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Highly Efficient and Robust Enantioselective Liquid-Liquid Extraction of 1,2-Amino Alcohols utilising VAPOL- and VANOL-based Phosphoric Acid Hosts.

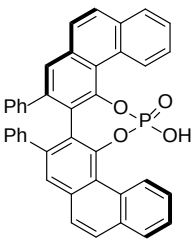
Erik B. Pinxterhuis,[†[a]] Jean-Baptiste Gualtierotti,[† [a]] Sander J. Wezenberg,[a] Johannes G. de Vries*[b] and Ben L. Feringa*[a]

Abstract: The large-scale production of enantiopure compounds in a cost-effective and environmentally friendly manner remains one of the major challenges of modern day chemistry. The resolution of racemates *via* enantioselective liquid-liquid extraction was developed as a suitable solution but has remained largely underused due to a lack of highly efficient and robust chiral hosts to mediate the process. This paucity of hosts can in part be attributed to a feeble understanding of the underlying principles behind these processes hindering the design of more efficient selectors. Herein, we present an in depths study of a previously untested class of hosts, VAPOL and VANOL derived phosphoric acids, for the efficient enantioselective liquid-liquid extraction of 1,2-amino alcohols. A systematic investigation of extraction parameters was conducted revealing many key interactions, while DFT calculations illustrate the binding modes for the 1:1 complexes that are involved in chiral recognition. The resulting, now optimised, procedures, are highly robust and easy to implement. They are also easily scalable as was demonstrated by U-tube experiments.

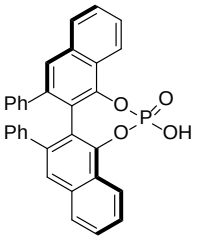
Introduction

One of the major challenges of modern day chemistry is to obtain enantiopure compounds on large scale for the agrochemical, pharmaceutical, fine chemical or fragrance & flavor industries.[1] Whereas some chiral compounds can be obtained by agriculture or fermentation, [2] large scale production *via* synthetic or separatory routes have proven more efficient in yielding the amounts, and more importantly, the variety needed.[3] While the synthetic route has provided much in terms of variety, it often struggles somewhat in providing the required amounts in a cost-efficient manner.[4] Alternatively, the separation of racemates offers far better scalability and cost-efficiency but suffers from lower versatility and technical issues such as problems with solids handling in the case of resolution by crystallization.[5] Attempts at expanding the versatility of separatory techniques have been made but have encountered similar cost-effectiveness issues.[6] Enantioselective Liquid-Liquid Extraction (ELLE) was investigated as an alternative method combining cost-efficiency, simplicity of handling, scalability and versatility. Based on the early work of Cram on chiral recognition,[7] multiple reports exist that demonstrate its potential in all these categories.[6c, 8] Relying on the continuous, selective, transport by a host of preferentially one of the enantiomers of a racemate from one phase to another, an ELLE process can be operated using a series of mixing separation devices working in countercurrent flow. Since hosts and solvents can continuously be recycled, this is potentially a highly economical and environmentally friendly system. Currently, the main drawback of this method, which, to the best of our knowledge, prevents it from being industrially applicable, is a lack of highly enantioselective and robust chiral hosts (α_{op} > 1.5[9]).[1a, 10]Known host categories,[7, 10-11] (crown ethers, amino acid derivatives, BINOL derivatives, Cu, Ln, Zn, Co, Ru complexes, tartrates, quinines or guanidinium derivatives) function, except for isolated examples, only at a proof of concept level. This can in part be attributed to a feeble understanding of the underlying principles behind these processes hindering the design of more efficient selectors. The field of ELLE has therefore stagnated in recent years with only a few new results appearing such as the work of Schuur[12] and Tang[13] who have expanded upon these systems. Therefore achieving a deeper understanding of the chemical principles and physical properties behind this technique is vital if new, more selective hosts are to be developed for the ELLE of a wider range of compounds. Our recent work on highly selective SPINOL based phosphoric acid hosts has demonstrated the efficiency of this approach..[14] However in view of their lengthy synthesis these SPINOL based hosts are not readily available, therefore, in an attempt to further expand the scope of ELLE and deepen our understanding of the mechanism of action of chiral phosphoric acids towards this process, we turned our attention to more readily available backbones such as VAPOL and VANOL (Fig. 1).

Since their discovery in 1993[15], both have served as highly efficient organocatalysts due to their unique vaulted structure[16]. Their synthesis on multigram scale being well described,[17] VAPOL and VANOL phosphoric acids (**PA1-2**) have the significant advantage of being readily available and are therefore easily applicable in ELLE on both laboratory or industrial scale.



(*S*)-VAPOL **PA-1**



(*S*)-VANOL **PA-2**

Figure 1. Phosphoric acid hosts used for Enantioselective Liquid-Liquid Extraction.

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Principles of Enantioselective Liquid Liquid Extraction

For a better understanding of the fundamentals of ELLE and therefore of the reach of this manuscript, we will give here a short description of the methodology used and an explanation of the meaning of the units employed. Enantioselective Liquid Liquid Extraction (ELLE) employs the principles of asymmetric host-guest interaction chemistry in combination with extraction or transport over multiple phases. A typical ELLE system contains two immiscible liquid phases, where one phase is composed of a solution of a racemic guest, while the other holds a solution of the chiral host. As described by Lehn[20] and Cram[7], enantioselective extraction occurs via chiral recognition between the host and one enantiomer of the guest resulting in the formation of a single diasteriomeric complex which is soluble only in the host phase. This results in phase separation of both guest enantiomers inducing an enantiomeric excess, opposite in sign, in either phase. A subsequential back extraction in a third phase, usually employing the same solvent as for the feeding phase, allows for liberation of the bound enantiomer and regeneration of the host, allowing for the setup of a continuous flow system.

The efficiency of this process is usually described by three different parameters, the enantiomeric excess of one of the two phases (ee, herein the aqueous phase), the distribution (D) and the operational selectivity (α_{op}). The distribution D is the ratio between the concentration of one of the enantiomeric guests in the organic host phase and its concentration in the aqueous phase (Eq 1b). The operational selectivity is defined as the ratio between the distributions of the two enantiomers (Eq 1a) and thus gives a quantitative evaluation of the overall efficiency of the process. Although the ee can give a first impression of the value of a given extraction, it is the α_{op} that really determines the usefulness. One of the main advantages of an ELLE is that full resolution of each enantiomer can be obtained with only a relatively small α_{op} by employing a multistage extraction system.[10,14] The number of sequential counter-current extractions required to achieve full resolution determines the viability of the system. From a practical point of view, it is commonly accepted that an α_{op} of 1.5,[10] representing 25 stages is the minimal threshold for a system to be viable. The relationship between the operational selectivity and the minimal number of fractional stages need to obtain a given level of resolution is described by the Fenske equation (Eq1c) depicted in Fig. 2 for ee = 99%. A decrease in number of stages with an increase of α_{op} is clearly visible, leading to an ideal, seldom reached, situation at $\alpha_{op} \geq 7$ where a further decrease in stages becomes minimal.

a) $\alpha_{op} = \frac{D_R}{D_S}$ b) $D_i = \frac{[i]_{org}}{[i]_{aq}}$ $(i = R, S)$ c) $N_{min} = \frac{ln\left(\frac{x_R/(1-x_R)}{x_S/(1-x_S)}\right)}{\ln \alpha_{op}}$ (Eq 1)

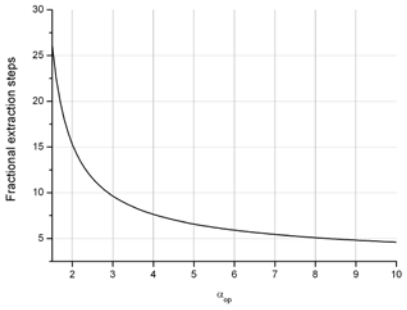
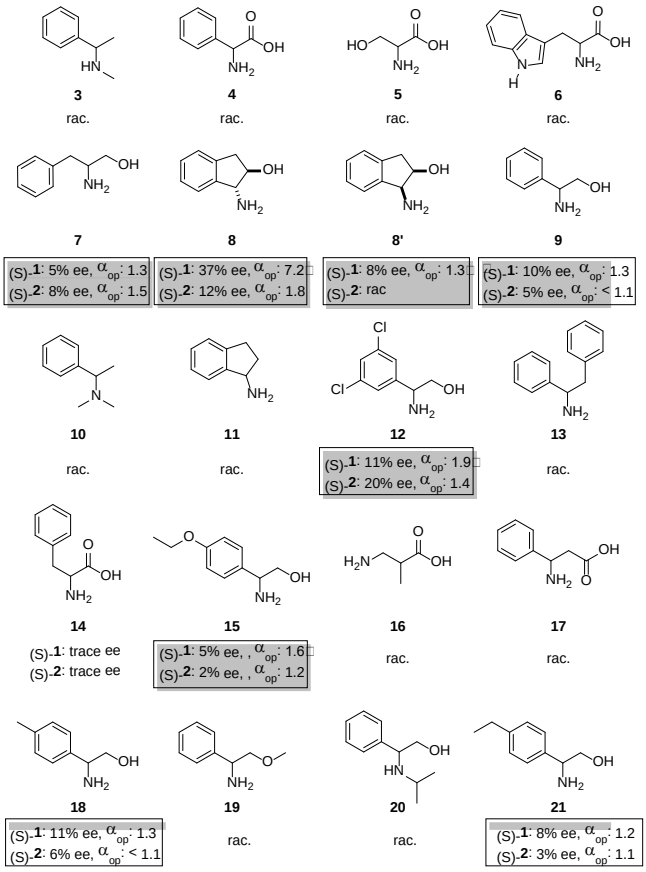


Figure 2. Relationship between number of stages and α_{op} according to eq. 1c for ee = 99%

Results and Discussion

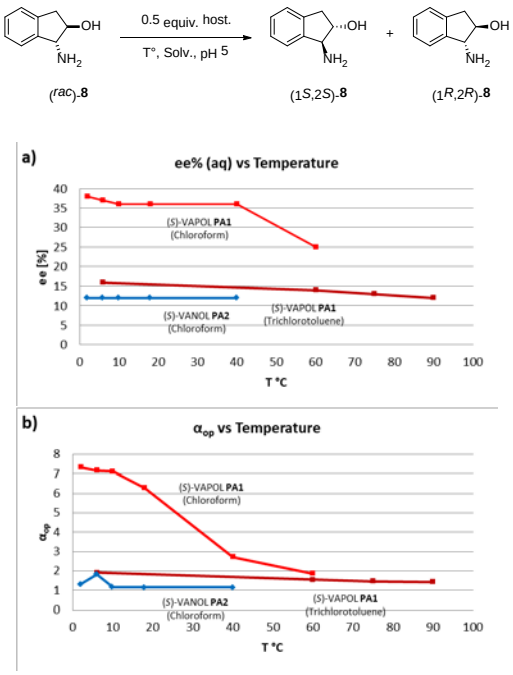
We began our investigations by screening a wide range of chiral guests to determine which classes could be extracted in an enantioselective manner with these hosts. Overall, high selectivities towards 1,2-aminoalcohols were observed, while amino acids or amines were extracted as racemates. (*S*)-VANOL **PA2** extracted phenylalaninol **7** with 8% ee and a good 1.5 α_{op} while (*S*)-VAPOL **PA1** extracted linear 1,2-aminoalcohols **9**, **12** and **15** with 10, 11 and 5% ee and an α_{op} of 1.3, 1.9 and 1.6, respectively (Scheme 1). Para substituted 1,2-aminoalcohol **18** and **21** could be extracted with similar selectivities as the unsubstituted **9,** whereas no selectivity was achieved in the extraction of O-methyl phenylglycinol **19** and N-isopropyl phenylglycinol **20** using either host. These findings underline the importance of the presence of both the free amine and free alcohol moieties of the guest. The best results were obtained with cyclic 1,2-aminoalcohols. Indeed, when a racemic mixture of *trans*-1-amino-2-indanol (**8**), dissolved in a pH 5 phosphate buffer solution was placed in contact with a chloroform solution containing **PA1** and left to stir at 6 °C till equilibrated, (1*S*,2*S*)-*trans*-1-amino-2-indanol ((*S*)-**8**) was extracted preferentially with an impressive ee of 37%, and α_{op} of 7.2. The use of **PA2** resulted in 12% ee and 1.8 α_{op} under the same conditions. In the case of *cis*-1-amino-2-indanol (**8'**) good selectivity was also obtained (8%, 1.3 α_{op}). In all cases the (*S*)-enantiomer of the host extracted preferentially the (*S*)-enantiomer of the amino alcohol.

This level of selectivity has, to the best of our knowledge, never been achieved before with cyclic 1,2-aminoalcohols. To the synthetic chemist the selectivites reported here may initially appear relatively low. They are actually highly interesting as the use of multi-staged counter-current extraction enables the full separation of the racemate based on these values. We have already demonstrated this possibility in the past with a different host-guest couple using a cascade of 6 centrifugal contactor separators in series and another one for the back extraction of the product.[18]



Scheme 1. ELLE screening of chiral substrate classes with (S)-VAPOL **PA1** and (*S*)-VANOL **PA2**. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution ($CHCl_3$), 6 °C. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

Encouraged by these results we studied the effect of the extraction parameters as temperature, solvent and pH are known to have marked effects on the efficiency of the process. Starting with temperature, we measured the selectivity of the ELLE of **8** over a 2-90 °C range.[20] While an optimum was observed at 2 °C for (*S*)-VAPOL **PA1**, yielding impressively high selectivities with 38% ee and an α_{op} of 7.3, the process proved surprisingly robust towards changes in temperature with ee's remaining stable over the 2-40 °C range (38-36%, Scheme 2a) and only dropping significantly above this point (25% ee at 60 °C). When the solvent was switched to trichlorotoluene, which is a less efficient solvent for the extraction but which allowed us to probe a wider temperature range, the ee dropped only by 4% when heating from 6 °C to 90 °C (16% and 12% ee, respectively). With **PA2** we found a similar robustness, with ee's remaining stable over the 2-40°C range. Operational selectivities also dropped less than expected (Scheme 2b), from 7.3 at 2 °C to 1.8 at 60 °C (2.7 at 40 °C) when using **PA1**, and dropping slightly from 1.8 at 6 °C to 1.2 at 40 °C when using **PA2**. This high temperature stability allows some design flexibility when adapting this ELLE process to large scale mixing separation devices, which could potentially be run at room temperature while retaining good α_{op} (6.3 at 18 °C) avoiding therefore the need for cooling and its inherent cost.

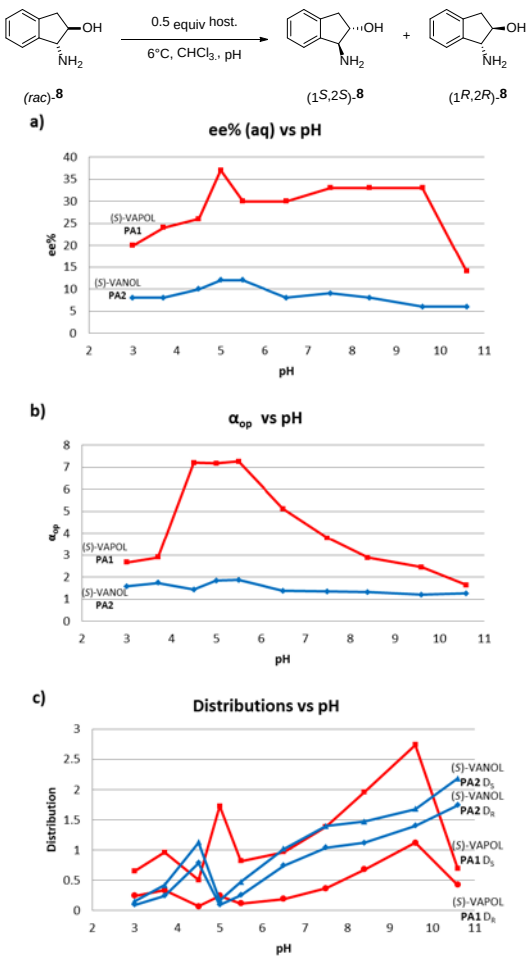


Scheme 2. Temperature screening for the ELLE of 8 with **PA1** and **PA2**. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 16h. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

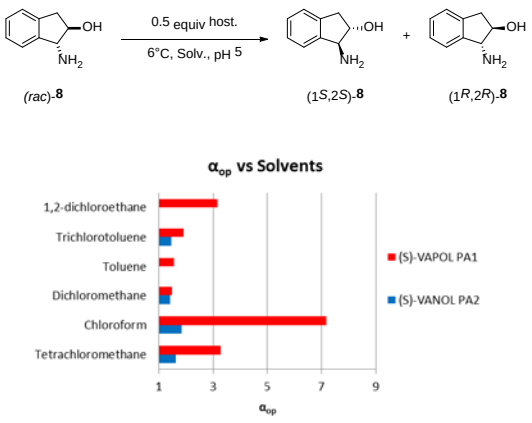
We then turned our attention to the pH dependency of the ELLE of **8** (Scheme 3). Both hosts showed similar behaviors with an optimal pH around 5. Selectivities dropped significantly at more acidic or basic pH. Interestingly, in the case of **PA1**, the operational selectivity of the extraction proved remarkably stable in a ±0.5 pH unit window centered around pH 5 which is unusual for such a system[21] (Scheme 3a). Such a behavior renders the system more robust towards small local variations in pH. It should be noted that while α_{op} remains stable around pH 5 the distributions vary greatly (Scheme 3c) as the pH varies probably due to a combination of variations in complex stability and solubility.

The effect of the host phase solvent was next studied (Scheme 4). Chloroform proved optimal for both hosts in terms of ee and α_{op}; other haloalkane based solvents resulted in lower selectivites while aromatic solvents, both halogenated and not, gave relatively unfavorable results.[22]

With optimal conditions in hand we next investigated the scalability of the process. In addition to a good distribution and operational selectivity, the ability to dynamically recover the guest from the host is of vital importance. To measure this we employed a U-tube (Fig. 3), based on a modified design by Cram [21,18a], which is a good procedure to establish the capability of the host to release the enriched guest into a receiving phase. In addition, it will demonstrate that the host can selectively transport the desired enantiomer in a catalytic fashion between the feeding and receiving phase with multiple turnovers. A blank



Scheme 3. pH screening for the ELLE of **8** with **PA1** and **PA2**. Conditions: 2 mM guest solution (H_2O, phosphate buffer) vs 1 mM host solution ($CHCl_3$), 6 °C., 16h. Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.



Scheme 4. Solvent screening for the ELLE of **8** with **PA1** and **PA2**. Conditions: 2 mM guest solution (H_2O, pH 5 phosphate buffer) vs 1 mM host solution, 6 °C. Determination of the ee, distribution andα_{op} via reverse phase HPLC of aqueous phase aliquots.

extraction, run at pH 5 for 24 hours in the absence of host, showed that no background leaching of guest from the feeding to the receiving phase occurred, indicating that all observed extraction would be due to transport by the host. When a U-Tube extractor composed of a 20 mM feeding phase and a 0.5mM host solution was run, an ee of 41% could be observed after 10 minutes in the receiving phase which remained stable over one hour. As the feeding phase became depleted in one enantiomer, the host increasingly transported the second enantiomer resulting in a slow erosion of the ee of the receiving phase, reaching 30% after two hours and dropping to 14% after four. At the end of the run 10 turnovers were reached. Overall these results clearly indicated that the enantioselective extraction process was catalytic and can be scaled up. We have previously established that large-scale racemate separation can be performed highly

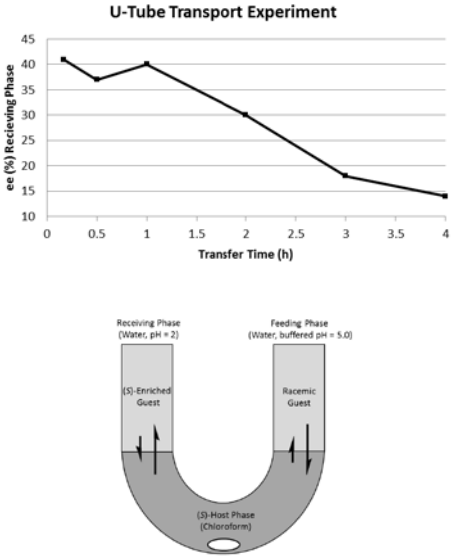


Figure 3. U-Tube model reactor. Conditions: Host phase: **PA1** in chloroform (0.5 mM,10 ml). Feeding phase: 8 in H_2O (20.0 mM pH 5 phosphate buffer). Receiving phase: aq. HCl (5 ml, pH 2), 6°C Determination of the ee, distribution and α_{op} via reverse phase HPLC of aqueous phase aliquots.

efficiently in counter-current flow using a number of centrifugal mixing separation devices[18, 23] in series enhancing the ee at each step according to the Fenske equation. The high α_{op} observed would allow such a process to be run with as little as 5-6 stages with a final ee of up to 99% in the final stage as was shown by us in the case of 3,5-dinitrobenzoyl-(R),(S)-leucine.[18]
To gain a better understanding of the origin of the remarkable selectivity in the extraction of *trans*-1-amino-2-indanol (**8**) using VAPOL phosphoric acid (**PA1**), DFT energy minimizations were carried out. The geometries of **PA1**⊃(*S,S*)-**8** and **PA1**⊃(*R,R*)-**8** were optimized at the B3LYP/6-31G++(d,p) level of theory, using an IEFPCM $CHCl_3$ solvation model (Fig.4).[24][18] The hydrogen bond lengths in the structure with (*S,S*)-**8** (N···O = 2.60 Å; O···O = 2.70 Å) are slightly shorter than those found in the structure with the (*R,R*)-enantiomer (N···O = 2.61 Å; O···O = 2.72 Å). Furthermore, where the (*S,S*)-guest nicely points outwards from

the binding pocket offered by the phosphoric acid, there appears to be some steric repulsion between the (*R,R*)-guest and the phenanthrene moiety of the host. The Gibbs free energy calculated for **PA1**⊃(*S,S*)-**8** is 3.8 kJ mol^{-1} lower than for **PA1**⊃(*R,R*)-**8**, which is in line with experiment [that is, selective extraction of the (*S*,*S*)-enantiomer, *vide supra*]. This steric interaction is absent in the structures calculated for **PA2** (see the Supporting Information), which corroborates with the lower ee in the extraction experiments.

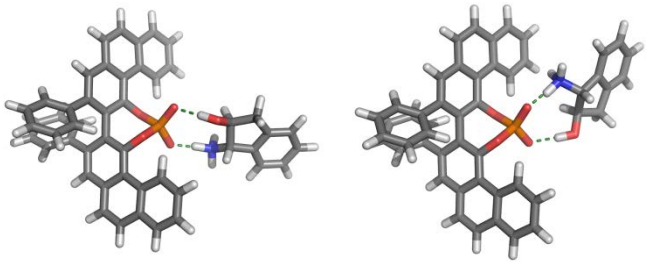


Figure 4. DFT energy minimized structures [B3LYP/6-31G++(d,p)] for the diastereomeric complexes **PA1**⊃(*S,S*)-**8** (left) and **PA1**⊃(*R,R*)-**8**.

In summary, we have investigated the efficiency of VAPOL- and VANOL-based phosphoric acids as chiral hosts for the enantioselective liquid-liquid extraction of a range of 1,2-aminoalcohols. These previously unexplored hosts proved to be good selectors for several 1,2-aminoalcohols, offering a particular cost-efficient process for their resolution due to the relatively easy synthetic availability of these phosphoric acids and the high selectivity reached. In particular, (*S*)-VANOL **PA2** allows for the resolution of phenylalaninol (**7**) while (*S*)-VAPOL **PA1** proved particularly efficient for the ELLE of *trans*-1-amino-2-indanol (**8**) yielding an ee of 37% and impressive operational selectivity of 7.2. DFT calculations have been used to shine light on the origin of the remarkable selectivity showing clear preference for binding of one of the enantiomers. The extraction process proved also to be highly robust, tolerating small variations in optimal conditions with little or no impact on its efficiency. The U-tube experiments show the catalytic nature of the extraction process as well as the feasibility of an efficient back-extraction. In view of the high operational selectivity, this process could be easily scaled up using as little as 5-6 stages.

Experimental Section

To a vial with a stirring bar, a solution of the racemic guest (0.4 ml, 2.0 mM) dissolved in a phosphate buffer solution (buffer strength 0.1 M, indicated pH) was added to a solution of the host in $CHCl_3$ (0.4 ml, 1.0 mM). After capping the vial, the mixture was cooled to the indicated temperature and stirred at 900 rpm for 16 h. The phases were allowed to separate over a period of 2 min. The aqueous phase was removed and an aliquot was injected into a reverse phase HPLC for determination of the ee, distribution and α_{op}. All extraction experiments were carried out *in triplo* and with a simultaneous blank reaction (concentration of host = 0.0 mM).

Acknowledgements

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Keywords: Enantioselective extraction • Amino alcohols • Phosphoric acids • Chiral Resolution• Host-guest complexes

[1] a) H. Lorenz, A. Seidel-Morgenstern, *Angew. Chem. Int. Ed.* **2014**, *53*, 1218-1250. *Angew. Chem.* **2014**, *126*, 1240-1274; b) D. J. Ager, *Handbook of Chiral Chemicals* Marcel Dekker: New York, **2005**; c) G. M. R. Tombo, D. Belluš, *Angew. Chem. Int. Ed.* **1991**, *30*, 1193-1215. *Angew. Chem.* **1991**, *103*, 1219-1241

[2] a) P. K. Ajikumar, K. Tyo, S. Carlsen, O. Mucha, T. H. Phon, G. Stephanopoulos, *Mol. Pharm.* **2008**, *5*, 167-190. ; b) M. J. Waites, *Industrial Microbiology*, Blackwell Science, Oxford, **2001**; c) D. Cascaval, C. Oniscu, A. I. Galaction, *Biochemical Eng. J.* **2001**, *7*, 171-176. ; d) M. Reschke, K. Schügerl, *Chem. Ing. Tech.* **1984**, *56*, 141-141.

[3] a) A. N. Collins, G. N. Sheldrake, J. Crosby, *Chirality in Industry II: The Commercial Manufacture and Applications of Optically Active Compounds*, New York, Wiley and Sons, **1997**; b) R. A. Sheldon, *J. Chem. Technol. Biotechnol.* **1996**, *67*, 1-14. ; c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**; d) T. Hayashi, in *Comprehensive Asymmetric Catalysis Vol. 1-3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer-Verlag, Berlin, Heidelberg, **1999**, pp. 351-364.

[4] a) J. G. de Vries, A. H. M. de Vries, *Eur. J. Org. Chem.* **2003**, *5*, 799-811. ; b) N. M. Maier, P. Franco, W. Lindner, *J. Chromatogr. A* **2001**, *906*, 3-33.

[5] a) M. Leeman, G. Brasile, E. Gelens, T. Vries, B. Kaptein, R. Kellogg, *Angew. Chem. Int. Ed.* **2008**, *47*, 1287-1290. *Angew. Chem.* **2008**, *120*, 1307-1310; b) E. Fogassy, M. Nogradi, D. Kozma, G. Egri, E. Palovics, V. Kiss, *Org. Biomol. Chem.* **2006**, *4*, 3011-3030. ; c) D. Kozma, *CRC Handbook of Optical Resolutions Via Diastereomeric Salt Formation*, CRC Press LLC Boca Raton, **2002**; d) A. Bruggink, *Rational Design in Resolutions, in Chirality in Industry II*, A. N. Collins, G. N. Sheldrake, J. Crosby ed., John Wiley & sons Ltd., Chichester, **1997**; e) F. Faigl, E. Fogassy, M. Nógrádi, E. Pálovics, J. Schindler, *Tetrahedron: Asymmetry* **2008**, *19*, 519-536.

[6] a) R. Xie, L.-Y. Chu, J.-G. Deng, *Chem. Soc. Rev.* **2008**, *37*, 1243-1263. ; b) G. B. Cox, *Preparative Enantioselective Chromatography*, Blackwell Publishing Ltd, **2007**; c) M. Steensma, N. J. M. Kuipers, A. B. De Haan, G. Kwant, *Chirality* **2006**, *18*, 314-328. ; d) A. Maximini, H. Chmiel, H. Holdik, N. W. Maier, *J. Membr. Sci.* **2006**, *276*, 221-231. ; e) G. Guebitz, M. G. Schmid, *Chiral Separations*, Humana Press, Totowa (NJ), **2004**; f) F. Toda, *Enantiomer Separation: Fundamentals and Practical Methods,*, Kluwer Academic Publishers, Dordrecht, **2004**; g) K. W. Busch, M. A. Busch, *Chiral Analysis*, Elsevier, Amsterdam, **2004**; h) C. A. M. Afonso, J. G. Crespo, *Angew. Chem. Int. Ed.* **2004**, *43*, 5293-

5295. *Angew. Chem.* **2004**, *116*, 5405-5407; i) G. Zenoni, F. Quattrini, M. Mazzotti, C. Fuganti, M. Morbidelli, *Flavor Frag. J.* **2002**, *17*, 195-202. ; j) E. Francotte, T. Leutert, L. La Vecchia, F. Ossola, P. Richert, A. Schmidt, *Chirality* **2002**, *14*, 313-317. ; k) G. Subramanian, *Chiral Separation Techniques: A Practical Approach*, Wiley-VCH, Weinheim, **2001**; l) T. Jira, A. Bunke, M. G. Schmid, G. Gübitz, *J. Chromatogr. A* **1997**, *761*, 269-275. ; m) S. Ahuja, *Chiral Separations: Application and Technology*, ACS, Washington DC, **1997**.

[7] D. J. Cram, J. M. Cram, *Container Molecules and Their Guests*, The Royal Society of Chemistry, **1997**.

[8] a) R. M. C. Viegas, C. A. M. Afonso, J. G. Crespo, I. M. Coelhoso, *Sep. Purif. Technol.* **2007**, *53*, 224-234. ; b) M. Steensma, N. J. M. Kuipers, A. B. de Haan, G. Kwant, *Chem. Eng. Sci.* **2007**, *62*, 1395-1407. ; c) J. Koska, C. A. Haynes, *Chem. Eng. Sci.* **2001**, *56*, 5853-5864. ; d) A. B. D. Haan, B. Simandi, *Extraction Technology for the Separation of Optical Isomers, in Ion Exchange and Solvent Extraction*, Marcel Dekker, Inc, New York, **2001**; e) P. J. Pickering, J. B. Chaudhuri, *Chem. Eng. Sci.* **1997**, *52*, 377-386. ; f) J. C. Godfrey, M. J. Slater, *Liquid-Liquid Extraction Equipment*, John Wiley & Sons, New York, **1994**; g) E. Eliel, S. Wilen, L. Mander, *Stereochemistry of organic compounds*, John Wiley & Sons, New York, **1994**; h) M. Steensma, N. J. M. Kuipers, A. B. de Haan, G. Kwant, *Chem. Eng. Process. Process Intensif.* **2007**, *46*, 996-1005.

[9] See SI for full details on how operational selectivity is calculated and judged in terms of applicability.

[10] B. Schuur, B. J. V. Verkuijl, A. J. Minnaard, J. G. de Vries, H. J. Heeres, B. L. Feringa, *Org. Biomol. Chem.* **2011**, *9*, 36-51.

[11] a) A. Galan, D. Andreu, A. M. Echavarren, P. Prados, J. De Mendoza, *J. Am. Chem. Soc.* **1992**, *114*, 1511-1512. ; b) H. Tsukube, J.-i. Uenishi, T. Kanatani, H. Itoh, O. Yonemitsu, *Chem. Commun. (Cambridge, U. K.)* **1996**, *4*, 477-478. ; c) K. Naemura, K. Nishioka, K. Ogasahara, Y. Nishikawa, K. Hirose, Y. Tobe, *Tetrahedron: Asymmetry* **1998**, *9*, 563-574. ; d) J. Lacour, C. Goujon-Ginglinger, S. Torche-Haldimann, J. J. Jodry, *Angew. Chem. Int. Ed.* **2000**, *39*, 3695-3697. *Angew. Chem.* **2000**, *20*, 3830-3832; e) B. J. V. Verkuijl, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Org. Chem.* **2009**, *74*, 6526-6533.

[12] B. Schuur, M. Blahušiak, C. R. Vitasari, M. Gramblička, A. B. De Haan, T. J. Visser, *Chirality* **2015**, *27*, 123-130.

[13] P. Zhang, C. Liu, K. Tang, J. Liu, C. Zhou, C. Yang, *Chirality* **2014**, *26*, 79-87.

[14] E. B. Pinxterhuis, J.-B. Gualtierotti, H. J. Heeres, J. G. de Vries, B. L. Feringa, *Chem.Sci.* **2017**, *8*, 6409-6418.

[15] J. Bao, W. D. Wulff, A. L. Rheingold, *J. Am. Chem. Soc.* **1993**, *115*, 3814-3815.

[16] a) D. Parmar, E. Sugiono, S. Raja, M. Rueping, *Chem. Rev.* **2014**, *114*, 9047-9153. ; b) S. Lou, S. E. Schaus, *J. Am. Chem. Soc.* **2008**, *130*, 6922-6923. ; c) Y. Deng, Y. R. Lee, C. A. Newman, W. D. Wulff, *Eur. J. Org. Chem.* **2007**, *2007*, 2068-2071. ; d) D. P. Heller, D. R. Goldberg, W. D. Wulff, *J. Am. Chem. Soc.* **1997**, *119*, 10551-10552.

[17] A. A. Desai, L. Huang, W. D. Wulff, G. B. Rowland, J. C. Antilla, *Synthesis* **2010**, *2010*, 2106-2109.

[18] B. Schuur, A. J. Hallett, J. G. M. Winkelman, J. G. de Vries, H. J. Heeres, *Org. Process Res. Dev.* **2009**, *13*, 911-914.

[19] This threshold is the operational selecivity of at least 1.5 that was mentioned beforehand. See ref 10 for full details on the Fenske formula and how it is used to determine this threashold.

[20] Measurments below 2°C become unreliabale as the aquous phase freezes.

[21] B. J. V. Verkuijl, J. G. de Vries, B. L. Feringa, *Chirality* **2011**, *23*, 34-43.

[22] While the reason for this is unclear, we believe it due, in part, to changes in the solubility of the G/H complex in the organic phase.

[23] a) A. J. Hallett, G. J. Kwant, J. G. de Vries, *Chemistry-a European Journal* **2009**, *15*, 2111-2120. ; b) B. Schuur, J. Floure, A. J. Hallett, J. G. M. Winkelman, J. G. de Vries, H. J. Heeres, *Organic Process Research & Development* **2008**, *12*, 950-955.

[24] See SI for full details.

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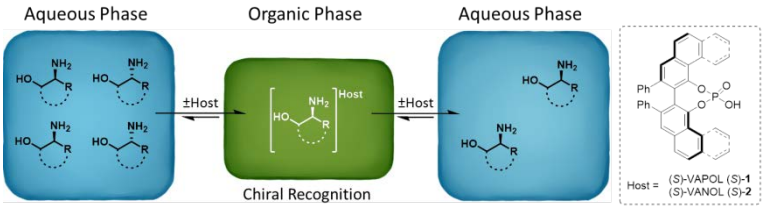

Divorced with prejudice. Resolution of 1,2-amino alcohol racemates is achieved via enantioselective liquid-liquid extraction using chiral VANOL- and VAPOL- based phosphoric acids in high operational selectivity. The study of the diverse parameters governing the extraction shows it to be highly robust and amenable to scale up.

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Highly Efficient and Robust Enantioselective Liquid-Liquid Extraction of 1,2-Amino Alcohols utilising VAPOL and VANOL Phosphoric Acid hosts.