3,3′-Diaryl-BINOL Phosphoric Acids as Enantioselective Extractants of Benzylic Primary Amines

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ABSTRACT We report that 3,3′-diaryl-BINOL phosphoric acids are effective enantioselective extractants in chiral separation methods based on reactive liquid–liquid extraction. These new extractants are capable of separating racemic benzylic primary amine substrates. The effect of the nature of the substituents at the 3,3′-positions of the host were examined as well as the structure of the substrate, together with important parameters such as the organic solvent, the pH of the aqueous phase, and the host stoichiometry. Titration of the substrate with the host was monitored by FTIR, NMR, UV–Vis, and CD spectroscopy, which provided insight into the structure of the host–guest complex involved in extraction. *Chirality 23:34–43, 2011.*

KEY WORDS: BINOL; enantioselective; host–guest; reactive extraction

INTRODUCTION

Enantiomerically pure intermediates are of increasing importance to the pharmaceutical and agricultural industries. Several approaches are used to obtain these compounds, most notably applying resolution by diastereomeric selective crystallization, asymmetric synthesis, fermentation, biocatalysis, and chiral pool synthesis.[1] Nevertheless, classic resolution is still the most frequently used and fastest method in the chemical and pharmaceutical industry, despite its theoretical maximum of 50% yield.[2] Occasionally, the undesired isomer can be racemized so that it can be recycled.[3] However, this crystallization-based method is typically labor intensive, and suffers frequently from unreliable reproductivity.[4] Hence, new, high-yielding, low-cost chiral separation methods are a major target in current research.[5] Among the alternative methods currently available are resolution with in situ racemization,[6] membrane-assisted separations,[7] diastereomer separation by distillation,[8] separation using inclusion complexes,[9] and the use of simulated moving bed,[10–14] supercritical extraction,[15–17] and fractional reactive extraction.[18,19]

Enantioselective liquid–liquid extraction (ELLE), in which an enantiopure host is used to react enantiospecifically and reversibly with a racemic guest (see Fig. 1) is a promising alternative approach to enantioselective extraction. If the host is confined to one phase in a biphasic system, a separation of enantiomers can take place between the two phases in a single step. If the separation is imperfect, a fractional extraction scheme is necessary.[20,21] A widely accepted minimal selectivity of 1.5 is viewed as being necessary to avoid an excessive number of fractional extraction steps.[22] Another important feature is the potential versatility of the approach. A flexible host, i.e., a host able to separate various racemic members from a certain class of compounds, would be similar to chiral chromatography, where a single type of column is usually effective in the separation of an entire class of racemic compounds.[23]

In the field of ELLE, a considerable effort has been devoted to the separation of functionalized primary amines, in particular protected amino acids and amino alcohols, due to their importance for the fine chemical and pharmaceutical industries. The seminal work of Cram et al. on the extraction of amino acid esters using crown ethers featuring a chiral BINOL backbone,[24,25] resolution of amino alcohols with good selectivities using azophenolic crown-ethers[18,26] and the recent work of Kim et al. on the separation of amino alcohols using stereoselective imine hydrolysis[27] demonstrate the potential of ELLE.

Typically, U-tubes or membranes are employed in separation schemes in which the chiral host is used in a catalytic fashion. Use of a number of membranes in series has even allowed for complete separation of enantiomers in specific cases.[28] Maier and coworkers have reported the use of a centrifugal partition chromatograph containing an MTBE solution of bis-1,4-(dihydroquinidinyl)phthalazine as the stationary chiral host solution and they were able to fully separate the herbicide 2-(2,4-dichlorophenoxy)propionic acid (dichlorprop), which was fed to the system in aqueous buffer mobile phase.[29] Recently some of us have demonstrated the use of centrifugal contact separators as a highly efficient method for continuous extraction.[30–32] Use of a number of these devices in series as a counter-

Additional Supporting Information may be found in the online version of this article.

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Received for publication 27 October 2009; Accepted 7 January 2010
DOI: 10.1002/chir.20834
Published online 10 March 2010 in Wiley Online Library (wileyonlinelibrary.com).

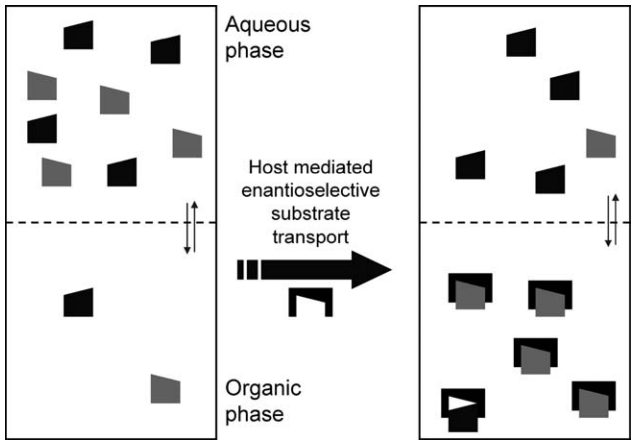

Fig. 1. Schematic representation of ELLE. Symbols: ■ and ■: substrate enantiomers; ⊓: host.

current cascade also allows for full separation of a racemate.[33]

In addition to the technological aspects, a pressing issue is the development of improved chiral host compounds. Compounds with a phosphoric acid functionality have proven to be suitable hosts in reactive liquid–liquid extraction. Bis(2-ethylhexyl) hydrogen phosphate (D2EHPA) showed to be an effective host for the reactive liquid–liquid extraction of metal cations[34] and amino acids.[35] In combination with a tartaric acid derivative, Luo et al. have reported ELLE combined with classic resolution by crystallization of tryptophan with an operational selectivity up to 5.3.[36]

However, one of the main challenges within the field of ELLE is the selective extraction of nonfunctionalized primary amines. Until now, additional groups in the host and in the substrate were needed for enantioselective host–guest recognition. Hence, intermediates such as α-methylbenzylamine (MBA) and phenylpropylamine (PPA), which contain only a primary amine at a benzylic position, are not easily separated. An enantiomerically pure host bearing a phosphoric functionality would be an excellent candidate to solve this problem.

In this article, we demonstrate that the newly developed hosts, 3-3′-disubstituted-binaphthyl-phosphoric-acids (BNPA), can be used to achieve these important targets. These hosts are capable of extracting PPA with the highest operational selectivity reported to date. The hosts are also capable of extracting a range of amino alcohols with significant selectivity.

The design of the host has to meet a number of conditions to achieve general application to a particular substrate class. Ideally, an ELLE system consists of an organic phase and a buffered aqueous phase. Hence, the host should be confined to one phase of the system and the physical partition of the host should be as low as possible. In the majority of systems reported to date, a lipophilic host confined to the organic phase is employed. Furthermore, the substrate must have a physical partitioning as low as possible, to avoid nonenantioselective diffusion into the organic phase and, by default, the substrate must be susceptible to reactive extraction. To make the system useful for fractional extraction, back extraction of the substrate must be also possible, which may entail adjusting the pH of the aqueous layer to achieve full back extraction.

In this study, a 3,3′-disubstituted BINOL was chosen as the chiral motif in the host shown in supporting information. Its axial chirality makes enantioselective recognition possible.[37] A phosphoric acid functionality is used to set the axial structure and to increase the Brønsted acidity of the host and additionally acts as a Lewis base and may generate further hydrogen bonding interactions.[37]

The axial chirality of the host provides for enantiomeric recognition at the phosphoric acid site. The recognition is expected to be enhanced by placing substituents at the 3,3′-positions of the BINOL backbone to generate a "chiral cleft" (see Fig. 2). Electron-deficient phenyl rings, e.g., 3,5-bis-trifluoromethyl-phenyl moieties (PA1), may enable enhanced π–π-stacking interactions with the electron-rich benzylic amines. The nonsubstituted BNPA (PA2) is used as a reference compound whereas PA3 is employed to examine the role of the trifluoromethyl groups of PA1. The biphenyl functionality in PA4 is employed to introduce additional steric bias (Fig. 3).

MATERIALS AND METHODS

Units and Parameters

The distribution (D) is defined as the ratio of the concentration of a substrate (A) over two phases.

$$D(\text{org/aq}) = \frac{[\text{A}]_{\text{org,allforms}}}{[\text{A}]_{\text{aq,allforms}}}$$

The physical partition [P (org/aq)] is defined as the distribution of the substrate in absence of a host. The operational selectivity (α_{op}) is defined as the ratio of the distributions of both enantiomers of the substrate.

$$\alpha_{op} = \frac{D_R}{D_S}$$

Chemicals

(*R*)- and (*S*)-2-Phenylglycinol (98%), *rac*-2-phenylglycinol (98%), *rac*-norephedrine hydrochloride (99+%), (*R*)- and (*S*)-α-methylbenzylamine (99%), and *rac*-α-methylbenzyl-

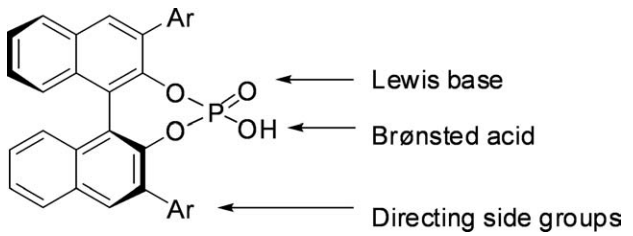

Fig. 2. Host design.

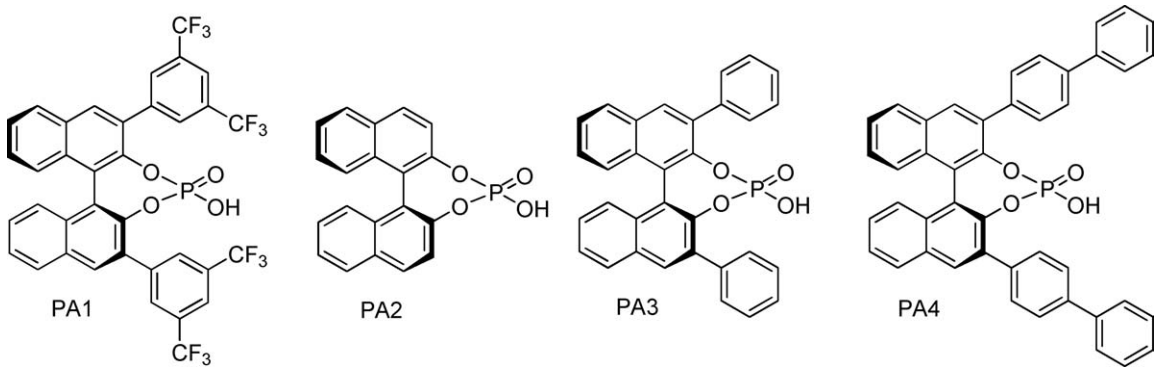

Fig. 3. BINOL-based phosphoric acids (PA1–PA4).

amine (99%) were obtained from Acros. *rac*-1-Aminoindan (98%), (*R*)- and (*S*)-aminoindan, (*1R,2R*)-(−)-*trans*-1-amino-2-indanol (97%), (*1S,2S*)-(−)-*trans*-1-amino-2-indanol (97%), (*1S,2R*)-(−)-*cis*-1-amino-2-indanol (97%), and (*1R,2S*)-(−)-*cis*-1-amino-2-indanol (97%) were obtained from Sigma-Aldrich. (*S*)-*1*-Phenylpropylamine (99%) and (*R*)-*1*-phenylpropylamine (99%) were obtained from Alfa Aesar. Water was doubly distilled prior to use.

All buffers were prepared using NaH_2PO_4, obtained from Merck at a concentration of 100 mM and subsequent addition of HCl (aq) or NaOH (aq). The pH was measured using a Hanna Instruments pH 213 Microprocessor pH meter (Fig. 4).

Extraction Experiments and Chemical Analysis

All extraction experiments were carried out in 1.5 ml screw capped vials. In a standard experiment, a 1.0 mM solution of the host in the organic phase was combined with a 2.0 mM solution of the substrate in the buffered aqueous solution in equivolumous amounts (0.40 ml). Reactions were carried out *in duplo* and with a simultaneous blank extraction [c (host) = 0.0 mM] to determine the physical partition of the substrate. The two phase systems were stirred overnight at T = 6°C and subsequently allowed to settle for at least 30 min. The aqueous phase was analyzed by RP-HPLC, using Shimadzu CC-20AD pumps, a Crownpak CR(+) chiral column (Daicel, Japan) equipped with a guard column and a SPD-M20A diode array detector. A calibration curve was prepared in the concentration range employed for the determination of the distribution. Uncertainties were typically between 0.5 and 2.0%. Perchloric acid solutions (pH = 1.0, 1.5, or 2.0) were used as eluent for the RP-HPLC analysis.

U-Tube Experiments

Feeding phase: V_{fp} = 5.0 ml; aqueous phosphate buffer (0.100 M) pH = 5.0; c (PGL) = 20 mM. Transport phase: V_{tp} = 10.0 ml; carbon tetrachloride; c (PA1) = 0.5 mM. Receiving phase: V_{rp} = 5.0 ml; aqueous phosphate buffer (0.100 M); pH = 2.2. The phases were placed into the U-tube according to Figure 11. The tube was placed in a cooled chamber at T = 6°C. The magnetic stirrer was set to 900 rpm. For analysis, aliquots of 0.20 ml were removed from the receiving phase and were replaced by 0.2 ml of buffer.

Titration Experiments Followed by Spectroscopy

Organic solvents were presaturated with water and were employed to make stock solutions of the host and the substrate. The stock solutions were put together and shaken vigorously before the measurements. DCM was used for the UV–Vis, CD, and FTIR experiments. Deuterated chloroform was used as the organic solvent for the NMR experiments. Single extraction experiments with deuterated chloroform gave results corresponding to extractions with normal chloroform.

RESULTS AND DISCUSSION

Single Extraction Experiments

Substrate scope. PA1 was employed in the enantioselective extraction of a number of amines and amino alcohols to test the versatility of the system. The physical partition is 0.0 for all used substrates and the distribution of all substrates is in the range of 1.0 at this pH. With MBA, a distribution of 1.2 and an operational selectivity of 1.6

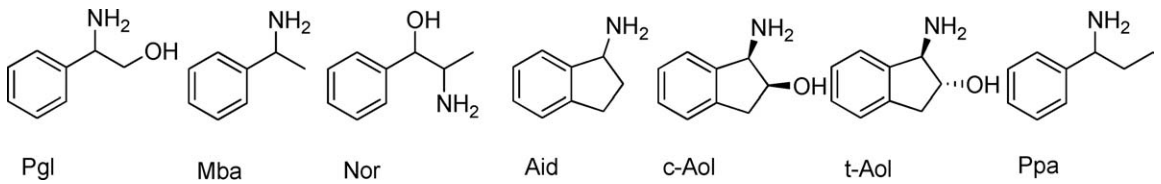

Fig. 4. Substrate structures. PGL, phenylglycinol; MBA, α-methylbenzylamine; NOR, norephedrine; AID, aminoindane; c-AOL, *cis*-1-amino-2-indanol; t-AOL, *trans*-1-amino-2-indanol; PPA, phenylpropylamine.

TABLE 1. Substrate scope

Entry	Substrate	*P* (org/aq)	*D* (org/aq)	α_{op}
1	MBA	0.0	1.2	1.6
2	PGL	0.0	1.2	1.9
3	NOR	0.0	1.1	1.0
4	PPA	0.0	1.2	1.1
5	AID	0.0	1.2	1.2
6	t-AOL	0.0	0.9	1.4
7	c-AOL	0.0	0.7	1.1

Conditions: host = PA1; organic phase = CCl_4; pH (aqueous phase) = 5.0.

were obtained. A distribution exceeding 1.0 suggests the binding of a second guest molecule to the host.[38,39] The presence of an alcohol group in the substrate (PGL) leads to an increase in selectivity to 1.9. Interchanging the alcohol and amine positions in the amino alcohol structure in the substrate (NOR) results in complete loss in selectivity. This indicates that the amine functionality needs to be at the benzylic position to obtain selectivity. The results with PPA (Entry 4) show that the addition of an extra methyl group has a large effect and leads to an almost complete loss of selectivity. Hence, the ability of PA1 to extract a substrate in an enantioselective manner is highly dependent on the substrate's structure (Table 1).

When the relative position of the amine and the aromatic ring are fixed, as in AID, a partial loss in selectivity is observed. Comparing PGL with t-AOL, the amine and alcohol of the t-AOL appear not to be in an optimal spatial configuration, and this is more so in the case of c-AOL. The relative rotational freedom of the amine and the alcohol present in the PGL appears to be essential for selectivity.

Influence of the host structure. The structure of the host has a critical impact on the operational selectivities observed. With the exception of PA1, all of the hosts gave a suspension when CCl_4 was used as the organic phase.

TABLE 2. Host structure

Entry	Host	Substrate	*D* (org/aq)	α_{op}[b]
1	PA1	PGL	1.0	1.7 (*S*)
2	PA2[a]	PGL	0.2	–
3	PA3	PGL	0.8	1.2 (*S*)
4	PA4	PGL	0.7	–
5	PA1	MBA	1.2	1.4 (*S*)
6	PA2[a]	MBA	0.0	-
7	PA3	MBA	1.0	1.3 (*R*)
8	PA4	MBA	1.1	1.4 (*S*)
9	PA1	PPA	1.2	–
10	PA2[a]	PPA	3.5	1.2 (*R*)
11	PA3	PPA	1.1	1.2 (*R*)
12	PA4	PPA	0.9	1.7 (*S*)

Conditions: organic phase = $CHCl_3$; pH (aqueous phase) = 5.0.
[a]*c* (PA2), 2.0 mM.
[b]The preferred extracted enantiomer is added in brackets.

Hence chloroform was chosen to compare the relative selectivity of the hosts.

The role played by the 3,3′-substituents in the enantiospecific interaction between PA1 and PGL is evident from entries 1–4 of Table 2. A high selectivity is observed for PA1. The lack of the 3,3′-substituents (Entry 2) leads to a complete loss of selectivity and also a large decrease in the extraction efficiency. Entry 3 demonstrates the necessity of the trifluoromethyl groups in achieving selectivity, where the phenyl-substituted host provides an α_{op} of only 1.2.

With MBA and PPA, a remarkable reversal in α_{op} is observed. In both cases, PA3 shows a preference for the (*S*) enantiomer (Entries 7 and 11) with moderate selectivity. This preference is reversed to the (*R*) enantiomer when a 4,4′-biphenyl group is present in the host (Entries 8 and 12), whereas PA4 is able to separate PPA with high selectivity (Entry 12).

Influence of the solvent. The organic solvent can have a profound influence both on the distribution and the operational selectivity in enantioselective host–guest complexations, not at least due to the influence that the solvent can have on the conformation of the complex.[40]

The physical partition of the substrates PGL, MBA, and PPA is 0.0 throughout the library of organic solvents presented here, with the exception of PPA in toluene as seen in Entry 23 of Table 3. The distributions fall within the range of 0.7–1.2. The ELLE of MBA shows solvent dependence of the selectivity. In polar solvents, such as 1-octanol or nitrobenzene (Entries 1 and 2), selectivity is not

TABLE 3. Solvent dependency on *P* (org/aq), *D* (org/aq), and α_{op} with MBA, PGL, and PPA

Entry	Substrate	Solvent	*P* (org/aq)	*D* (org/aq)	α_{op}
1	MBA	1-Octanol	0.0	0.9	1.0
2	MBA	Nitrobenzene	0.0	1.2	1.1
3	MBA	1,2-Dichloroethane	0.0	1.0	1.4
4	MBA	Dichloromethane	0.0	0.9	1.2
5	MBA	Chloroform	0.0	1.0	1.4
6	MBA	Chlorobenzene	0.0	1.2	1.3
7	MBA	Toluene	0.0	1.1	1.3
8	MBA	Carbon tetrachloride	0.0	1.2	1.6
9	PGL	1-Octanol	0.0	0.7	1.6
10	PGL	Nitrobenzene	0.0	1.0	1.7
11	PGL	1,2-Dichloroethane	0.0	0.9	1.6
12	PGL	Dichloromethane	0.0	0.8	1.6
13	PGL	Chloroform	0.0	0.8	1.7
14	PGL	Chlorobenzene	0.0	1.1	1.7
15	PGL	Toluene	0.0	1.0	1.6
16	PGL	Carbon tetrachloride	0.0	1.0	1.9
17	PPA	1-Octanol	0.0	0.9	1.0
18	PPA	Nitrobenzene	0.0	1.2	1.1
19	PPA	1,2-Dichloroethane	0.0	0.9	1.0
20	PPA	Dichloromethane	0.0	0.9	1.1
21	PPA	Chloroform	0.0	1.0	1.0
22	PPA	Chlorobenzene	0.0	1.2	1.0
23	PPA	Toluene	1.3	1.1	1.0
24	PPA	Carbon tetrachloride	0.0	1.2	1.1

Conditions: host = PA1; pH (aqueous phase) = 5.0; $T = 6°C$.

TABLE 4. pH dependency

Entry	pH	*P* (org/aq)	*D* (org/aq)	α_{op}
1	3.0	0.0	0.3	2.1
2	4.0	0.0	1.0	2.0
3	5.0	0.0	1.0	1.9
4	6.0	0.0	1.1	2.0
5	7.0	0.0	1.1	1.9
6	8.0	0.0	1.2	1.9

Conditions: host = PA1; substrate = PGL; organic solvent = CCl_4.

observed. In the case of the most apolar solvent (CCl_4, Entry 8), a maximum selectivity of 1.6 is obtained. Interestingly, the extraction of PGL does not show the same solvent dependence. In this case, the selectivity is essentially constant throughout the range of solvents examined, with the exception of CCl_4 that provides a higher selectivity (1.9). The ELLE of PPA shows, as with the other substrates, a constant distribution throughout the solvent range with the selectivity being independent of the solvent.

The selectivity in the extraction of MBA is proposed to be influenced by the intimacy of the ion pair formed by PA1 and MBA. The lower the polarity of the solvent, the closer the contact of the ion pair[41] and hence the higher the selectivity.[22,42] In the case of PGL, the alcohol functionality of the substrate is proposed to have a dominating effect. Another factor that might play a role is the presence of water in the system. Water is known to affect the enantioselectivity in organo catalyzed reactions with chiral phosphoric acid type catalysts.[43] Also, ab initio studies of complexes formed by triethylamine, formic acid, and water showed the preference of forming a neutral monohydrated complex over a monohydrated ion pair.[44]

Influence of the pH of the aqueous phase. The pH of the aqueous phase was varied to study its influence on the distribution and operational selectivity of the extraction. In the pH-range of 3.0–8.0, the extraction was examined using the optimal organic solvent CCl_4 (*vide supra*). An aqueous suspension is obtained at pH values above 8.0, due to back extraction of host into the aqueous phase.

TABLE 5. Dependence of *D* (org/aq), α_{op}, and e.e. on host–substrate stoichiometry

Entry	*c* (Host) (mM)	*D* (org/aq)	α_{op}	e.e. (aq)	e.e. (org)
1	0.4	0.1	2.3	4	36
2	0.6	0.2	2.2	5	33
3	0.8	0.2	2.2	7	32
4	1.0	0.3	2.3	9	32
5	1.2	0.4	2.2	10	29
6	1.4	0.4	2.2	11	28
7	1.6	0.5	2.2	13	26
8	2.0	0.6	2.2	15	23

Conditions: host = PA1; substrate = PGL; organic phase = CCl_4; pH (aq phase) = 3.0.

At pH values below 4, the distribution is reduced due to the preferential ammonium state of the substrate. For example, the distribution at pH = 3.0 (Entry 1) in the case of carbon tetrachloride is 0.3 (Table 4); a value that increases to 1.0 at pH = 4.0 (Entry 2). At pH 4.0, the substrate is largely confined to the aqueous phase as its ammonium cation. The pK_b of phenylglycinol is 5.5. Altogether, the phenylglycinol is >99% in its ammonium cation state at pH = 4.0 and at this pH value, a *D* (org/aq) of 1.0 is still achieved. This is presumably due to a high-association constant between the host and the substrate. The operational selectivity is between 1.9 and 2.1 with CCl_4 as a solvent in the pH range 3.0–8.0. Within this pH range, no clear correlation between the operational selectivity and the pH is observed.

Influence of the host–guest stoichiometry. In Table 5, the results of a study on the relationship between the stoichiometry of the host and the substrate are shown. The substrate is held at a constant concentration (2.0 mM), whereas the host concentration was varied over the range 0.4–2.0 mM. The pH of the aqueous phase was maintained at 3.0, to keep the distribution at values between 0.1 and 0.6. The distribution and the e.e. in the aqueous layer increase with the increase of the host stoichiometry. The e.e. (org) shows a reversed relationship, i.e., the e.e. in the organic layer decreases as the host–guest stoichiometry increases. The operational selectivity is independent of the host–substrate stoichiometry.

Influence of the temperature and the concentration. The extraction of PGL with PA1 in CCl_4 showed no significant change of distribution and selectivity from T = 6°C to RT. The concentration of the substrate can be increased from 2.0 to 100.0 mM, with the host concentration being increased accordingly. The e.e. is constant over this range. For applications, this is an important property, since concentrations in the 0.1 M regime are necessary to achieve a satisfying throughput in a contact separator cascade.

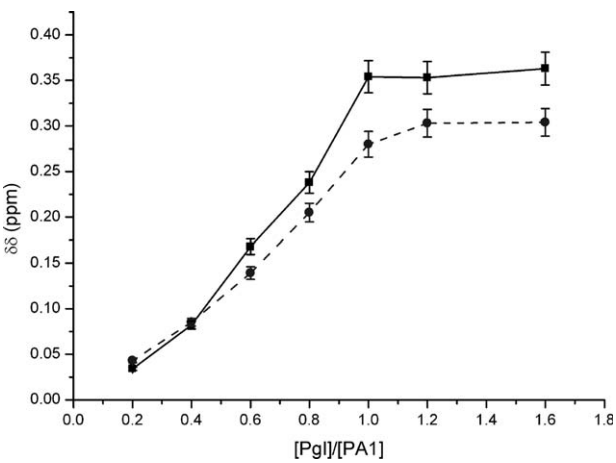

Fig. 5. Change in chemical shift of the phosphoric acid proton of PA1 upon titration of (*R*)-PGL (solid) and (*S*)-PGL (dashed). Error bars represent 5% standard deviation.

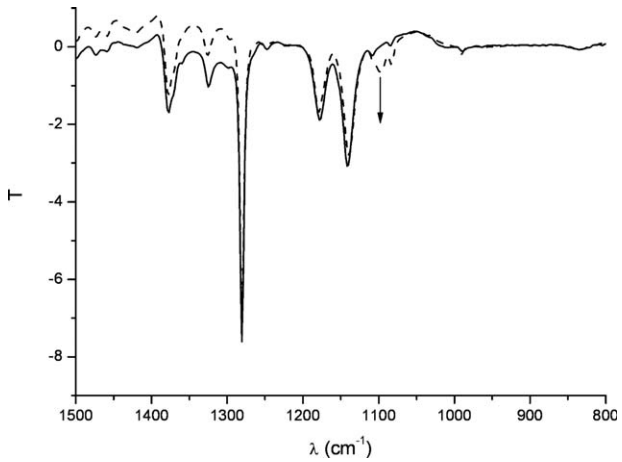

Fig. 6. FTIR spectra of PA1 (solid line) and after addition of (*R*)-PGL (dashed line).

Spectroscopy

Because of the high α_{op} in extraction, the chiral separation of PGL using PA1 was chosen as a benchmark system in spectroscopic studies with the aim of gaining further insight into the mechanism of host–substrate complexation.

^{1}H-NMR spectroscopy. NMR spectroscopy can be a powerful tool in the determination of the stoichiometry and equilibria involved in host–guest complexation.[45] If the phosphoric acid in the host is susceptible to hydrogen bonding or ion pairing with an appropriate guest, a change in the ^{1}H-NMR spectra is anticipated.

Titration curves for both of the enantiomers of PGL in $CDCl_3$ with the host PA1 are shown in Figure 5. The concentration of PA1 is held constant at c = 1.0 mM, i.e., the ordinate represents both the concentration of PGL (mM) and the [PGL]/[PA1] ratio. The change in chemical shift of the ^{1}H-NMR absorption of the proton of the phosphoric acid group PA1 is plotted against the [PGL]:[PA1] ratio.

This absorption shifts toward lower field upon titration with PGL. This downfield shift is consistent with the interaction of the acidic proton with an amine group.[46] The maximum is reached at a ratio of [PGL]/[PA1] = 1.0, supporting the formation of a 1:1 complex of the host with the substrate. The maximum of the change in chemical shift is at 0.36 ppm for (*R*)-PGL and 0.30 ppm for (*S*)-PGL, reflecting the difference between the chemical shifts of the diastereomeric complexes.

FTIR spectroscopy. FTIR spectroscopy titration experiments were performed in a similar manner to the NMR-titration experiments described earlier. The concentration of PA1 was held constant at c = 1.0 mM, and the concentration of PGL was increased incrementally from 0.2 to 1.4 mM. The FTIR spectra of PA1 with (*R*)-PGL are depicted in Figure 6. PGL shows no absorption bands in the region given here. PA1 shows the absorption bands as described in the literature (1474, 1462, 1427, 1377, 1358, 1335, 1281, 1236, 1182, 1140, 1036, 989, 897, and 845 cm^{-1}).[47]

Upon titration with (*R*)- or (*S*)-PGL in a monophasic system of water-saturated dichloromethane and PA1 kept at c = 1.0 mM, an additional band appears at 1098 cm^{-1}. Ramirez et al.[48] reported the appearance of bands between 1070 and 1080 cm^{-1} of the phosphates formed by complexation of phosphodiesters and primary amines, which can be assigned to the stretching vibrations of the phosphoryl bond of the phosphate. Corresponding results were obtained by allowing equimolar amounts (c = 10.0 mM) of diphenyl phosphate to react in dichloromethane with octyl amine and (*S*)-PGL, respectively. The FTIR spectra of the resulting phosphates both show an absorption at 1088 cm^{-1}. These results support the formation of a phosphate in the complexation of PGL to PA1.

These titration spectra can also be used for quantitative analysis. The results are shown in Figure 7. The spectra are normalized to the absorption band at 1297 cm^{-1}. In accordance with the data obtained by ^{1}H-NMR spectroscopy (see Fig. 5), an absorption maximum is obtained at [PGL]/[PA1] = 1.

UV–Vis and CD spectroscopy. UV–Vis and CD spectroscopies were employed to probe the effect of complexation on binding to the host in DCM as a solvent. Figure 8a shows the titration of PGL in which PA1 is kept at a constant concentration (c = 1.0 mM). The concentration of (*R*)-PGL was increased from 0.0 to 1.2 mM. Two isosbestic points can be seen at λ = 307 nm and λ = 330 nm in Figure 8. (*R*)-PGL does not absorb at these wavelengths and the total concentration of PA1 and complexed PA1 is constant throughout the titration. The absorption reaches a maximum when (*R*)-PGL = 1.0 mM, supporting the formation of the complex in a 1:1 ratio. A difference in absorption is observed at λ = 340 nm. Addition of the (*R*)-PGL substrate to PA1 shows a larger increase in absorption at λ = 340 nm than seen with addition of the (*S*)-PGL to

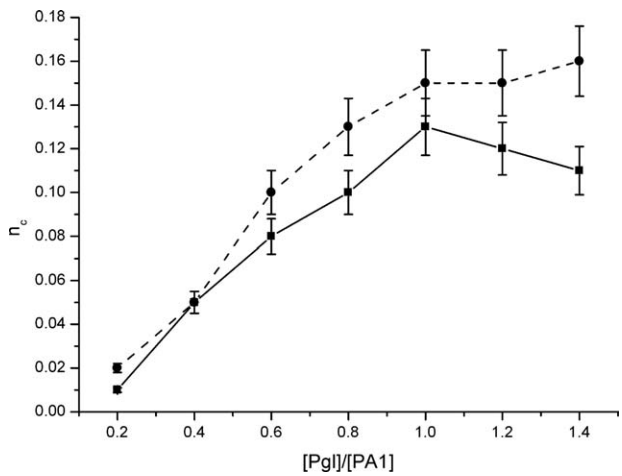

Fig. 7. Normalized FTIR absorption values (n_c) of PA1 phosphate formation upon titration of (*R*)-PGL (solid) and (*S*)-PGL (dashed). Error bars represent 10% standard deviation.

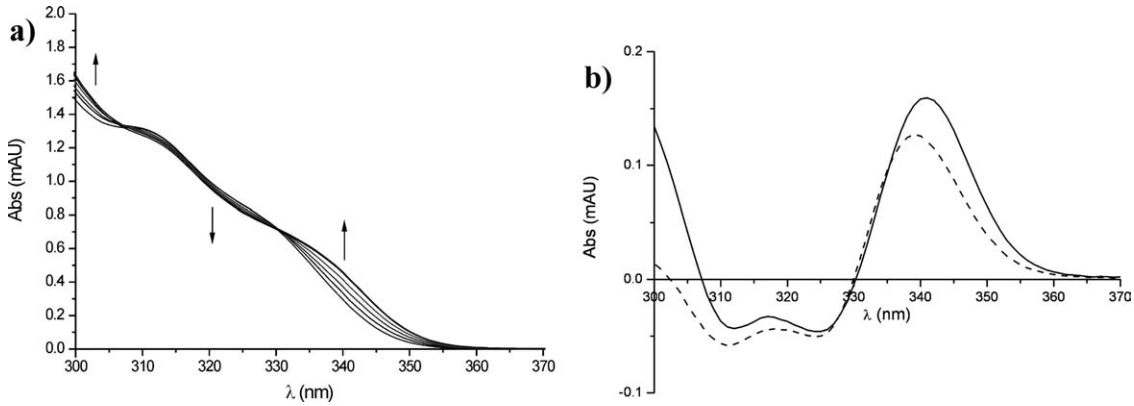

Fig. 8. UV–Vis spectra (**a**) of PA1 (1.0 mM) upon titration of (*R*)-PGL (0.0–1.2 mM) and differential spectra (**b**) of (*R*)-PGL (1.0 mM, solid line) and (*S*)-PGL (1.0 mM, dashed line).

PA1, which is most apparent in the UV–Vis differential spectra depicted in Figure 8b.

A titration of PA1 with either tetrabutylammonium hydroxide (TBAOH) or triethylamine (TEA) was followed by UV–Vis and CD spectroscopy (see Fig. 9) to determine the effect of deprotonation on the spectral properties of PA1. The UV–Vis spectrum (Fig. 9a) shows a change in absorption which is more pronounced, e.g., at $\lambda = 336$ nm, especially in the case of TBAOH, than in the case of PGL (Fig. 8a). A large change in molar ellipticity is observed by CD spectroscopy in this region also. Since TBAOH is a strong base, the resulting complex can be considered as a fully formed ion pair. Hence, the change in ellipticity at $\lambda = 336$ nm can be attributed to deprotonation of the host. The change in electron density at the phosphate group will have an effect on the structure of the BNPA backbone and ultimately the observed ellipticity, due to the C_2 symmetry in the BNPA backbone, changes.[49]

Examining the change in absorption and ellipticity at both $\lambda = 312$ and $\lambda = 336$ nm shows the changes are different for the PA1-TEA complex compared with the PA1-TBAOH complex. Both the change in absorption in the UV–Vis spectrum at $\lambda = 336$ nm (Fig. 9a) and the change in ellipticity at $\lambda = 336$ nm in the CD spectrum (Fig. 9b) are less pronounced in the case of PA1-TEA compared with PA1-TBAOH. This is possibly due to the PA1-TEA complex having partial more hydrogen bonding character or forming a tighter ion pair. In contrast, the change in ellipticity at $\lambda = 312$ nm is more pronounced for PA1-TEA than PA1-TBAOH. This may be due to a change in conformation of PA1, caused by steric interactions with TEA, i.e., a tighter ion pair with PA1 than observed with TBAOH.

The CD spectra obtained while following the titration of (*R*)-PGL and (*S*)-PGL to PA1 are shown in Figure 10. The CD spectra show an increase in ellipticity both at $\lambda = 314$ nm and $\lambda = 336$ nm. The change in magnitude of the ellipticity at $\lambda = 336$ nm is relatively less pronounced than in the cases of TEA and TBAOH (Fig. 9b). This is an indication that the binding of the PGL substrates to PA1 has a strong hydrogen bonding character, more than it resembles the formation of a fully dissociated ion pair. The binding of both enantiomers of PGL to PA1 results in a corresponding change in ellipticity at $\lambda = 336$ nm.

The change in ellipticity at $\lambda = 314$ nm is more pronounced for (*R*)-PGL (Fig. 10a) than for (*S*)-PGL (Fig. 10b). The higher ellipticity of (*R*)-PGL at $\lambda = 314$ nm compared with (*S*)-PGL can be ascribed to a change of the

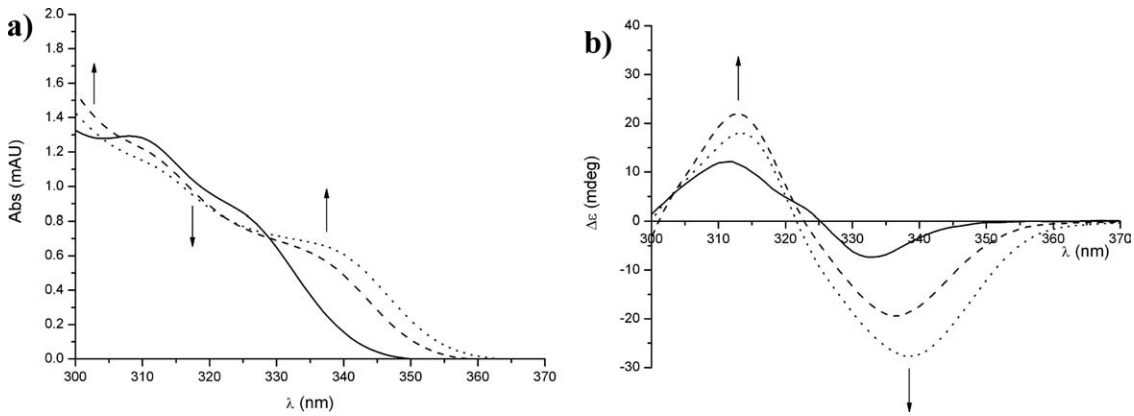

Fig. 9. UV–Vis (**a**) and CD spectra (**b**) of PA1 (1.0 mM) before and after addition of TEA (5.0 mM, dashed) or TBAOH (5.0 mM, dotted).

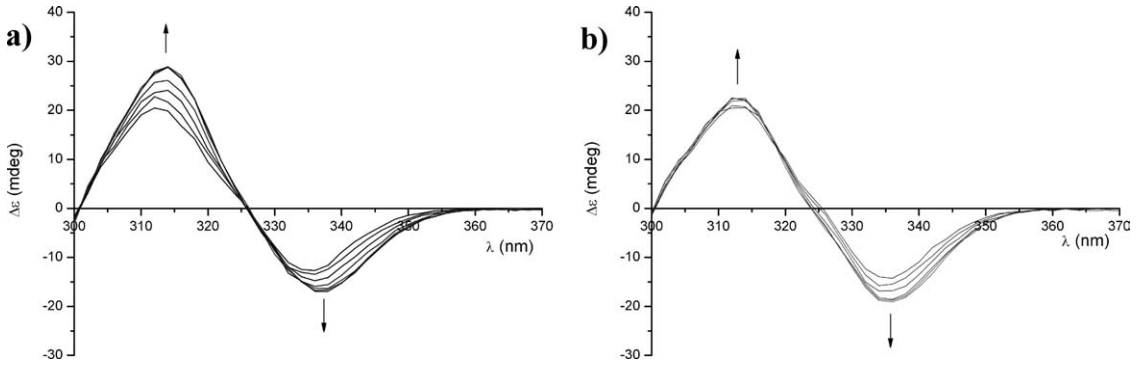

Fig. 10. CD spectra of PA1 (1.0 mM) upon titration of (*R*)-PGL (**a**) and (*S*)-PGL (**b**) (0.0–1.2 mM).

conformation of PA1, which may be a result of steric interactions upon the formation of the PA1-(*R*)-PGL complex, comparable with the change of ellipticity observed for the PA1-TEA complex (Fig. 9b). It should be noted that the single extraction experiments *vide supra* showed that (*S*)-PGL is the preferred enantiomer in extraction. The additional steric interactions indicated by CD spectroscopy for (*R*)-PGL may be related to this selectivity, i.e., (*S*)-PGL requires less disturbance to the PA1 backbone and hence the free energy of complexation is lower.

Transport Experiments and Reversibility

Reversibility of the complexation of PGL to PA1 was proven by bulk membrane transport experiments. The U-tube depicted in Figure 11 was used to transport PGL from the feeding phase to the receiving phase via the transport phase, using PA1 as an enantioselective carrier.

The bulk membrane transport experiment shows that the host PA1 is able to transport the substrate PGL catalytically through the bulk membrane (Table 6). The e.e. of the receiving phase decreases with time as a result of the change in concentrations in the feeding phase. The transport experiments demonstrate the reversible nature of the host–substrate complexation, which can be controlled by the pH of the aqueous phases.

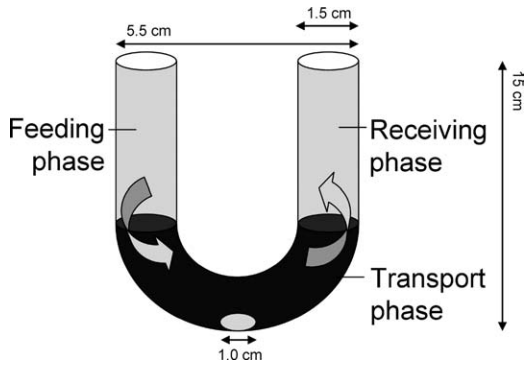

Fig. 11. Bulk membrane transport system.

CONCLUSIONS

We have shown that chiral BINOL-based phosphoric acids can be used in the ELLE of amino alcohols. Both the nature of the host as well as the substrate are important in optimizing the operational selectivity. The distribution can be controlled by the pH of the buffered aqueous phase. In the case of MBA extracted by PA1, the operational selectivity shows a dependency on the polarity of the organic phase: the lower the polarity, the higher the selectivity. This may be either due to ion pair formation or the decreased amount of water in the organic phase. The e.e. in both phases can be controlled by tuning both the pH and the stoichiometry of the host with respect to the substrate. However, this has no effect on the operational selectivity. Bulk membrane transport experiments demonstrate the possibility of catalytic enantioselective transport and reversible extraction. Titration studies by ^{1}H-NMR and FTIR confirm the formation of a 1:1 complex of the phosphoric acid host and the primary amine substrate. The 1:1 complex formation is also demonstrated by UV–Vis and CD spectroscopy. The CD spectra suggest a relation between the change in magnitude of the ellipticity and the mechanism of complexation of the substrate to the host. Additional interaction of the unfavored substrate is supposed to be responsible for the enantioselectivity of the host with respect to the substrate. The bulk membrane transport experiments prove the reversibility of the system. For future application in a cascade, the system meets

TABLE 6. Bulk membrane transport numbers

t (h)	*c* (aq) (Receiving phase)	e.e. (aq) (Receiving phase)
2.0	0.07	24
3.0	0.10	24
4.0	0.21	23
5.0	0.27	23
6.0	0.38	23
22.0	3.46	16

Conditions: feeding phase: V_{fp} = 5.0 ml; aqueous phosphate buffer (0.100 M) pH = 5.0; *c* (PGL) = 20 mM. Transport phase: V_{tp} = 10.0 ml; carbon tetrachloride; *c* (PA1) = 0.5 mM. Receiving phase: V_{rp} = 5.0 ml; aqueous phosphate buffer (0.100 M); pH = 2.2.

the required properties such as a sufficient selectivity for a number of substrates, full reversibility, and control of distribution.

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