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Prebiotic Chemistry

# Chiral Amplification of Phosphoramidates of Amines and Amino Acids in Water

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***Abstract:*** *The origin of biomolecular homochirality continues to be one of the most fascinating aspects of prebiotic chemistry. Various amplification strategies for chiral compounds to enhance a small chiral preference have been reported, but none of these involves phosphorylation, one of nature's essential chemical reactions. Here we present a simple and robust concept of phosphorylation-based chiral amplification of amines and amino acids in water. By exploiting the difference in solubility of a racemic phosphoramidate and its enantiopure form, we achieved enantioenrichment in solution. Starting with near racemic, phenylethylamine-based phosphoramidates, ee's of up to 95 % are reached in a single amplification step. Particularly noteworthy is the enantioenrichment of phosphorylated amino acids and their derivatives, which might point to a potential role of phosphorus en-route to prebiotic homochirality.*

Homochirality, the single handedness of its essential building blocks such as amino acids, carbohydrates and DNA, is a characteristic of biological systems and is known as "a signature of life".[1] The origin of homochirality ranks among the most fundamental questions directly associated with biogenesis and represents a key challenge in prebiotic chemistry.[2] The presence of single enantiomers is considered a prerequisite for chemical evolution and several theoretical and experimental approaches towards the emergence of biomolecular homochirality point to two fundamental issues: i) the symmetry breaking event to yield an imbalance of enantiomers,[3] and ii) the amplification mechanism(s) to sustain and propagate a small chiral bias to provide a large set of chiral building blocks and induce chirality at different length scales.[3] Focusing on chiral amplification, we now discovered that phosphorylation of chiral amines to phosphoramidates results in an exceptional large difference in solubility between enantiomers and racemates allowing readily enhancement of enantiomeric excess (*ee*) up to 95 % in a single dissolution step in water.

It should be emphasized that in the past decades several approaches to chiral amplification have been reported and various distinct mechanism proposed in the context of prebiotic chemistry[2,3] such as asymmetric autocatalysis,[4] preferred crystallization[5–7] and amplification in supramolecular systems.[8,9] As for any model system on the origin of the building blocks of life,[10] as well as selection and amplification mechanisms (including the chiral amplification presented here), a note of caution is appropriate regarding the relevance and nature of the molecules, transformations and conditions as recently discussed by Kitadai and Maruyama[11] in view of the inherent uncertainty associated with prebiotic chemistry.

Approaches to achieve amplification and enrichment of homochirality, following the intriguing model proposed by Frank[12a] nearly 70 years ago, and investigations into nonlinear effects by Kagan,[8d,f,12b] include asymmetric autocatalysis pioneered by Soai,[4] and various physical models[13] based on differences in solubility of enantiomers and racemic compounds,[14a–e] crystallization[15] or sublimation[16] (i.e. conglomerates vs. racemates),[14f,g,17] aggregation behavior,[8] amplification through supramolecular chirality[8] and supramolecular self-amplifying catalysis.[9] Especially the attrition-enhanced deracemization involving conglomerates (through Ostwald ripening),[5] following the fascinating initial results by Viedma,[6] enabled various groups[7] to demonstrate how to readily obtain solid phase homochirality.

To arrive at enantiomer-enriched compounds in solution advantage is taken of the eutectic model[14b,18] with selective partitioning of enantiomers between liquid and solid phase and preferred crystallization of racemic (heterochiral) material. The models, mechanism and experimental demonstration of solution phase amplification were explored by Morowitz,[19] Breslow,[14a,d,e] Blackmond,[14b,18] Hayashi[14c] and others[20] for, for example, amino acids and applied in chirality transfer in, for instance, catalytic asymmetric aldol reactions.[14b] Taking advantage of the sensitivity of molecular composition in a co-crystallization process to achiral additives as shown by Lahav,[21] Blackmond and co-workers developed elegant methods to modify eutectic *ee* values resulting in enhanced solution phase enantiomeric enrichments of several amino acids.[14b,c]

As part of our ongoing program on chiral amplification[8f,16a,22] and addressing the challenge to design potential

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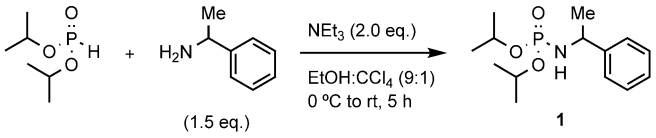
prebiotic relevant systems in order to achieve high enantiomeric enrichment in water, we focused on simple derivatization reactions changing solubility and crystallization behavior (i.e. conglomerate vs. racemate formation). Distinct from the previous reports on solution-phase enantioenrichment,[14] we envisioned the introduction of a phosphate functionality in our design for the chiral amplification of amines in the form of phosphoramidates. Since various phosphorus compounds have been discussed regarding their role in prebiotic chemistry[11,23] and as phosphorus derivatives are ubiquitous in nature, and pivotal in, for example, membrane formation, replication, information (DNA, RNA), proper function of enzymes and proteins, glycolysis or energy metabolism,[24] we were intrigued by the possibility that simple derivatization with a phosphorus unit could contribute to chiral amplification of amines and amino acids by changing hydrogen bonding patterns and aggregation. From a molecular viewpoint we reasoned that in the formed phosphoramidates the additional hydrogen bonding between the P=O and N–H moiety might facilitate heterodimer formation of the racemic phosphoramidate. Profiting from these interactions, an increased stability of the racemic crystal might result in reducing its solubility. On the contrary, dimerization would be less favorable for an enantiopure phosphoramidate, as models indicate that in this case the phosphorus moiety will be more accessible and therefore more likely to undergo hydrogen bonding with the surrounding water molecules. This would result in enhanced solubility of the individual enantiomers and as a consequence in solution-phase enantio-enrichment starting from a small chiral bias towards one enantiomer.

At the onset of our studies, we selected the phosphoramidate of α-phenylethylamine (**1**) as our model compound. Both enantiomers and the racemate of **1** were prepared via an Atherton–Todd[25] reaction from diisopropyl phosphite and the respective amine (Scheme 1).




***Scheme 1.*** Synthesis of phosphoramidate **1** via Atherton–Todd reaction.

In preliminary experiments *rac*-**1** was isolated as a crystalline solid, whereas the enantiomerically pure compound was obtained as an oil. Furthermore, addition of a few mL of water to scalemic **1** with low enantiomeric excess (*ee* = 7 %), to our delight, resulted in preferential dissolution of a single enantiomer of **1** providing an aqueous solution with high *ee* (over 90 %). Focusing on reproducible conditions for the chiral amplification the following simple procedure was adopted; first, marginally enantioenriched mixtures were prepared by completely dissolving both enantiomers followed by solvent removal. These scalemic solids were then suspended in water, stirred and subsequently, the suspension was filtered followed by freeze-drying and the initial and final *ee's* were determined by chiral HPLC analysis. All the chiral amplification experiments were conducted as triplicates (for detailed experimental procedures and various control experiments, see Supporting Information).

In order to have a better understanding about the phase behaviour, the solubility and the eutectic composition of phosphoramidate **1** in water, a ternary phase diagram (TPD) for the system (*S*)-**1**/(*R*)-**1**/double distilled $H_2O$ (*dd*$H_2O$) was constructed (Figure 1). The solvent *dd*$H_2O$ is presented at the apex and pure (*S*)-**1** and (*R*)-**1** at the left and right vertices, respectively. The concentrations are expressed as mole fractions and both concentration in the aqueous phase and *ee* values were determined by chiral HPLC (see Supporting Information).

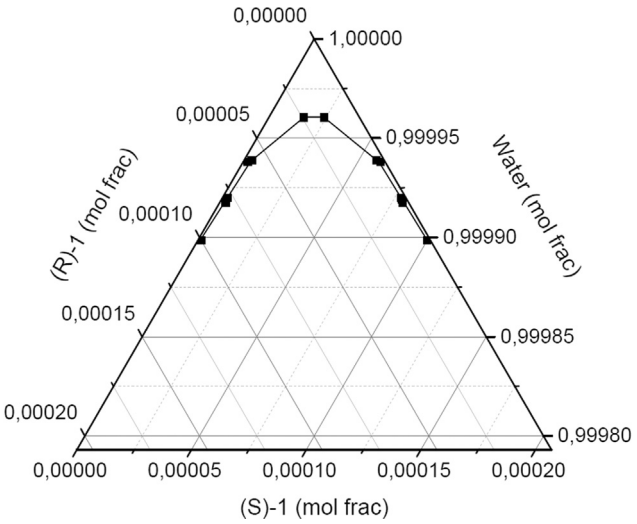



***Figure 1.*** Zoom in of the ternary phase diagram of (*S*)-**1**, (*R*)-**1** and water at 26 °C.

Based on the TPD in Figure 1, no eutectic point for phosphoramidate **1** in water could be observed. Therefore, theoretically an enantiomeric excess of around 97 % *ee* for **1** in solution can be reached irrespective of the initial *ee* which has be experimentally shown starting from 10 % *ee* and higher (see Supporting Information).

To test our hypothesis of preferred heterodimer formation (i.e. racemate instead of conglomerate of the racemic phosphoramidate), a single crystal X-ray analysis of *rac*-**1** was performed. It was found that racemic phosphoramidate **1** indeed crystallizes as a dimer containing both enantiomers (Figure 2). Since we were not able to crystallize the enantiopure compound **1** (being an oil), we reasoned that formation of the homochiral dimer is less favorable due to additional steric hindrance.

Encouraged by these results, we investigated key parameters including pH, salinity, temperature, concentration, additives and agitation and their potential influence on the chiral amplification of **1**. The results are displayed in Table 1 (see Supporting Information for further details).

From all the tested conditions, the amount of suspended phosphoramidate **1**, used to prepare the oversaturated solution, proved to be the most influential parameter (Entry 1, Table 1). Upon increasing the amount of scalemic

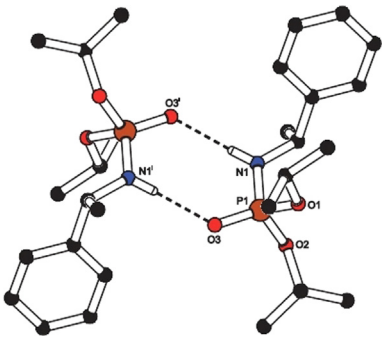



***Figure 2.*** Structure of racemic dimer phosphoramidate *rac*-**1** in the crystal. C–H hydrogen atoms are omitted for clarity.[29]

***Table 1:*** Parameters for chiral amplification of **1** in water.

| Entry | Parameters | Influence | Effect[i] |
|---|---|---|---|
| 1 | Amount of **1**[a] | Yes | Increased $ee_{final}$ by 50% |
| 2 | Time[b] | No | – |
| 3 | Temperature[c] | No | – |
| 4 | pH[d] | No | – |
| 5 | Salinity[e] | Yes | Increased $ee_{final}$ in 1 M aq. $MgSO_4$ by 10% |
| 6 | $H_2O$ grade[f] | No | – |
| 7 | Additives[g] | No | – |
| 8 | Agitation[h] | No | – |

[a] 0.14 mmol–1 mmol of scalemic **1** in 1 mL *dd*$H_2O$. [b] 1 h–2 d. [c] 0 °C–50 °C. [d] pH 2–11. [e] 1 M and saturated solutions of salts of alkali metals, alkali earth metals, transition metals and $NH_4Cl$. [f] *dd*$H_2O$, *d*$H_2O$, tap $H_2O$, $D_2O$. [g] Addition of *t*BuOH (5% and 15%), diisopropyl phosphite (5 mol%), *rac*-α-phenylethylamine (5 mol%), (*S*)-α-phenylethylamine (5 mol%), (*R*)-α-phenylethylamine (5 mol%). [h] Speed of stirring at 450 rounds per minute (rpm) and 1000 rpm, magnetic stirring bar size 6×3 mm and 10×6 mm, added 6 pieces of 2 mm diameter borosilicate glass beads, sonification for 2 h or 19 h. [b–h] Performed using 0.14 mmol and 0.5 mmol of scalemic **1** in 1 mL water. [i] For additional information about the effect on final *ee* measured in solution ($ee_{final}$) see main text and Supporting Information.

**1** with an initial *ee* of 3.6%, from 0.14 mmol to 0.5 mmol in 1 mL of water, a significant enhancement of the final *ee* by 50% was observed (0.14 mmol: $ee_{final}$ 24%; 0.5 mmol: $ee_{final}$ 77%), while further increase of the amount of scalemic **1** (up to 1 mmol in 1 mL of *dd*$H_2O$) did not result in any improvement. The subsequent efforts to further promote the amplification by altering time or temperature did not result in any significant improvement (Entry 2 and 3, Table 1). Also, the influence of pH, ranging from 2–11, was examined but no clear trend could be observed (Entry 4, Table 1) and hydrolysis was not observed.[26,27] Therefore, we reasoned, that rather than pH, the salts used in the buffer solutions might influence the solubility of **1**. The chiral amplification was therefore conducted in aqueous solutions of 10 different salts, with concentrations ranging from 1 M to saturated solution. Salts of alkali metals, alkali earth metals, transition metals, differing in cation radii, with both mono- and polyatomic anions were used to examine their influence on the solubility. Slight improvement of the final *ee* of about 10% was achieved in 1 M aq. sol. of $MgSO_4$ (Entry 5, Table 1) compared to standard amplification conditions in *dd*$H_2O$. Investigation of different grades of water (i.e. *dd*$H_2O$, *d*$H_2O$, tap $H_2O$, $D_2O$ and a mixture of *dd*$H_2O$/*t*BuOH, see Supporting Information) (Entry 6 and 7, Table 1) also showed no effect on the amplification outcome. Based on these experiments and testing the influence of agitation (i.e. speed of stirring, grinding with 2 mm glass beads, and sonication—Entry 8, and Supporting Information), we chose 0.5 mmol phosphoramidate in 1 mL *dd*$H_2O$ and stirring for 17 h at 26 °C as our general conditions for further experiments.

Next, the amplification starting from different *ee's* of both enantiomers of phosphoramidate **1** was examined (Figure 3).

As apparent from Figure 3, an enantioenrichment starting from 2% *ee* to 65% *ee* and from 7% to 90% *ee* was observed and the threshold of a final 95% *ee* was reached by amplification of material, in a single dissolution step, starting from an initial *ee* of 10%. This result is in good agreement with the previously determined eutectic *ee* of 97%. We reasoned that a small amount of the racemate could be dissolved in the aqueous phase together with the pure enantiomer slightly diminishing the final *ee*. Much to our surprise, we also observed an enantioenrichment of the racemic phosphoramidate **1** using freshly prepared purely racemic starting material (Figure 3). Although, minor amplification was observed, varying approximately between 5 and 8% for the final *ee*, nearly 30 amplification reactions conducted under the same conditions and with various sources of racemic amine to prepare **1** resulted in amplification to exclusively the (*S*)-enantiomer (see Supporting Information). This unexpected observation might be attributed to a presence of a minute chiral impurity or another potential *ee* bias (including stochastic behavior), in the theoretically racemic phosphoramidate **1**, which could not be observed within the detection limits of our analysis methods including NMR, chiral HPLC and optical rotation measurement. In this context, we further speculated whether the decomposition of *rac*-phosphoramidate **1** to its starting materials could induce some enantioenrichment. Eventually, this assumption was refuted by addition of diisopropyl phosphite and *rac*-/(*R*)-/(*S*)-α-phenylethylamine which did not have any effect on the amplification result (Entry 7, Table 1). As the focus is here on chiral amplification

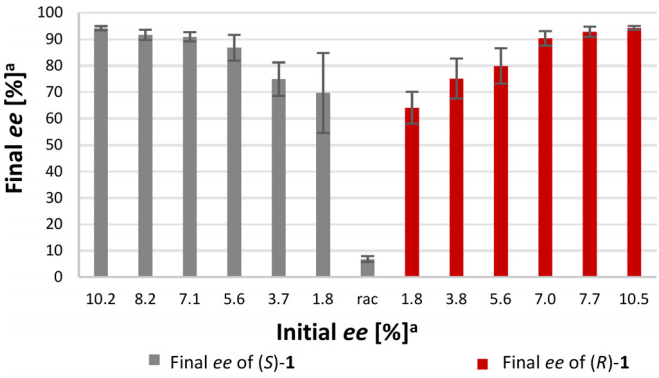



***Figure 3.*** Chiral amplification of (*S*)-/(*R*)-/*rac*-diisopropyl (1- phenylethyl)phosphoramidate **1** in water at 26 °C. [a] Determined by chiral HPLC analysis.

through a phosphoramidate dissolution/crystallization mechanism we refrain from speculation and leave the origin of this puzzling behavior of racemic phosphoramidate **1** to a detailed forthcoming study.

To provide further insight into the amplification behavior, we were curious to see whether the nature of alkoxy-substituents at the phosphorus as well as the variation in amine moiety would influence solubility and the chiral aggregation. Therefore, a small library of racemic and enantioenriched phosphoramidates was prepared (Figure 4) and the subsequent chiral amplification in water examined (Figure 5, Figure 6).

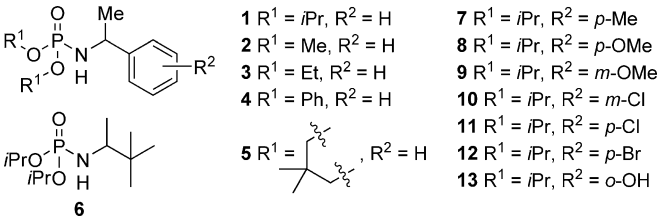



***Figure 4.*** Phosphoramidates.

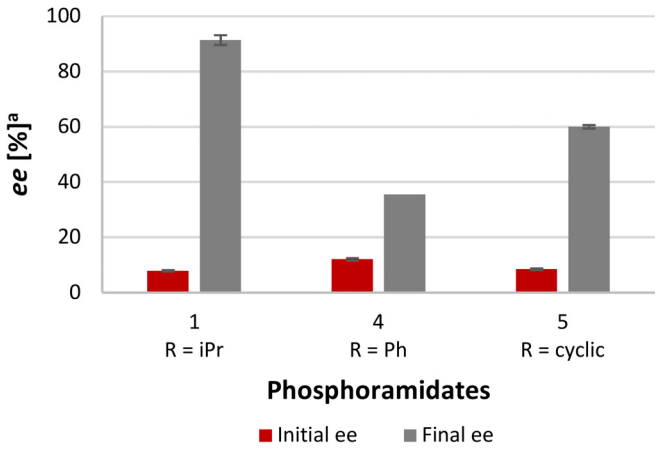



***Figure 5.*** Chiral amplification results of phosphoramidate **1**, **4** and **5** in water at 26 °C [a] Determined by chiral HPLC analysis.

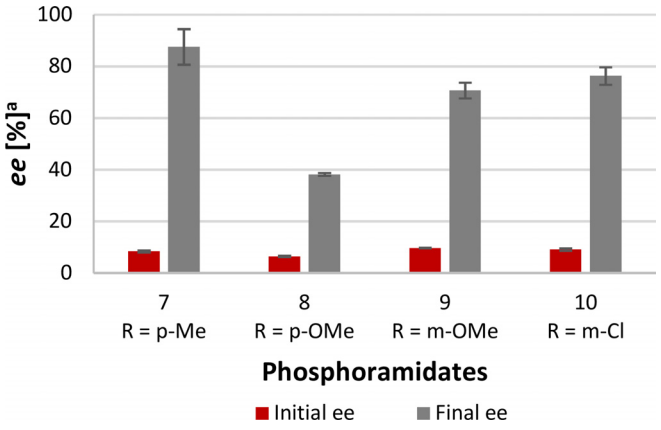



***Figure 6.*** Chiral amplification results of phosphoramidate **7**, **8**, **9** and **10** in water at 26 °C. [a] Determined by chiral HPLC analysis.

Replacing the diisopropoxy-groups of substrate **1** by methoxy- and ethoxy-groups afforded phosphoramidates **2** and **3** respectively. The racemates of both **2** and **3**, however, were oils and no TPD could be constructed nor amplification employing our method could be performed. On the contrary, the phenoxy-substituted phosphoramidate **4** was obtained as a solid and amplification from initial 12 % *ee* to final 35 % *ee* was observed (Figure 5). Compared to the compound **1**, the sterically constrained cyclic phosphoramidate **5** showed less pronounced differences in solubility and the chiral amplification of **5** resulted in 60 % *ee* from an initial 8 % *ee*, after a single cycle in water (Figure 5).

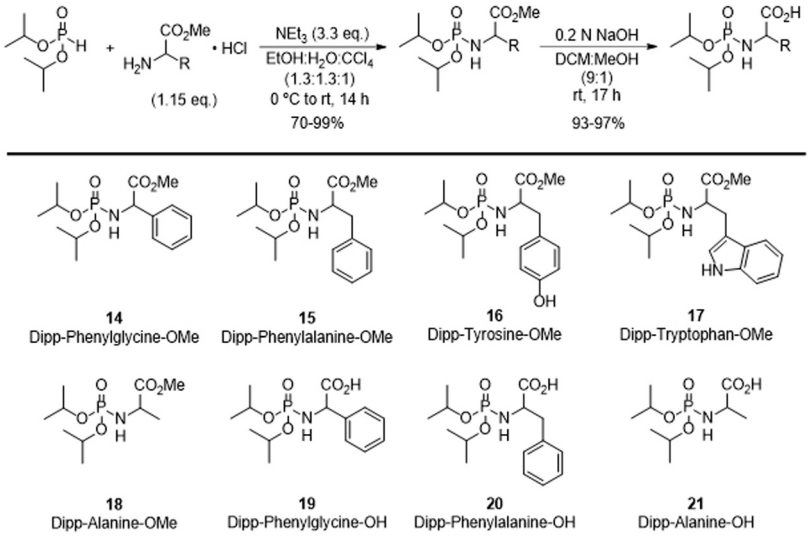
Continuing studying the general nature and structural variations on the chiral amplification we turned our attention to alterations of the amine moiety. First, the phenyl group was replaced by an aliphatic chain, such as in phosphoramidate **6**, which caused diminished differences in solubility of the racemic compound compared to its enantiopure form, and resulted in smaller enantioenrichment from initial 11 % *ee* to final 16 % *ee*. Therefore, we further concentrated on phenylethylamines bearing different substituents. Testing of the phosphoramidates **7**–**13** depicted in Figure 4, revealed that substituents including methyl, methoxy, and chloro, in *para*- or *meta*-positions, were well tolerated for chiral amplification using our new methodology. For example, similar to **1**, the *para*-methylated phosphoramidate **7** showed a very large difference in solubility of the racemate relatively to the enantiomerically pure compound and therefore chiral amplification in water resulted in enantioenrichment in the solution from initial 8 % *ee* to final 88 % *ee* (Figure 6).

Chiral amplification of phosphoramidates prepared from *p*-methoxy (**8**), *m*-methoxy- (**9**) and *m*-chloro-substituted α-phenylethylamine (**10**), starting from 6–10 % initial *ee*, reached a solution-phase enantioenrichment of 38 % *ee*, 71 % *ee* and 76 % *ee*, respectively (Figure 6).

It became evident during these studies that subtle structural modifications can have a major effect on crystal packing and preferential racemate or conglomerate formation. In contrast to the initial compound **1** and particularly to the *m*-chlorinated phosphoramidate **10**, the *p*-chloro- and *p*-bromo-substituted phosphoramidates **11** and **12** presented entirely different solid–liquid partition behavior. Surprisingly, no difference in the solubility of the enantiopure and the racemic form of phosphoramidates **11** and **12** was observed. X-ray analysis of **12** supports this observation showing that racemic **12** crystallizes as a conglomerate (a mixture of enantiomerically pure crystals, with the overall solid being racemic[14f,28]) where in addition to hydrogen bonding between N–H and P=O moiety a non-covalent halogen bond between bromine and the P=O moiety was observed (see Supporting Information for further details). We anticipate that this additional bonding might be responsible for the distinct crystallization behavior of both *para*-halogenated phosphoramidates **11** and **12** making them not suitable substrates for chiral amplification using our preferred dissolution method although we did not observe the reverse that is, solid phase[5,7a–d,g] amplification (vide infra for amino acid **21**).

The experimental data presented here shows a novel chiral amplification mechanism in aqueous media for various scalemic liquid amines using phosphorylation to modulate their solubility and non-covalent interactions. Basically, the oils are converted into phosphoramidates which show distinct differences in aqueous solubility being racemates or enantiomers resulting in enormous chiral enrichment by simple dissolution-precipitation. Based on these results we finally performed chiral amplification experiments using phosphorylated amino acids[25d,e] and their derivatives which were prepared according to Scheme 2.




***Scheme 2.*** Synthesis and structures of phosphorylated amino acids and their methyl ester derivatives **14**–**21** (Dipp = diisopropyloxyphosphoryl).

Gratifyingly, a chiral amplification of phosphorylated non-proteinogenic natural amino acid phenyl glycine **19** from 10% to 86% *ee* was achieved by a single dissolution in water (Figure 7). The methyl ester derivative **14**, however, although still showing enrichment had a significantly lower amplification effect, providing a final 32% *ee* starting from 4% *ee*. Interestingly, no amplification was observed for the methyl ester of phosphorylated phenyl alanine (**15**) whereas the phosphorylated phenyl alanine **20** amplified from 7% *ee* to 67% *ee*. Furthermore, the methyl esters of phosphorylated tyrosine **16** and tryptophan **17** showed substantial enantioenrichment from initial 16% and 11% *ee* to final 94% and 73% *ee*, respectively (Figure 7). Finally, phosphorylated aliphatic amino acid derivatives **18** and **21** were investigated. The racemic Dipp-Alanine-OMe (**18**) was an oil and therefore was not suitable for our amplification method. Interestingly, Dipp-Alanine-OH (**21**) was a solid material showing an opposite effect than previously tested substrates where an enantioenrichment of the solid residue was observed. Specifically, the chiral amplification of the scalemic phosphoramidate **21** with initial 10% *ee* resulted in final 13% *ee* of the filtrate and 87% *ee* of the solid residue.

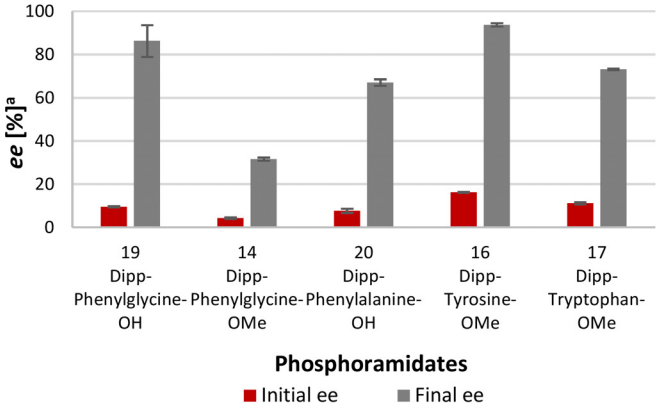



***Figure 7.*** Amplification of phosphorylated amino acids and methyl ester derivatives **14**, **16**, **17**, **19** and **20** in water at 26 °C. [a] Determined by chiral HPLC analysis.

Although chiral amplification based on the selective partitioning between solid and aqueous solution of unmodified amino acids was demonstrated by Blackmond and Breslow,[14a–d] our preliminary findings with amine- and amino acid-based phosphoramidates reveal a complementary chiral amplification pathway.

In conclusion, we demonstrated a facile and robust model for amplification of chirality of amines using phosphorylation and taking advantage of solubility differences between the racemic and enantiopure phosphoramidates in water. A ternary phase diagram for phosphoramidate **1** provided theoretical *ee* values possible using this strategy. The ability to tune the stereospecific intermolecular interactions applying this simple derivatization method of oily substances, allowed highly enantioenriched solutions in water and racemic solids to be obtained from an initial small chiral excess within a single amplification cycle. Finally, single step chiral amplification of phosphorylated amino acids and their methyl esters up to 94% *ee* was accomplished, emphasizing again the potential relevance of equilibrium solid–liquid phase behaviour of scalemic compounds as asymmetric amplification strategy.[14a–e,18] In a more general perspective it has been noted that starting with an initial tiny chiral bias and considering repeated cycles of rain (solubilizing), flow and heat (evaporation), preferred dissolution and crystallization methods might provide relevant options[1,2,14] in the search for the emergence of homochirality.

## Acknowledgements

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** amino acid · chiral amplification · origin of life · phosphoramidate · phosphorylation


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