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Development of a Liquid-Phase Process for Recycling Resolving Agents within Diastereomeric Resolutions

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Abstract:

This paper describes a liquid-phase process for recycling of resolving agents used in the diastereomeric resolution of chiral bases. The process is applicable to the resolution of any chiral base by an organic acid resolving agent which takes place in a polar solvent. The resolving agent is first of all separated from the diastereomeric complex by addition of aqueous HCl. The initial stage of process development is selection of a water-immiscible extracting organic solvent to recover the resolving agent from the resulting acidic aqueous solution. Either distillation or organic solvent nanofiltration is subsequently used to exchange the resolving agent from the extracting organic solvent back into the polar resolution solvent. This choice between these two technologies for solvent exchange depends on the relative boiling points of the two solvents. The resolution of PPI2, a racemic amine by di-*p*-toluoyl-L-tartaric acid (DTTA), was selected as an example of a typical resolution used in an organic process. Using the conventional process, this resolution requires 1.75 mol equiv of DTTA for each mole of racemic base fed to resolution, and thus the bulk of the DTTA ends up in the mother liquor. Using the recycling process, DTTA from both mother liquor and crystals was recovered and recycled over seven consecutive resolutions, while the final product enantiomeric excess and resolution yield were maintained at 100% and 40%, respectively. In this way the DTTA requirement was decreased from 1.75 to 0.26 DTTA mol equiv, reducing the amount of fresh resolving agent needed for each resolution by 85%.

Introduction

Diastereomeric resolution by crystallisation is the predominant technique employed in resolution of chiral bases.[1] In this well-known method a chiral acid is employed as a resolving agent to form two diastereomeric salts. The eutomer (the S enantiomer in this work) is usually isolated via the crystallisation of the less soluble of these two salts.[2] L-Tartaric acid is easily isolated from nature; as a result, this acid and its derivatives are a popular choice for resolving chiral bases, accounting for half of all the acid resolving agents used in resolutions between 1960 and 1970.[3] Furthermore, of 1368 resolutions of chiral bases reported by Kozma,[4] 33% of them were performed using tartaric acid and 25% by two of its derivatives, di-*O*,*O*′-toluyl-tartaric acid (DTTA) and di-*O*,*O*′-*p*-benzyl-tartaric acid (DBTA). For cases in which the more soluble salt is formed by the eutomer and the natural form of the resolving agent, it may be desirable to replace the chiral resolving agent by its non-natural enantiomeric pair. This procedure usually results in an inversion in diastereomeric salt solubilities, ensuring that the eutomer is isolated in the less soluble salt. However, resolving agents obtained by synthesis are substantially more expensive that those derived from natural sources.

Resolving agents derived from tartaric acids have two chiral centres and two carboxylic acid groups; as a result, they can form either neutral or acidic salts with the chiral bases. An acidic salt comprises one molecule of chiral base for each molecule of dicarboxylic acid, while a neutral salt is formed between two moles of chiral base and one mole of dicarboxlyic acid. Analysis of diastereomer equilibria in solution dictates that many DTTA resolutions are best performed through formation of acidic salts. Theoretically, higher resolution yields (Y)[5] and enantiomeric excesses (ee)[6] can be achieved under these conditions, because the amount of eutomer left free in the mother liquor is minimized and the formation of mixed neutral salts containing both *R*- and *S*-enantiomers is avoided. Formation of acidic salts is usually achieved via addition of a molar ratio of resolving agent to racemic base so that the molar ratio between resolving agent and base in the resolution reaction (Γ_{react})[7] is higher than 1.5 mol equiv. The drawback of this procedure is the quantity, and associated cost, of the chiral resolving agent employed. This in turn has motivated the development of resolving agent recovery processes.

Two methods for the recovery of tartaric acid and derivatives from aqueous alkaline post resolution streams

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(1) Müller, S.; Afraz, M. C.; Gelder, R.; Ariaans, G. J. A.; Kaptein, B.; Broxterman, Q. B.; Bruggink, A. *Eur. J. Org. Chem.* **2005**, *6*, 1082−1096.

(2) Armstrong, M. D. *J. Am. Chem. Soc.* **1951**, *73*, 3(9), 4456−4457.

(3) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates and Resolutions*; Krieger Publisher: Malabar, FL, 1994.

(4) Kozma, D. *CRC Handbook of Optical Resolution via Diastereomeric Crystallisation*, CRC Press: Boca Raton, FL, 2002.

$$(5)\ Y\,(\%) = \frac{S \text{ in crystals (mol)}}{\text{racemic base fed to resolution (mol)}} \times 100$$

$$(6)\ \text{ee}\,(\%) = \frac{S \text{ in crystals (mol)} - R \text{ in crystals (mol)}}{S \text{ in crystals (mol)} + R \text{ in crystals (mol)}} \times 100$$

$$(7)\ \Gamma_{react}\,(\text{mol}\cdot\text{mol}^{-1}) = \frac{\text{resolving agent present in resolution (mol)}}{\text{racemic chiral base fed to resolution (mol)}} \times 100$$

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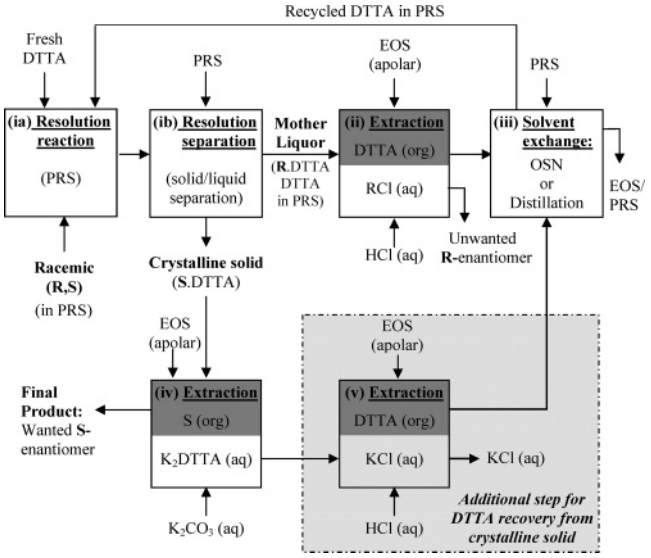


Figure 1. **Proposed process for resolution of amine (*R*,*S*) via diastereomeric resolution with recycle of resolving agent (e.g., DTTA).**

have been reported in the patent literature.[8,9] These streams arise from the alkaline cracking of diastereomeric salts either present in the recovered crystals or dissolved in the mother liquor. In both methods the tartaric acids are crystallized, which contributes to the purification of the recovered material. It also isolates them in the same physical form in which they are usually registered for use as starting materials, making for easier regulatory approval. On the other hand, the design of processes involving recycling solid chemical compounds is more challenging than recycling liquid solutions. Moreover, drying is required to desolvate the crystals and obtain the pure resolving agent. Due to the thermal instability of tartaric acid derivatives, this requires long vacuum filtration times at moderate temperatures, which can lead to high equipment occupancy during recovery and resolution cycles.

The aim of this work is to develop a generic process able to maintain $\Gamma_{react} > 1.5$ mol equiv, while decreasing the moles of fresh resolving agent fed to the process per mole of racemic base fed (Γ_{fed}),[10] thus improving process economy. The strategy followed to achieve this aim is to recycle the resolving agent within the process in liquid phases, while the chiral base enters in the process as a *rac*-*R*,*S* and leaves it as separated *S*- and *R*-enantiomers.

Liquid-Phase Recycle Process. The proposed process is illustrated schematically in Figure 1. In step ia, 1.75 mol equiv of resolving agent (e.g., DTTA) reacts with *rac*-*R*,*S* to form two acidic diastereomeric salts (*S*-DTTA and *R*-DTTA). The less soluble salt (*S*-DTTA) crystallizes out from the polar resolving solvent (PRS), e.g., acetone/water (97:3 wt %), while the more soluble salt (*R*-DTTA) and the excess DTTA remain dissolved in the mother liquor. By way of illustration, assuming a *Y* of 40% and a Γ_{react} of 1.75, about 0.4 mol equiv of DTTA is held in the crystal phase, and the remaining 1.35 equiv of DTTA remains in the mother liquor. Crystals and mother liquor are separated in step ib, and the crystals are washed with additional PRS. In step ii, after cracking of the diastereomeric salts in the mother liquor by a strong achiral acid, such as hydrochloric acid (HCl), DTTA is partitioned into an extracting organic solvent (EOS). The distomer leaves the process in the aqueous phase from this extraction as an organic chloride salt (R^+Cl^-). In step iii, the DTTA is then solvent exchanged from the EOS into the PRS using distillation or organic solvent nanofiltration (OSN). Distillation is the preferred option, and membrane solvent exchange is selected only when the boiling point of the EOS is higher than that of the PRS, or the enantiomer or resolving agent is thermally labile. The use of OSN is limited to cases in which there is good compatibility between membrane and solvents.

Finally, DTTA is recycled into the resolution step i. In the first cycle, fresh DTTA is added at a Γ_{fed} value of 1.75 mol equiv, which corresponds to the Γ_{react} value required for successful resolution. For subsequent cycles, Γ_{react} employed in step i comprises: (a) DTTA recycled within the process from step iii, and (b) fresh DTTA added at a value of Γ_{fed} chosen to compensate for any DTTA leaving the process with the crystals, and other losses. Most of the DTTA required for resolution is recycled from stage iii, and thus in the second and subsequent cycles, Γ_{fed} is significantly lower than in the first cycle.

Step iv is the conventional route for recovery of the *S*-enantiomer-enriched product from the crystals. After alkaline cracking of diastereomeric salt by a base, e.g., K_2CO_3, the *S*-enantiomer is extracted into a water-immiscible solvent, and the DTTA remains dissolved as an alkali metal carboxylate salt in the aqueous phase. An additional step (v) is required when it is desirable to increase DTTA recovery by reclaiming the 0.4 mol equiv of DTTA from the crystal phase. In step v, the alkaline aqueous phase arising from step iv is neutralized with HCl, and the neutral DTTA is extracted into an EOS, which is fed to step iii for suitable solvent exchange and further recycle into the resolution step i. In a further refinement of the process, steps ii and v can be coupled together, and to simplify the process, the EOS should be the same for both steps.

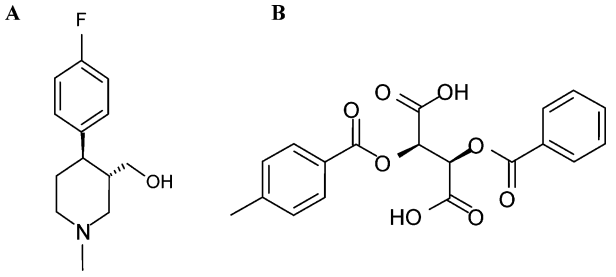
The recycle process is applicable to the resolution of any chiral base by any tartaric acid derivative that takes place in a polar solvent. The generality of the process arises from (a) the selection of a water immiscible EOS, which independently of the PRS employed, is able to efficiently recover DTTA from acid cracking of the diastereomeric salts in the mother liquor and alkaline streams; and (b) selection of the technology able to solvent exchange the DTTA from EOS back to the PRS, regardless the combination of the boiling point of these two solvents.

The resolution of a piperidine of pharmaceutical interest (PPI2) by di-*p*-toluoyl-L-tartaric acid (DTTA) was selected as a model system for this work (Figure 2). The resolution of this amine was performed at Γ_{react} of about 1.75 mol equiv, and thus the bulk of the DTTA employed for each crystal-

(8) Kremer K. A. M. WO Patent WO 2001/47856, 2001.

(9) Martin, S.; Piergentili, D. WO Patent WO 2003/042131, 2003.

(10) $$\Gamma_{fed}(\text{mol}\cdot\text{mol}^{-1}) = \frac{\text{fresh resolving agent fed to process (mol)}}{\text{racemic chiral base fed to resolution (mol)}} \times 100$$



A: (3*S*, 4*R*) piperidine of pharmaceutical interest: **S-PPI**
B: (2*R*, 3*R*)-di-*O*,*O*'-*p*-toluyl-L-tartaric acid: **(-) DTTA**

Figure 2. **Chemical structure of model chiral amine and diacid resolving agent.**

lisation ends up in the mother liquor. In this paper we initially applied the recycle process to the recovery and recycling of DTTA from the mother liquor. Distillation and OSN are explored as alternative techniques for DTTA solvent exchange, depending on the EOS employed. Finally, DTTA from both the mother liquor and the crystal phase was recovered and recycled over several resolution cycles. Process efficiency is evaluated through $\Gamma_{fed,}$ *Y*, and ee over the successive cycles.

Results and Discussion

Selection of EOS. The EOS employed in stages ii and v has to be a water-immiscible solvent for which the resolving agent (in this case DTTA) has a high affinity. Therefore, the first approach in the selection process was to estimate DTTA solubility in several water-immiscible solvents at 22 °C. The data obtained are summarised in Table 1.[11] PRS is carried from step i into step ii. Therefore, PRS partitions between the aqueous and EOS phases can affect the DTTA solubility in the organic phase at the end of step ii. The PRS of the model system is a homogeneous solution of 97:3 wt % acetone/water. Therefore, DTTA solubility was also measured in 50:48.5:1.5 wt % EOS/acetone/water. Values in Table 1 show that for these systems the presence of acetone in the organic phase significantly increases the DTTA solubility (Table 1) in the organic phase.

Table 1. **Screening of DTTA solubility in several water-immiscible EOS at 22 °C**

	DTTA solubility limit (wt %)	
EOS	pure solvent	solvent mixture[11]
EtOAc	63.7	
DCM	14.2	43.8
MtBE	24.3	
2-octanol	30.0	41.5
hexane	< 0.1	
toluene	< 0.1	27.5

To simulate the acid cracking of the resolution mother liquors, followed by DTTA extraction in step iii, a 5 M aqueous solution of HCl was added to a solution of 7.5 wt % DTTA in PRS. A homogeneous solution was obtained, and EOS was then added to obtain a biphasic aqueous/organic system and extract the DTTA into the organic phase. EOS/5M HCl(aq)/PRS were used in proportions of 2:1:1 by mass. The resulting phases were separated and weighed. The mass ratios of organic phase to aqueous phase ($W_{org/aq}$) obtained are reported in Table 2a. Experiments in which only one phase was obtained, or in which the DTTA precipitated out as a solid, are indicated in Table 2, as "one phase" or "prec.", respectively.

PRS can be completely extracted into the organic phase ($W_{org/aq} = 3$), remain entirely in the aqueous phase ($W_{org/aq} = 1$), or partition between the two phases ($1 < W_{org/aq} < 3$). It is also possible that, in the presence of PRS, a fraction of the water is extracted into the organic phase ($W_{org/aq} > 3.0$). Potentially, when PRS partitions into the EOS, the affinity of DTTA for the resulting organic phase increases, and thus values of $W_{org/aq} \geq 3.0$ are marked in bold in Table 2a. For the biphasic systems, the concentrations of DTTA were measured in the organic and aqueous phases obtained at the end of the extraction. Table 2b shows the extraction

Table 2. **Selection of EOS with respect to the PRS used at 22 °C**

(A) Weight Ratios of Organic Phase to Aqueous Phase ($W_{org/aq}$) Obtained at the End of the Extractions

EOS\PRS	acetone	MeOH	EtOH	^{i}PrOH	bp (°C)
EtOAc	1.0	one phase	one phase	one phase	**77.0**
DCM	**2.8**	1.0	1.0	**1.9**	39.9
2-octanol	**7.5**	**5.1**	**29.4**	**34.5**	**177.5**
MtBE	0.9	one phase	one phase	one phase	55.5
Et_2O	**1.3**	0.4	0.1	one phase	34.6
hexane	1.0	0.8	0.8	prec.	**68.0**
toluene	**2.0**	1.0	1.0	1.1	**110.0**
bp (°C)	56.0	64.7	78.0	82.0	

(B) Extraction Efficiencies[12] Calcd as the Percentage Fraction of the Total DTTA Fed That Is Extracted into the Organic Phase

EOS\PRS	acetone	MeOH	EtOH	^{i}PrOH	bp (°C)
EtOAc	84.3	one phase	one phase	one phase	**77.0**
DCM	95.6	89.5	85.5	86.9	39.9
2-octanol	98.0	99.2	>99.9	>99.9	**177.5**
MtBE	96.0	one phase	one phase	one phase	55.5
Et_2O	90.4	66.7	50.2	one phase	34.6
bp (°C)	56.0	64.7	78.0	82.0	

efficiency calculated as the percentage of the total DTTA fed which is extracted into the organic phase.[12] Notice that the results were obtained without exploring the effect of relative feed proportions of the three feed solvents involved, or operating temperature, on phase separation and DTTA extraction efficiencies. Thus, the conditions employed may be far from the optimum values. However, this experiment works as an initial screening of EOS types that can be used in this process.

The presence of the PRS in the aqueous phase can have negative effects on stage ii, via solubilization of the DTTA in this phase, or in a worst case scenario, yielding a homogeneous phase from the three solvents. The later scenario corresponds to the cases in which the EOS is either ethyl acetate (EtOAc) or methyl *tert*-butyl ether (MtBE) and the PRS is any of the alcohols tested (Table 2a). The solubility of DTTA in pure EtOAc suggests that this solvent is the most promising EOS. However, even when acetone is used as PRS and a biphasic system is obtained, the acetone remains on the aqueous phase ($W_{org/aq} = 1.0$), leading to a DTTA extraction efficiency of only 84.3% for this system. Diethyl ether (Et_2O) is flammable and volatile; therefore, despite its regular use in organic laboratories, it is not a preferred solvent for industrial application; also for Et_2O systems, most of the PRS remains in the aqueous phase, and thus the DTTA extraction efficiencies for this solvent were not exceptional.

On the other hand, the extraction of PRS into EOS ($W_{org/aq} > 1$) has several beneficial implications for the process: (a) it increases DTTA partitioning into the organic phase, reducing the losses of DTTA to the acidic aqueous phase; (b) it increases the DTTA solubility in the organic phase and thus increases the DTTA loading of this phase, with the result that a smaller volume of EOS has to be fed to the process in step ii and removed in step iii, (for example, dichloromethane (DCM) and toluene, due to their intermediate or low solubilisation of DTTA, would be considered uninteresting EOS candidates, but in the presence of acetone they became quite interesting solvents for this process); and (c) it simplifies the solvent exchange of DTTA into PRS, since PRS is already partially present in the organic phase fed to step iii.

DCM shows a good separation between the two phases and fair DTTA extraction efficiencies for all cases. The main limitation on the use of DCM as an EOS is that the DTTA load in this solvent can be restricted to values below 14 wt %, the DTTA solubility in DCM (Table 1). Therefore, higher volumes of DCM may have to be employed in extraction steps ii and v. Nevertheless, for the PRS used in our model system, this limitation is fortuitously overcome since DCM extracts acetone (Table 2a, $W_{org/aq} = 2.8$), increasing the DTTA solubility limit in the organic phase to relatively high values (Table 1, 43.8 wt %). The toluene system follows the behaviour of the DCM system, but taken to an extreme; DTTA is virtually insoluble in pure toluene, and thus it would not be considered as an EOS on its own. However, toluene also extracts acetone (Table 2a, $W_{org/aq} = 2.0$), dramatically increasing the DTTA solubility in the resulting organic phase (Table 1, 27.5 wt %). Finally, 2-octanol shows a high extraction efficiency for DTTA and extracts all of the four PRS tested, as well as substantial part of the water present (Table 2a, $W_{org/aq} > 3.0$).

Selection of Technology for Solvent Exchange: Distillation vs OSN. The second key aspect of this paper is the selection of the technology used for exchange of the resolving agent from the EOS back into the PRS in step iii. Usually, the PRS is selected from ketones or alcohols, such as acetone, methanol (MeOH), ethanol (EtOH) or 2-propanol (^{i}PrOH), which have relatively low boiling points. Many of the water immiscible solvents used as EOS, such as EtOAc, 2-octanol, or toluene, have higher boiling points. For these cases it is challenging to use distillation for solvent exchange in step iii, and OSN is used as an alternative unit operation to exchange the resolving agent from EOS back into PRS. The boiling points (bp) of each PRS and EOS are included in Table 2, and when the bp values of an EOS are higher than those of the PRS, they are marked in bold. Higher temperatures may also be an issue for thermally sensitive resolving agents. For example the bp of 2-octanol is quite high (177.5 °C), and data collected show that 30% of the DTTA dissolved in 2-octanol, when exposed over 3 h to a temperature of 132 °C, is degraded or reacts into by-products. Therefore, OSN is proposed to solvent exchange DTTA from 2-octanol to MeOH. EtOAc and toluene could also be used as EOS for our model acetone/water (97:3 wt %) system, but their bp's are higher than those of the four PRS; as a result DTTA solvent exchange from these EOS solvents would also require OSN.

No visible degradation or reduction in DTTA content was observed over a period of 3 h for DCM and EtOAc solutions of DTTA, boiling at 40 and 77 °C, respectively. DCM has a lower bp (39.9 °C) than any of the screened PRS; hence, DTTA can be exchanged from DCM back into the resolution step i by distillation. Particularly for our model PRS, acetone is extracted into DCM, increasing the DTTA solubility to about 44 wt % and thus allowing a significantly higher DTTA load in the stage ii organic phase. Therefore, DCM is selected as the preferential EOS for our model system, offering high extraction efficiencies in stage ii and facilitating DTTA solvent exchange by distillation in stage iii between two solvents that have a bp difference of 16 °C.

Feasibility Studies for DTTA Solvent Exchange by OSN. Solvent exchange by OSN was tested, from (a) EtOAc into our model PRS (acetone/water, 97:3 wt %) or (b) from 2-octanol into MeOH. 40 mL of a synthetic solution of 7 wt % DTTA in EOS (EtOAc or 2-octanol) was fed to the first filtration. DTTA solvent exchange was performed in four

(11) Solvent mixture is a homogeneous solution comprising 50:48.5:1.5 wt % of EOS/acetone/water. DTTA solubility limit in pure acetone or in acetone/water, (97:3 wt %) is about 50 wt %.

(12) $$\text{Extraction effciency (\%)} = \frac{\text{DTTA in organic phase (mol)}}{\text{DTTA fed to extraction (mol)}} \times 100$$

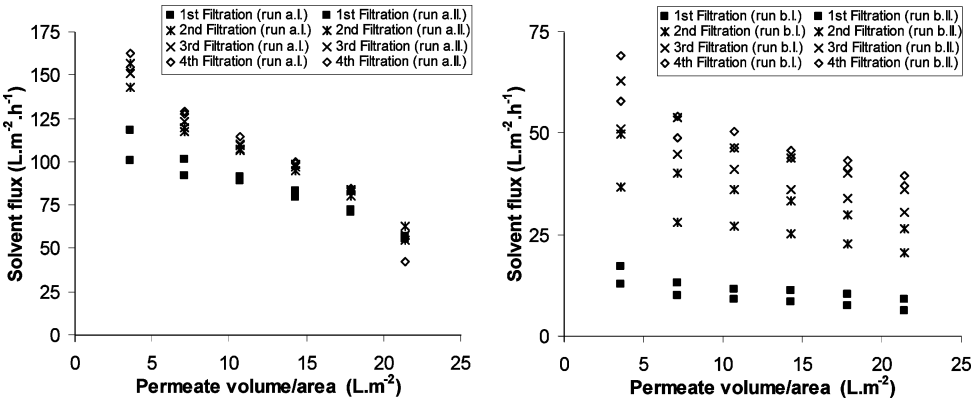


Figure 3. **(A) OSN solvent fluxes obtained during DTTA solvent exchange from EtOAc to acetone/water (97:3 wt %) through STARMEM 122 membranes at 22 °C and 30 bar. (B) OSN solvent fluxes obtained during DTTA solvent exchange from 2-octanol to MeOH through STARMEM 122 membranes at 22 °C and 30 bar.**

Table 3. **Feasibility of DTTA solvent exchange by OSN from (A) EtOAc to acetone/water (97:3 wt %); and (B) from 2-octanol to MeOH**

			EtOAc to acetone/water (97/3 wt %)				2-octanol to MeOH			
	calculated values		rejection (%)[14]		DTTA losses (%)		rejection (%)[14]		DTTA losses (%)	
filtration number	EOS (v/v%)	DTTA losses (%) (R_j = 99%,[14] R_t = 97%[15])	run I	run II	run I	run II	run I	run II	run I	run II
1	100.0	2.9	99.1	98.1	3.2	4.0	97.9	98.1	4.3	3.4
2	25.0	5.7	98.0	99.2	5.1	7.5	98.0	97.9	7.7	6.7
3	6.3	8.5	99.1	98.9	8.2	12.6	97.9	98.6	10.6	8.8
4	1.6	11.2	98.9	98.9	12.1	17.2	97.8	98.4	14.1	11.5

successive batch filtrations. STARMEM122,[13] a solvent resistant membrane, was selected on the basis of its molecular weight cut off (MWCO) of 220 g·mol^{-1} and the molar weight of DTTA (M_w 386 g·mol^{-1}). All the solvent mixtures in these experiments resulted in homogeneous solutions, and the filtrations were carried out until 30 mL of solvent had permeated the membrane. Thirty milliliters of fresh resolution solvent, (a) acetone/water, 97:3 wt % or (b) MeOH, was added at the start up of filtrations 2, 3, and 4.

Calculated values, shown in Table 3, predict that four successive filtrations are required to enrich the solution in PRS, bringing down the EOS level to values that can be considered negligible (<1.6%). EOS remaining in the retentate was calculated on the basis of OSN feed and permeated volumes, and assuming no membrane selectivity between the two solvents comprising the homogeneous solution. DTTA losses were calculated cumulatively, as the percentage fraction of the moles of DTTA fed which were lost in the OSN permeates. A theoretical value of 11.2 wt % of DTTA was calculated to be lost through permeates from the four filtrations (Table 3). Such values were estimated on the basis of a membrane rejection of 99%,[14] which corresponds to a retention of 97%.[15] These predictions were compared to experimental values obtained through solvent-exchange experiments. Samples from the feed, retentate, and permeate were taken for analysis, and experimentally measured rejections and DTTA losses are reported in Table 3. Average DTTA rejections of 98.8% and 98.1% were obtained, respectively, for the exchange (a) from EtOAc to 97:3 wt % acetone/water and (b) from 2-octanol to MeOH (Table 3).

Pure solvent fluxes through STARMEM 122 were estimated at stable values of 12, 159, 314 and 440 L·m^{-2}·h^{-1} for 2-octanol, EtOAc, MeOH and acetone, respectively. Notice that for these particular cases, the fluxes through the membrane are higher for PRS than for EOS. The observed fluxes for filtrations of DTTA solutions are shown in Figure 3. They are significantly lower than in pure solvent, and flux decline was observed throughout each filtration. This decline is expected, due to the increase in DTTA concentration in the retentate as the filtration progresses, leading to an increase in the solution viscosity and the osmotic pressure.[16] Moreover, measured membrane fluxes increase with filtration number, because the homogeneous DTTA solutions are enriched in PRS, which has a higher membrane flux. This observation is most evident for the 2-octanol/MeOH system. For both systems tested, solvent fluxes and DTTA losses

(13) STARMEM 122 membranes were kindly supplied by MET Ltd., www.membrane-extraction-technology.com; filtrations were carried out at 22 °C and using N_2 gas to apply 30 bar pressure in a SEPA cell (13.9 cm^2 area), at a stirring speed of 700 rpm. Membranes were preconditioned by filtration of 4 × 100 mL of PRS.

(14) $$R_j = \left(1 - \frac{C_p}{C_r}\right) \times 100$$

(15) $$R_t = \frac{V_r \cdot C_r}{V_r \cdot C_r + V_p \cdot C_p} \times 100 \quad \text{and} \quad \frac{R_t}{100} = \frac{1}{1 + \left[1 - \left(\frac{R_j}{100}\right) \cdot \left(\frac{V_p}{V_r}\right)\right]}$$

(16) Peeva, L. G.; Gibbins, E.; Luthra, S. S.; White, L. S.; Stateva, R. P.; Livingston, A. G. *J. Membr. Sci.* **2004**, *236* (1−2), 121−136.

Table 4. **First process feasibility test (failed): DTTA was recycled only from mother liquor[a]**

resolution number	Y (%)[5]		ee (%)[6]		DTTA mol equiv: DTTA/PPI2 into resolution (mol·mol^{-1})					
					Γ_{fed}[10]		experimental Γ_{react}[7]		estimated Γ_{react}[7]	
	run A	run B	run A	run B	run A	run B	run A	run B	run A	run B
1	39.0	41.3	100.0	100.0	1.77	1.76	1.77	1.76	1.77	1.6
2	47.5	50.3	51.9	63.1	0.51	0.50	1.18	1.20	1.28	1.26
3	43.0	45.5	18.9	22.6	0.50	0.51	0.93	0.92	0.91	0.91
4	−	36.2	−	7.6	−	0.50	−	0.75	−	0.66

[a] EtOAc was employed as EOS, and DTTA was solvent exchanged into acetone/water (97:3 wt %) via OSN. An average $\Gamma_{fed} = 0.5$ mol equiv was used for cycles 2−4.

Table 5. **Second feasibility test: DTTA was recycled only from mother liquor[a]**

resolution number	Y (%)[5]		ee (%)[6]		DTTA mol equiv: DTTA/PPI2 into resolution (mol·mol^{-1})					
					Γ_{fed}[10]		experimental Γ_{react}[7]		unaccounted DTTA losses[17]	
	run A	run B	run A	run B	run A	run B	run A	run B	run A	run B
1	40.3	33.8	100.0	100.0	1.78	1.77	1.78	1.77	0.00	0.00
2	34.2	39.1	100.0	100.0	0.91	0.88	1.58	1.63	0.79	0.68
3	38.5	43.3	100.0	100.0	0.88	0.88	1.70	1.76	1.10	1.03
4	32.3	39.5	100.0	100.0	0.87	0.88	1.80	1.73	1.49	1.52

[a] DCM was employed as EOS, and DTTA was solvent exchanged into acetone/water (97:3 wt %) via distillation. An average $\Gamma_{fed} = 0.88$ mol equiv was used for cycles 2−4.

are acceptable for industrial application, and therefore it is concluded that, when DTTA solvent exchange by distillation is not feasible, OSN is a viable solution. Further minimization of DTTA losses can be achieved by using a lower MWCO membrane and by optimising operating conditions and configurations. However, OSN requires compatibility between the solvents and membrane employed. For example, the STARMEM 122 membrane used in this work is compatible with all solvents listed in Table 2 except for DCM, and thus solvent swaps involving DCM cannot be undertaken with the membrane.

Recycle of Resolving Agent from Mother Liquor into Resolution Stage. As previously mentioned, the model resolution system selected for this study requires a Γ_{react} of 1.75 mol equiv in step ia and usually produces $Y = 40\%$, implying that after step 1b, about 1.35 mol equiv of DTTA remains in the mother liquor. Therefore, in the two initial tests, DTTA was recovered and recycled only from the mother-liquor phase. Two replicate experiments have been performed (experiments A and B) over four consecutive cycles.

The results for this first process feasibility test are summarised in Table 4. EtOAc was selected as the EOS for stage ii, due to the high solubility of DTTA in this solvent (Table 1). Since EtOAc has a higher bp than acetone, DTTA was exchanged in stage iii using OSN. In the first resolution Γ_{fed} of 1.77 mol equiv of fresh DTTA was added into the resolution step i, resulting in a Γ_{react} of 1.77 mol equiv. For the subsequent resolutions, the experimental Γ_{react} employed in step i comes from DTTA recycled from step iii and addition of an average value of Γ_{fed} of 0.50 mol equiv. This fresh DTTA was added into the resolutions to compensate for DTTA leaving the process via the crystals, and was our calculated estimate of what was required to maintain Γ_{react} at around 1.77. However, $\Gamma_{fed} = 0.5$ did not adequately compensate for the DTTA losses incurred in steps ii and iii of the process. As a result, the process feasibility test was a failure, with the Γ_{react} employed dramatically decreasing over consecutive cycles. This led to dramatic decreases in ee, confirming that the success of the resolution requires a $\Gamma_{react} > 1.5$ mol equiv.

An average DTTA membrane rejection of 98.7% (coefficient of variation 1.9%) was measured in this test, which is in good agreement with that previously found for DTTA solvent exchange from synthetic EtOAc solutions (Table 3, average value of 98.8, with a coefficient of variation of 0.5%). To evaluate where in the process the DTTA was lost, an estimated Γ_{react} was calculated on the basis of independent experiments using synthetic DTTA solutions. DTTA losses in step ii were quantified via the extraction efficiency of 84.3% (see Table 2), which accounts for (a) about 0.28 mol equiv of DTTA leaving the process via the aqueous phase in step ii and (b) an average of 15.7% DTTA losses (12.1−17.2 in Table 3), which corresponds to about 0.22 DTTA mol equiv of DTTA leaving the process via OSN permeate, step iii. In conclusion, this first attempt had failed because, the Γ_{fed} employed was only about 0.5 mol equiv, but the total DTTA leaving the process was about 1.0 mol equiv (0.5 mol equiv of DTTA leaving the process through the crystals and another 0.5 equiv being lost in stages ii and iii).

Armed with the more detailed study of partitioning data reported in Table 2, a second process feasibility test was undertaken, and the results are summarised in Table 5. In this test, minimization of DTTA losses was attempted by employing DCM as the EOS. This leads to better extraction efficiencies than those with EtOAc in step ii (95.6% against 84.3%, Table 2b.). Moreover, since DCM has a lower bp

Table 6. **Third feasibility test: DTTA was recycled from resolution crystals and mother liquor[a]**

resolution number	Y (%)[5]		ee (%)[6]		DTTA mol equiv: DTTA/PPI2 into resolution (mol·mol^{-1})			
					Γ_{fed}[10]		experimental Γ_{react}[7]	
	run A	run B	run A	run B	run A	run B	run A	run B
1	38.6	39.5	100.0	100.0	1.76	1.77	1.76	1.77
2	43.2	43.2	100.0	100.0	0.37	0.40	1.92	2.02
3	43.8	44.2	100.0	100.0	0.35	0.34	2.94	3.10
4	30.0	41.4	100.0	100.0	0.32	0.33	2.47	1.84
5	38.3	40.0	100.0	100.0	0.26	02.7	2.14	2.47
6	40.4	39.5	100.0	100.0	0.27	0.26	1.82	2.57
7	40.0	38.5	100.0	100.0	0.28	0.27	2.27	2.47

[a] DCM was employed as EOS, and DTTA was solvent exchanged into acetone/water (97:3 wt %) via distillation. An average $\Gamma_{fed} = 0.35$ and 0.27 mol equiv was used for cycles 2−4 and 5−7, respectively. Over the 7 cycles an average $\Gamma_{fed} = 0.44$ mol equiv was used.

than acetone, DTTA was solvent exchanged between these two solvents by a "put and take" batch distillation. The vessel was immersed in a 65 °C water bath, and 75% of the total volume of the solvent mixture was evaporated and replaced by fresh acetone; this was repeated three times. Additionally, Γ_{fed} in cycles 2, 3, and 4 was increased to an average value of 0.88 mol equiv, which corresponds to about half of Γ_{react} (i.e. half of Γ_{fed} used in the first cycle). This should compensate not only for the DTTA leaving the system through the crystals but for any other DTTA losses as well. The experimental Γ_{react} was measured as the sum of the fresh DTTA added to the resolution plus that recycled from stage iii, and was maintained at an average value of 1.73 mol equiv This test was successful, with all the resolutions yielding 100% enantiopure S-PPI, with an average Y of (37.6 ± 3.8)%.

The unaccounted DTTA losses[17] mol equiv (Table 5) were calculated as the difference between the total fresh DTTA added and the cumulative amount of DTTA that leaves the process via the crystals (about 0.4 mol equiv). An average value of 0.5 mol equiv of DTTA was calculated to be lost per recycle. This is rather high, especially since no losses of DTTA during distillation are expected and only about 4.4% loss is predicted due to the DCM extraction. The high loss may be related to the fact that experiments were carried at a small scale so that losses during vessel transfer can be significant and difficult to avoid. To minimize these losses, the third test was performed using the same flask for distillation solvent exchange and resolution, and an additional re-extraction of the acidic aqueous phase with fresh DCM was performed for DTTA extraction stages (ii and iv in Figure 2), washing any DTTA left on the extracting vessels. The four DCM phases obtained were then fed to the solvent exchange stage (step iii).

Complete Process: Recycle of Resolving Agent from the Mother Liquor and Crystals into the Resolution Stage. The results for the third process feasibility test are summarised in Table 6. In this test, DTTA was recovered and recycled from both mother liquor and crystals in two replicate experiments (runs A and B) over seven consecutive cycles. In the first resolution, Γ_{fed} of 1.77 mol equiv of fresh

(17) DTTA losses are calculated as the difference between Γ_{fed} and the cumulative amount of DTTA that leaves the process via the crystals (about 0.4 mol equiv for each resolution).

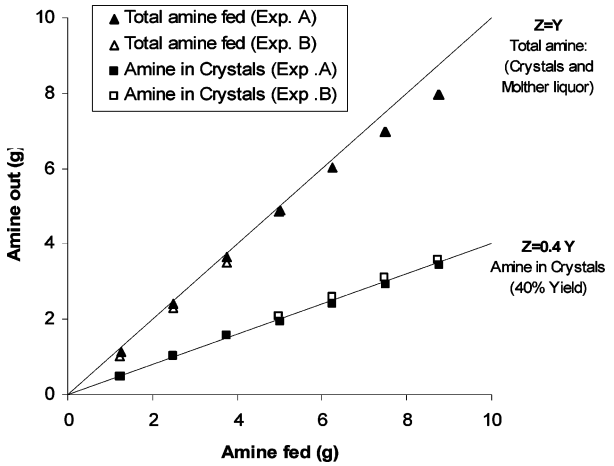


Figure 4. **Cumulative mass balance for amine throughout cycles of complete process.**

DTTA was added to the resolution step i. For subsequent resolutions, the experimental DTTA employed in step i comes from DTTA recycled from step iii and fresh DTTA added. Γ_{fed} was decreased in cycles 2−4 and 5−7, to average values of 0.35 and then to 0.27 mol equiv, respectively. Over the seven consecutive cycles an average value of $\Gamma_{fed} = 0.42$ mol equiv was employed. DCM was used as EOS for all the extractions (steps ii, iv, and v), and solvent exchange of DTTA from DCM to 97:3 wt % acetone/water was performed, as in the second test, by distillation at 65 °C. The experimental Γ_{react} was measured as the sum of the fresh DTTA added in the resolution with the one recycled from stage iii, and it was maintained at an average value of 2.26 mol equiv. This means DTTA was accumulated in the system so that Γ_{fed} could actually be further decreased. This test was successful, with all the resolutions yielding 100% enantiomeric pure S-PPI, with an average Y of (40.0 ± 3.5)%.

It is interesting to consider mass balances for this final test run. Figure 4 shows the balance between amine fed to the process and total amine leaving the process, the latter both as amine residing in the crystals and the sum of that residing in the crystals and in the mother liquor. The total mass balance for amine closes well. Figure 5 compares DTTA fed to the solvent-exchange step iii and recycled into the resolution step i. This shows that negligible DTTA losses were observed during distillation. Figure 6 compares the DTTA fed to the resolution step i and the DTTA in the

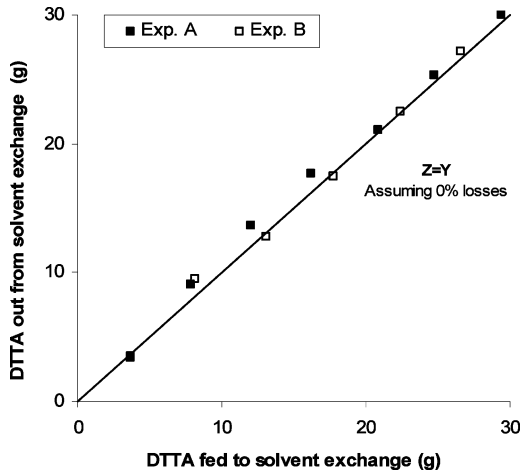


Figure 5. **Cumulative mass balance for DTTA in solvent exchange (step iii) throughout cycles of complete process.**

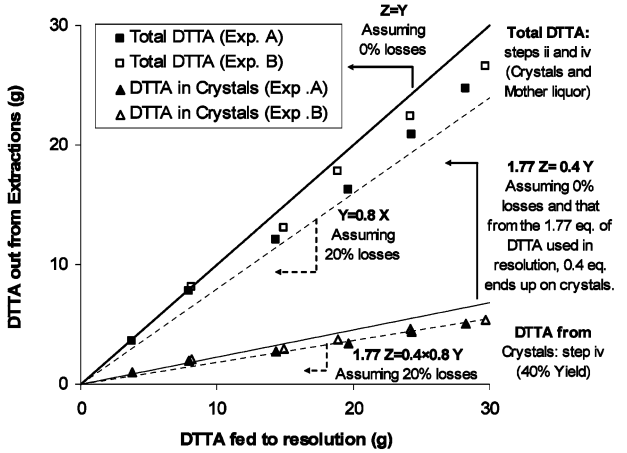


Figure 6. **Cumulative mass balance for DTTA in resolution and extraction steps throughout cycles of complete process.**

extracting phases at the end of the extraction steps ii and v, and shows total DTTA losses of about 20%. Figure 6 also shows that about 40% of the DTTA recycled came via the crystals, which is consistent with an average resolution yield of 40% and the formation of an acid diastereomeric salt, with a stoichiometry of 1:1 PPI2/DTTA.

Another aspect of the process that is important to consider relates to the solvent volumes employed. At the small operating scale at which this study was conducted, 15 g of PRS was used in each resolution (step ia), and a further 15 g of PRS was added to wash the crystals (step ib), giving 30 g of mother liquor. Thirty grams of DCM was fed to the extractions, corresponding to a 2.5 wt % DTTA loading in the organic phase of step v. This ensured that the extraction efficiencies were not affected by a DTTA load higher than the DTTA solubility (about 14 wt %, Table 1). In step ii a higher amount of DTTA is present (about 1.35 equiv, corresponding to a load of 8 wt % DTTA), but due to the extraction of acetone, the DTTA solubility limit is increased to 43 wt %. The volume of DCM employed in the extractions could be decreased with further work. However, in this preliminary study, the same amount of DCM was employed in all the extractions, ensuring DTTA loadings well below the solubility limits. At the end of solvent-exchange step, the recycled volume is decreased to 7.5 g, since racemic PPI2 is fed dissolved in a further 7.5 g of PRS required to make up the 15 g of PRS volume employed for the resolution (step ia).

Finally, an important aspect of the process which needs to be discussed is the pH of the aqueous phase from step iv. An alkaline pH high enough to completely dissociate the diastereomeric salt into alkali metal−DTTA salt and neutral amine is required, ensuring that all of the eutomer can be extracted. However, since DTTA is a diester, there is the risk of alkaline hydrolysis upon exposure to a strong alkaline environment for long periods. For that reason, a pH of 10.5 was used in step iv, and waiting times between steps iv and v were minimized. Crystal samples obtained for extractions at pHs 10.5 and 13.7 show small differences in the amount of amine extracted (about 6%). Therefore, instead of increasing the pH, which could compromise the DTTA stability, the remaining amine in the alkaline aqueous phase was re-extracted with a fresh 30 g of DCM. Upon HPLC analysis, no peaks characteristic of DTTA degradation products were detected.

Conclusions

This study shows that it is possible, without compromising the yield or ee, to efficiently recycle DTTA via a liquid-phase process. For the model resolution a reduction of resolving agent usage from 1.75 to only 0.26 DTTA mol equiv was achieved. While the process was applied to a specific model system, its applicability is general and independent of the chiral base resolved. The EOS employed should be selected according to the resolving agent and the PRS employed. When the EOS selected (e.g., DCM) has a lower bp than that of the PRS, the resolving agent can be exchanged back to the PRS by distillation. For resolution performed in polar alcohols, such as MeOH, EtOH, or ^{i}PrOH, it is recommended to use 2-octanol as the EOS, to maximize the resolving-agent extraction efficiencies. However, 2-octanol has a bp much higher than those of the other alcohols; thus, solvent exchange using distillation is challenging. For such cases, OSN was evaluated as an alternative solvent-exchange technique to distillation. The resolving agent was kept in solution over the whole recovery and recycle operation; thus, this process is also promising for development in the continuous or semi-continuous mode. In such a case, it would be desirable to control online the amount of fresh DTTA (Γ_{fed}) added to the resolution (step 1a), thus ensuring that Γ_{react} is maintained at values high enough (>1.5 mol equiv) to yield acidic diastereomeric salts while using the minimal Γ_{fed} necessary. Such control might be achieved with a feedback loop utilising an IR probe for DTTA measurements with flow control on the fresh DTTA stream line. Finally, no HPLC peaks characteristic of DTTA degradation products were found; consequently, the results are also quite promising in terms of resolving-agent stability over the several operations performed on the process.

Experimental Section

Materials. Solvents (HPLC grade) were employed from Aldrich-Sigma UK. K_2CO_3, NaOH and HCl were supplied

from BHD laboratory supplies. Di-*p*-toluoyl-L-tartaric acid was supplied by Fluka UK. Racemic PPI2 and pure S-PPI enantiomer were supplied by GSK Ltd.

Steps ia, ib: Resolution Protocol. Acetone/water, 97:3 wt % homogeneous solution was employed as the PRS. In 7.5 g of PRS was dissolved 1.25 g of racemic PPI2. For the first resolution of each run, 3.8 g of DTTA was dissolved in another 7.5 g of PRS. For the following cycles (2, 3, ...,) different amounts of fresh DTTA were added to the about 7.5 g of DTTA-enriched solution recycled from the solvent exchange (step iii). The amine and DTTA solutions were preheated at 40 °C and then added together at this temperature. The resulting solution was stirred at 40 °C for 30 min and then allowed to cool, slowly, under stirring, to room temperature for a further 30 min, and finally was aged for 60 min at 5 °C. The crystals obtained were filtered under vacuum and washed with a further 15 g of PRS. The crystals were dried at room temperature overnight and finally weighed.

Step ii: Acid Cracking of Mother Liquor with DTTA Extraction. The mother liquor solution, comprising the original 15 g of PRS employed in step (1a) plus the 15 g of PRS used in step (1b) to wash the crystals, were mixed with about 15 g of 5 M HCl aqueous solution to promote the cracking of the diastereomeric salts and DTTA neutralization. In the first process feasibility test the resulting solution was extracted with 20 g of EtOAc. In the second and third process feasibility tests the resulting solution was extracted with 30 g of DCM, yielding an organic phase of about 45 g of enriched in DTTA and acetone. In the third and final process feasibility test, the acidic aqueous phase was re-extracted with a further 30 g of DCM to extract any DTTA left, and this time, due to virtual absence of acetone, the resulting extracting organic phase was only of about 30 g. The extracting phases were fed to the solvent-exchange step iii. The distomer is left as an organic chloride salt (R^+Cl^-) in the aqueous phase.

Step iii-a: Solvent Exchange by OSN. DTTA was exchanged by OSN (a) from EtOAc into acetone/water, 97:3 wt % or (b) from 2-octanol into MeOH, using as feed 40 mL of synthetic solutions of 7 wt % DTTA, in EtOAc or 2-octanol. Solvent exchange was performed by filtering 30 mL of the 40 mL of DTTA solutions (i.e. the filtration progressed until permeation of 75% of the feed volume). To the 10 mL of solution retained was added 30 mL of fresh PRS (97:3 wt % acetone/water or MeOH), and the resulting homogeneous solution was filtered again. Four successive filtrations were performed.

In the first process feasibility test, EtOAc was used as EOS in step ii, and DTTA was solvent exchanged by OSN into 97:3 wt % acetone/water. The first filtration was fed with a mixture of 30 mL of fresh PRS and the organic phase (about 20 mL), and filtration was carried out until 40 mL had permeated. Thirty milliliters of fresh 97:3 wt % acetone/water was added to the 10 mL of solution retained. Four successive filtrations were performed.

Step iiib: Solvent Exchange by Distillation. In the second and third process feasibility tests, distillation was used to solvent exchange DTTA from DCM into 97:3 wt % acetone/water. The DTTA-enriched DCM solutions used as feed for this step arose (a) in the second test only from the mother liquor acid cracking (step ii) and (b) in the third test from the combined DCM phases obtained from both mother liquor and crystal cracking (steps ii and v). In both cases 30 mL of acetone was added to the DTTA-enriched DCM phase, and the resulting homogeneous solution was distilled at 65 °C until the solution volume decreased until 10 mL. A second volume of 30 mL of fresh acetone was added, and again the volume was reduced to 10 mL by distillation. Finally, 30 mL of 97:3 wt % acetone/water was added, and the volume of solution was once again reduced to 10 mL (ca. 7.5 g), which was then recycled into the resolution step i. The presence of water in the resolution step ia is important to generate the right crystal structure and thus provide the solubility difference between the two diastereomeric salts. Since water solubility in DCM is negligible, any water carried out from step i leaves the process in step ii throughout the acidic aqueous phase. Therefore, after solvent exchange of DTTA from DCM to acetone, the water content in the solution was adjusted and the resulting solution recycled into the resolution step ia.

Steps iv and v: Alkaline Cracking of Crystals with Amine Extraction and Alkaline Neutralization with DTTA Extraction. The crystals obtained in the resolution were suspended in 10 mL of water. This solution was stirred, and 1 M K_2CO_3 aqueous solution was slowly added until the pH of the solution reached a value of around 10.5, which typically required addition of 10 mL of K_2CO_3 solution. Thirty grams of DCM were then added. The two resulting phases were separated, and the aqueous phase was re-extracted with another 30 g of DCM to ensure the complete extraction of *S*-enantiomer. The two phases were separated, and the alkaline aqueous phase, containing dipotassium DTTA salt, was neutralized in step (v) by addition of 20 g of 5 M HCl aqueous solution. The resulting mixture was extracted with 30 g of DCM. The phases were separated, and the acidic aqueous phase was re-extracted with a second 30 g of fresh DCM to minimize DTTA losses. These two DCM phases, enriched in DTTA, were fed to the solvent-exchange step (iii). The aqueous phase is essentially composed of KCl and HCl added in excess.

Solubility and Partition Experiments. DTTA solubility experiments were performed by successive additions of known amounts of DTTA to pure solvents or homogeneous solvent mixtures. After each addition of DTTA the solution was stirred for about 20 min at 22 °C. The DTTA solubility limit in a given solvent system was taken as the weight of DTTA able to be dissolved in that solvent, divided by the total weight of the obtained solution. DTTA partition experiments were prepared by dissolving about 0.2 g of DTTA in 2.5 g of a given PRS. This solution was mixed with 2.5 g of aqueous HCl phase (5 M). To the resulting homogeneous solution was added 5 g of EOS, and the resulting solution was first stirred vigorously, and then allowed to separate into two phases at 22 °C. The weights

of the phases and the concentrations of DTTA in each of them were measured.

PPI Analysis. Amine concentration and ee analyses were carried out using a Gilson 712 HPLC, with the mobile phase comprising acetronitrile(ACN)/MeOH/trifluoroacetic acid-(TFA)/ammonia in the volume proportions of 94.97%:5.00%: 0.02%:0.01% and flowing at a rate of 0.70 mL·min^{-1} through a Cyclobond I 2000 AC (5 μm, 250 mm $\times$ 0.46 mm) column with the UV detector wavelength adjusted to 265 nm. For analysis of amine in the acidic aqueous phase of the acid mother liquor cracking (step ii) and in the crystals, an aliquot of each of these phases was dissolved in NaOH (2 M) and extracted into DCM; the phases were separated, and the DCM phase was sent for HPLC analysis. Samples of the DCM phase arising in step iv were diluted in DCM and sent directly for amine analysis. Calibrations have been prepared accordingly.

DTTA Analysis. Analyses of DTTA were carried out using a 712 Gilson HPLC with a Phenomex Luna C18 (2) (50 mm $\times$ 2.0 mm, 3 μm) column. Two independent solutions were employed as mobile phases, water and ACN, both containing 0.1% of TFA, and the flow rate was 0.50 mL·min^{-1}. For these analyses, a solvent gradient was employed from water to ACN solution in 20 min, followed by a plateau of 5 min for the ACN solution. The gradient was employed to separate the solvent in the injected sample and any impurities that could arise from DTTA degradation, such as toluic acid. The UV detector wavelength was adjusted to 259 nm. DTTA samples were diluted in an ACN solution containing 0.1% TFA. DTTA was analysed on the four phases arising from the acid extractions (steps ii and v) and on the stream leaving the solvent-exchange step (iii). Toluene is an aromatic compound, and thus it absorbs in the same UV region as DTTA. Therefore, when toluene was used as EOS it was not possible to quantify DTTA by UV spectroscopy, and as a result the extraction efficiencies of DTTA in toluene are not reported in Table 2b.

Nomenclature and Abbreviations

ACN	acetonitrile
C_p	concentration of DTTA in permeate (wt %)
C_r	concentration of DTTA in retentate (wt %)
DCM	dichloromethane
DTTA	di-*p*-toluoyl-L-tartaric acid
ee	enantiomeric excess (%)
EtOAc	ethyl acetate
EtOH	ethanol
Et_2O	diethyl ether
EOS	extracting organic solvent
HCl	hydrochloric acid
HPLC	high performance liquid chromatography
^{i}PrOH	2-propanol
K_2CO_3	potassium carbonate
ML	mother liquor
MtBE	methyl *tert*-butyl ether
MeOH	methanol
MWCO	molecular weight cut off
NaOH	sodium hydroxide
OSN	organic solvent nanofiltration
PPI2	racemic piperidine of pharmaceutical interest
PRS	polar resolution solvent
R-PPI	(3*R*,4*S*)-piperidine of pharmaceutical interest
R_j	rejection (%)
R_t	retention (%)
S-PPI	(3*S*,4*R*) piperidine of pharmaceutical interest
TFA	trifluoroacetic acid
V_p	volume of permeate (mL)
V_r	volume of retentate (mL)
Y	resolution yield (%)
Γ_{react}	resolving agent/racemic base fed to the resolution (mol equiv)
Γ_{fed}	resolving agent to racemic base fed to the process (mol equiv)
$W_{org/aq}$	ratios of the wt organic phase/wt aqueous phase

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