resolutions. Therefore, resolution of racemic **PhEA** with optically active **FoPhA** (Table 5a) and with a mixture of optically active **AcPhA** and **POAA** (Table 5b) was investigated.

The data in Table 5 verify that the kinetic control is also present at the reciprocal resolution, as it was observed in the direct resolution (**FoPhA-PhEA**). The positive effect of thermodynamic control was observed in the reciprocal resolution of **AcPhA-PhEA-POAA** system. When the reciprocal resolution of the same diastereomer salt crystallized, the influence of both kinetic and thermodynamic controls could be supposed.

A comparison of the results of the original resolutions with their reciprocal versions can be seen in Figures 1 and 2. In the normal and the reciprocal resolutions of **FoPhA** and **PhEA**, the ee values (measured in the crystallized diastereoisomeric salt) decreased in a similar way when the duration of crystallization was increased (Fig. 1) because the normal and the reciprocal systems were very similar: the same diastereoisomeric salt crystallized and the filtrate contained the other diastereoisomer and/or enantiomer, which were in a mirror image relationship with each other regarding the normal and the reciprocal resolution systems.

The **AcPhA-PhEA-POAA** system behaved differently (Fig. 2), probably because an achiral additive (**POAA**) and its salt remained in the filtrate together with the residue of the crystallized diastereoisomer, while the three component supramolecular structure in the solution influenced the chiral discrimination procedure in the normal resolution process much better (the position of the equilibrium) than that had occured in the reciprocal case.

The (*S*)-**AcPhA***(*R*)-**PhEA** diastereoisomeric salt slowly crystallized from the aqueous solution. The **POAA***(*R*)-**PhEA** salt crystallized faster but its solubility is higher and solvation was also faster than that of the diastereoisomeric salt. Therefore, from the aqueous solution of the mixture of these salts, the diastereoisomeric salt crystallized practically alone.

During the normal resolution process, when racemic **AcPhA**, **POAA** and (*R*)-**PhEA** are in the reaction mixture, the **POAA***(*R*)-**PhEA** salt crystallizes first. This salt is probably the catalyst of crystallization of the (*S*)-**AcPhA***(*R*)-**PhEA** diastereoisomeric salt and it also accelerates the stabilization of the equilibrium system. In the reciprocal resolution [in the solution there are (*S*)-**AcPhA**, **POAA** and the racemic **PhEA**] crystallization of the achiral **POAA***(±)-**PhEA** salt is the fastest and at the same time these crystals can initiate the crystallization of both diastereoisomeric salts. However, this process works against the stabilization of the equilibrium system, therefore, a longer crystallization time is necessary to achieve the thermodynamically controlled endpoint of the resolution.

3. Conclusions

On the basis of the experimental data we have concluded that the investigated structurally similar chiral compounds are suitable resolving agents for each other. In other words, pure enantiomers of the racemic starting compounds of the normal resolutions could be used as resolving agents of the racemic mixture of the first resolving agent (reciprocal resolutions).

These structurally similar compounds behaved analogously in both cases: as racemic compounds and as resolving agents in the separation of diastereomers. A practical consequence of these observations is the enlargement of the number of possible resolving agents for a given racemate by simple chemical modification of its enantiomer into a structurally similar derivative with opposite acidic or basic character related to the original racemate.

It was also demonstrated that the addition of achiral compounds with similar chemical structures to the resolving agents **BA**, or similar to the racemates **POAA** may strongly influence the efficiency of the resolutions. These achiral additives with relative structures work as special 'organocatalysts' influence the rate and the efficiency of the chiral discrimination processes. Their amplification effect could be observed both at the normal and at the reciprocal resolutions. The additives may affect the kinetics of the crystallization and the position of the thermodynamic equilibrium during diastereoisomeric salt forming resolutions, therefore, the duration of crystallization should be studied during the optimization of any normal or reciprocal resolutions, respectively.

4. Experimental

4.1. General

Chemicals were the products of Aldrich (Steinheim, Germany).

Optical rotation data were measured with a Perkin–Elmer 241 automatic polarimeter.

4.1.1. Resolution of *N*-acyl amino acids using bases with relative structure general method

A mixture of 20.0 mmol of the racemic *N*-acyl amino acid and 20.0 mmol of the resolving agent was dissolved in water under heating. After cooling the precipitate was filtered off after one day of standing, and washed with water (2 cm^3), after which it was suspended in water (10 cm^3) and reacted with concentrated HCl (4 cm^3). After standing for 4 h, the precipitate was filtered off and washed with water (2 × 1 cm^3).

The mother liquor of the diastereomeric salt was acidified with conc. HCl (5 cm^3), the precipitate was filtered off and washed with water (2 × 1 cm^3).

The results are shown in Table 1. Reproducibilities were good; the experimentally determined error limit of the enantiomeric purity was ±3%.

4.1.2. Resolution of racemic *N*-acetyl phenylalanine with a mixture of PhEA and POAA

To a mixture of 10.0 mmol of racemic **AcPhA**, 10.0 mmol of **POAA** and 18.0 mmol of (*R*)-(−)-**PhEA** was added 20 cm^3 of water

Table 4
The predominance of kinetic (a) and thermodynamic (b) control during crystallization of **FoPhA*PhEA** and **AcPhA*PhEA** salts

	Racemic compounds	Time hour	Resolving agents					
			PhEA			PhEA		
			oy[a]	*Y*	*F*	oy[a]	*Y*	*F*
a	FoPhA	2	90.8	44.0	0.40			
		168	65.1	58.4	0.38			
b	AcPhA + POAA	0.5				41.3	53.3	0.22
		15				87.5	61.5	0.54

[a] Optical yield; the maximum optical rotations of the *N*-acyl amino acids are known hence we expect that the optical yield will be very close to the enantiomeric excess (ee).

Table 5
The predominance of kinetic (a) and thermodynamic (b) control during crystallizations of diastereoisomeric salts in the reciprocal resolution

	Racemic compounds	Time hour	Resolving agents					
			FoPhA			AcPhA + POAA		
			oy[a]	*Y*	*F*	oy[a]	*Y*	*F*
a	PhEA	0.5	78.6	46.0	0.36			
		312	43.3	63.0	0.28			
b	PhEA	3				26.0	41.7	0.11
		168				49.3	57.0	0.28

[a] Optical yield; the maximum optical rotations of the *N*-acyl amino acids are known hence we expect that the optical yield will be very close to the enantiomeric excess (ee).

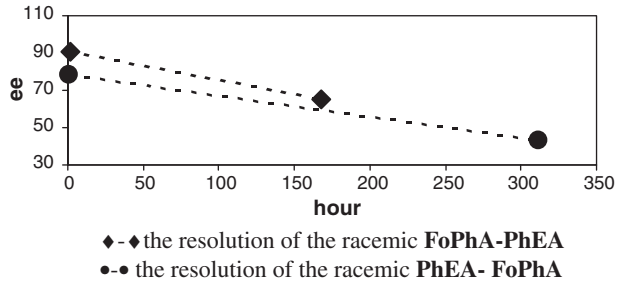


Figure 1. Changing the enantiomer content of the precipitated diastereoisomeric salt (ee) in kinetically controlled normal and reciprocal resolutions during a prolonged crystallization time.

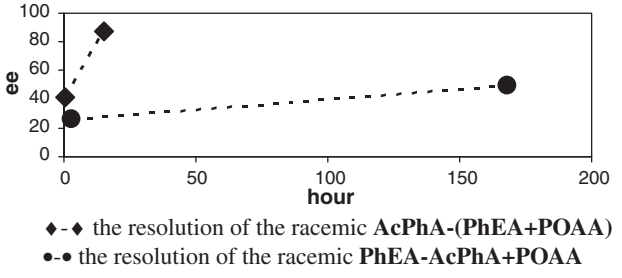


Figure 2. The change of the enantiomer content of the precipitated diastereoisomeric salt (ee) in thermodynamically controlled normal and reciprocal resolutions during a prolonged crystallization time.

under heating. After cooling, the precipitate was filtered off after standing overnight, and washed with water (2×1 cm^3). The diastereomeric salt was dissociated in water using concentrated HCl (2 cm^3). The crystals obtained were filtered after 1 h and washed with water (2×0.5 cm^3). After drying 0.65 g of (*S*)-(+)-**AcPhA** was obtained, $[\alpha]_D^{20} = +35.6$ (*c* 1, MeOH).

The mother liquor of the diastereomeric salt was acidified with concentrated HCl (2 cm^3), after which the precipitate was filtered off and washed with water (2×1 cm^3).

4.1.3. Resolution of racemic *N*-acetyl phenylglycine with a mixture of PhEA and POAA

To a mixture of 10.0 mmol of racemic **AcPhG**, 10.0 mmol of **POAA** and 18.0 mmol of (*S*)-(−)-**PhEA** was added 20 cm^3 of water under heating. After cooling, the precipitate was filtered off after standing overnight, and washed with water (2×1 cm^3). The diastereomeric salt was dissociated in 10 cm^3 of water using concentrated HCl (2 cm^3). The crystals obtained were filtered after 1 h, and washed with water (2×0.5 cm^3). After drying 0.93 g of (*S*)-(+)-**AcPhG** was obtained, $[\alpha]_D^{20} = +74.2$ (*c* 1, MeOH).

The mother liquor of the diastereomeric salt was acidified with concentrated HCl (2 cm^3), after which the precipitate was filtered off and washed with water (2×1 cm^3).

4.1.4. Resolution of racemic phenylethylamine with a mixture of AcPhA and POAA

To 18.0 mmol of racemic **PhEA** was added the mixture of 10.0 mmol of racemic **AcPhA**, 10.0 mmol of **POAA**, and was

dissolved in 25 cm^3 of water under heating. After cooling, the precipitate was filtered off, and washed with water (2×1 cm^3). The diastereomeric salt was dissociated in water using concentrated NH_4OH (2.5 cm^3). The crystals obtained were filtered after 1 h, and washed with dichloromethane (2×10 cm^3). After drying 0.65 g of (*R*)-(−)-**PhEA** was obtained, $[\alpha]_D^{20} = -10.5$ (*c* 1, EtOH).

The mother liquor of diastereomeric salt was acidified with concentrated HCl (2 cm^3), after which the precipitate was filtered off and washed with water (2×1 cm^3).

Acknowledgement

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