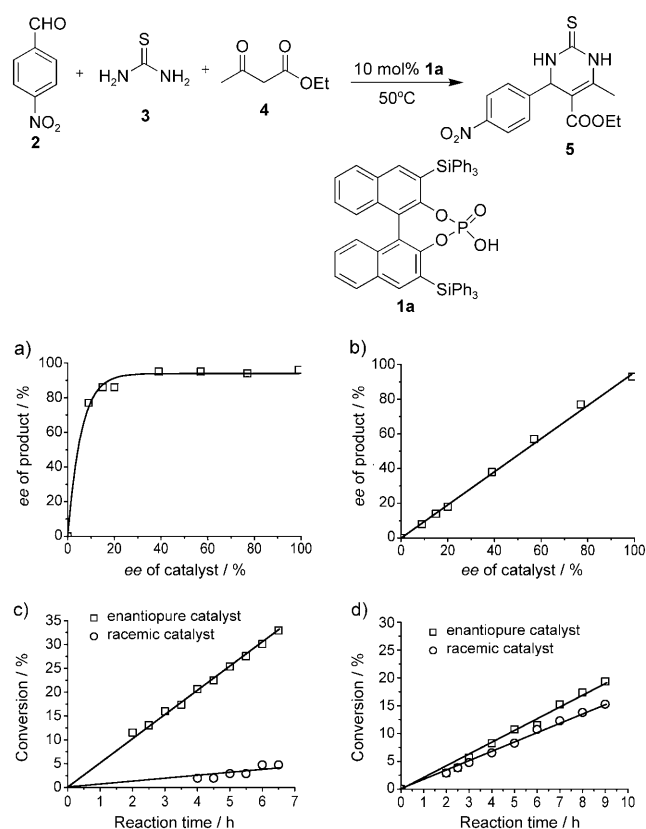# Asymmetric Amplification in Phosphoric Acid Catalyzed Reactions**

Nan Li, Xiao-Hua Chen, Shi-Ming Zhou, Shi-Wei Luo, Jin Song, Lei Ren, and Liu-Zhu Gong

Methodologies involving chiral resolution, chiral auxiliary induced transformations, and asymmetric catalytic reactions, including those catalyzed by metal, biological, and organic catalysts, have been developed and, typically, these processes have exploited optically pure catalysts to ensure high enantioselectivity. In these reactions, the enantiomeric excess (*ee*) of the reaction product was linearly proportional to the *ee* value of the chiral catalyst or auxiliary. However, chemists have observed numerous exceptions to this linear relationship, some characterized by a positive nonlinear correlation between the *ee* value of the reaction product and that of the chiral catalyst or auxiliary.[1–7] This phenomenon, termed asymmetric amplification, has not only provided cost effective asymmetric synthetic protocols in comparison with those using enantiomerically pure catalysts, but has also been considered a basis for the origin of homochirality in nature.[8–9] In the last decades, metal-based asymmetric amplified catalysis has undergone great advances.[6] Recent applications of asymmetric amplification in organocatalysis, particularly the use of biologically relevant molecules such as amino acids as catalysts, have advanced the long standing inquiry into the evolution of homochirality in the prebiotic system.[10–13] However, the importance of asymmetric amplification in reactions catalyzed by phosphoric acids and its derivatives,[14–18] an important class of pentavalent phosphorus compounds relevant to nucleic acids, has been less recognized.[19]

During our studies on the phosphoric acid catalyzed Biginelli reaction,[20] we found a strong positive nonlinear effect (NLE) for the reaction of *para*-nitrobenzaldehyde (**2**), thiourea (**3**), and ethyl acetoacetate (**4**) in the presence of 10 mol% of the non-enantiopure 3,3′-ditriphenylsilyl binol-derived phosphoric acid **1a** in toluene (Figure 1a).[21] In contrast, an absolutely linear effect was observed for the same reaction under almost identical reaction conditions except

Figure 1. Asymmetric amplification in the Biginelli reaction catalyzed by phosphoric acid **1a**. The reaction was catalyzed by **1a** at different optical purities: a positive NLE was observed in toluene (a) and a linear effect was observed in chloroform (b). Optically pure **1a** gave a much faster reaction than the racemate in [D$_8$]toluene (c), however similar reaction rate was observed for optically pure and racemic **1a** in CDCl$_3$ (d).

that chloroform was used as the reaction medium instead of toluene (Figure 1b). Kinetic studies revealed that the optically pure phosphoric acid afforded a much faster reaction in toluene (Figure 1c), but in chloroform, the optically pure and the racemic catalysts exhibited comparable catalytic activities (Figure 1d). Similarly, electron-rich benzaldehydes also participated in the reaction to show similar positive NLE as exemplified by 2-methylbenzaldehyde (see the Supporting Information).

The strong dependence of the NLE upon the solvent prompted us to investigate this observation in detail. In proline-catalyzed reactions, the nature of the solvent played a distinct role in the NLE, and this role was attributed to the solubility differences between racemic and optically pure samples.[12–13] In the phosphoric acid catalyzed Biginelli reaction, we speculated that the significant dependence of the asymmetric amplification upon the solvent is also

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001723.

attributed to the enhancement of *ee* value of the solution arising from the differences in solubility of the racemic and optically pure phosphoric acids. When we compared the solubility of racemic and optically pure phosphoric acid **1a** in toluene and in chloroform, we found that both the racemic and optically pure samples of phosphoric acid **1a** were soluble and formed a clear solution. However, with stirring of the toluene solution a large amount of solid precipitated from the solution containing the racemic phosphoric acid (Figure 2). Interestingly, the optically pure sample maintained a clear solution even with prolonged stirring (6 h). In contrast, both racemic and optically pure samples were very soluble in chloroform and remained as clear solutions after being stirred for 36 hours.
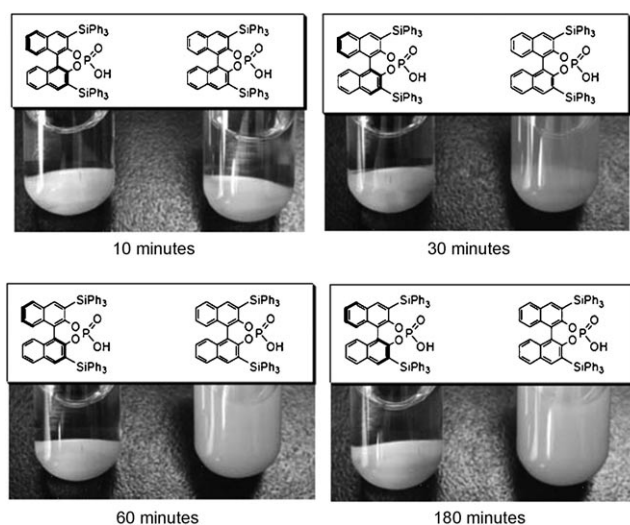
Figure 2. Observed changes to the toluene solutions of the pure enantiomer (left tube) and the racemic mixture (right tube) of the phosphoric acid with stirring at room temperature. The white object on the bottom is the stir bar.

We next measured the *ee* values of the toluene solutions of phosphoric acid **1a** having varying levels of enantiomeric excess (9–77%) at different concentrations (Table 1). The solid phosphoric acid **1a** that precipitated from the solution has an *ee* value of less than 5%, and is somewhat independent of the optical purity of the original samples. Notably, the solution *ee* value was greatly enriched. A high solution *ee* value was obtained (89%) even when the enantiopurity of the phosphoric acid **1a** was only 9% *ee* (entry 1). The solution *ee* value was slightly affected by the concentration of optically active phosphoric acid solution because increasing the concentration from 0.01 M to 0.02 M led to an enhanced optical purity, in particular for the samples with low optical purity (entries 1–3). In contrast, the precipitates were also obtained with *ee* values of less than 5%, and were independent of the concentration.

Previous reports have revealed that a mixture of enantiomers occasionally exhibits unusual physical and chemical properties attributable to the formation of diastereomeric species in solutions.[22–23] A racemic chiral compound had a ^{1}H NMR spectrum that significantly differed from that

Table 1: The *ee* values of the solution and precipitated solid measured for toluene solutions of **1a** having varying levels of enantiomeric excess.[a]


Entry	*ee* value of **1a** [%]	Solution *ee* [%][b]	Solid (precipitated) *ee* [%][b]
1	9	89 (93)	<5 (<5)
2	15	93 (97)	<5 (<5)
3	20	90 (98)	<5 (<5)
4	39	99 (99)	<5 (<5)
5	57	>99 (>99)	<5 (<5)
6	77	>99 (>99)	<5 (<5)

[a] The solution and solid *ee* values were obtained at a concentration of 0.01 M. The data within parentheses were obtained at a concentration of 0.02 M. [b] The *ee* value was determined by HPLC analysis.

obtained for the individual enantiomers.[24–26] The solubility of the racemic compound, as opposed to that of its enantiomer, might result in the ability of the racemic phosphoric acid to form an aggregate which is a more energetically preferable diastereomeric species compared to that obtained from the optically pure enantiomer and is more difficult to dissociate in a nonpolar solvent. To investigate this possibility, we performed ^{1}H NMR studies on the solution of phosphoric acid **1a**. Interestingly, the fresh solution of the racemic compound in [D_8]toluene gave a ^{1}H NMR spectrum identical to that of the optically pure enantiomer, whereas the OH proton of the racemic phosphoric acid shifted down field for about $\delta = 0.33$ ppm with elapsing time. In sharp contrast, the optically pure sample maintained an almost identical ^{1}H NMR spectrum (see the Supporting Information). This finding demonstrated that stronger intermolecular hydrogen-bonding interactions were present in the racemic system and enforced the association of racemic phosphoric acid molecules, thereby leading to the formation of heterochiral polymeric aggregates that were less soluble than aggregates of the homochiral polymers.

We then undertook crystallography studies on the structures of racemic and enantiomerically pure phosphoric acids (Figure 3). Powder X-ray diffraction (XRD) analysis showed that the solid formed from the powdered racemate **1a** was the same as those of the corresponding single crystals (see the Supporting Information). Single crystals of the racemic and the optically pure forms of **1a** were grown from toluene under an atmosphere of *n*-hexane vapors. Interestingly, the crystals had similar structural motifs, but different hydrogen-bonding patterns. In the heterochiral crystal, individual enantiomers of phosphoric acid **1a** assembled as a supramolecular chain stabilized by three hydrogen bonds formed between either the phosphoryl oxygen atom (P=O) or the hydroxy group with crystalline water (O1-OW3, O2-OW2, and OW2-OW3). The supramolecular chain is aligned parallel to the other chain consisting of the opposite enantiomer and features an addi-

a)

b)
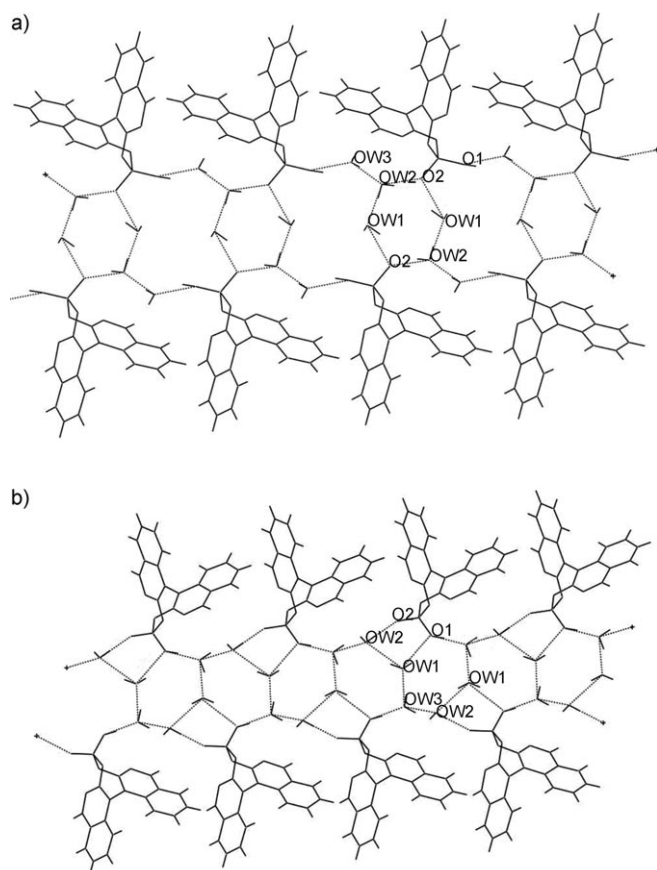
Figure 3. The crystal structures of racemic (a) and optically pure (b) 3,3′-triphenylsilyl phosphoric acid **1a**. To simplify the structure, the 3,3′-triphenylsilyl groups are omitted. The full structures are shown in the Supporting Information.

tional six-membered hydrogen-bonded network (O2-OW1 = 2.684 Å, OW1-OW2 = 2.519 Å), leading to a stable two-dimensional (2D) supramolecular sheet (Figure 3a). In the homochiral crystal (Figure 3b), the phosphoric acid also forms a supramolecular chain by forming two hydrogen bonds with crystalline water molecules. However, the two supramolecular chains are aligned antiparallel to each other and are connected by hydrogen bonds between OW1 and O1 as well as those between OW1 and OW2; these are much weaker than those in the heterochiral crystal, as indicated by longer hydrogen-bond lengths (O1-OW1 = 3.052 Å, OW1-OW2 = 2.973 Å), and lead to the formation of a somewhat distorted 2D supramolecular sheet. This finding is consistent with the conclusion drawn from the ¹H NMR studies. The difference between the heterochiral and the homochiral crystals suggests that the association of the racemate is more energetically favorable than that of the enantiomerically pure phosphoric acid, and therefore contributes to the easier formation of the less soluble heterochiral phosphoric acid aggregates, thereby facilitating the precipitation of the racemates from the enantiomerically enriched phosphoric acid solution (Figures 2 and 3). DFT calculations of the single-point energy for the dimer of both the racemic and enantiopure crystal structure of **1a** indicated that the dimer of the racemic catalyst is more

stable than the individual enantiomer by about 25.00 kcal mol⁻¹ (see the Supporting Information).

The preceding experimental evidence underpins the idea that, unlike the optically pure enantiomer, the racemic phosphoric acid forms energetically favored supramolecular aggregates that are less soluble in nonpolar solvents (e.g., toluene), and leads to the enhancement of solution *ee* value. The enhanced solution *ee* value resulted in the dramatic positive NLE observed in the phosphoric acid catalyzed Biginelli reaction. To investigate if this phenomenon is general for binol-derived phosphoric acids, we measured the solution *ee* value of 3,3′-diphenyl phosphoric acid (**1b**) and 3,3′-di(2-naphthyl) phosphoric acid (**1c**), which are typical privileged catalysts for several enantioselective transformations.[27–29] As shown in Figure 4, the enhancement in the solution *ee* value was observed in both cases, therefore asymmetric amplification should occur in the corresponding reactions catalyzed by these phosphoric acids when the precipitates, having low optical purity, are removed from the solution.

a)

b)
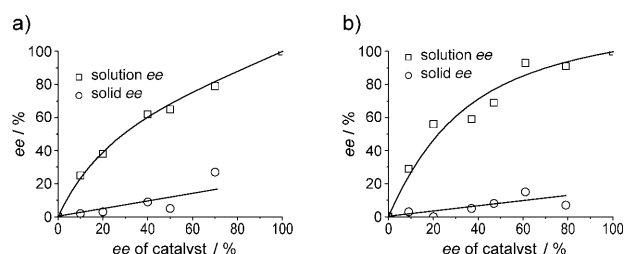
Figure 4. The *ee* values for a solution of and for the precipitated solid of 3,3′-diphenyl phosphoric acid **1b** (a) and 3,3′-di(2-naphthyl) phosphoric acid **1c** (b).

Finally, we investigated NLE in some reactions with or without removal of phosphoric acid precipitates having low *ee* values. In principal, if substrates and products do not contain hydrogen-bond-breaking elements and the reaction was performed in a solvent that shows different solubility for optically pure phosphoric acid and its racemic aggregates, a positive NLE should be observed even without removal of the precipitates. Indeed, we observed a positive NLE in the reaction of an imine with either an enamide[30] or ethyl diazoacetate[31] (Table 2, entries 1 and 2). However, a linear effect was obtained in the Friedel–Crafts reaction of indole (**11**) with nitrostyrene (**12**; Table 2, entry 3)[32] and in an asymmetric transfer hydrogenation (Table 2, entry 5).[33] This linear effect was probably a result of the presence of basic functional groups, such as amine and pyridine, which could break the aggregates of the insoluble racemic solid catalyst, thereby enabling them to dissolve in toluene and catalyze the reaction just as the enantiomerically pure phosphoric acids. In contrast, when the phosphoric acid precipitates were removed, a strong positive NLE was observed in the Friedel–Crafts and transfer hydrogenation reactions, respectively (Table 2, entries 4 and 6).

In summary, we have found an unprecedented asymmetric amplification in reactions catalyzed by phosphoric acids. The

Table 2: NLE in other reactions.[a]

Entry	Reaction	NLE[b]
1	6 + 7 →(1) 10 mol% 1b, RT, 0.5 h, toluene →(2) 48% HBr, MeOH, 3 h → 8 — 1b (ee%): 20 47 61 100; 8 (ee%): 23 50 62 78	+
2	6 + 9 →(10 mol% 1a, toluene, RT)→ 10 — 1a (ee%): 9 20 50 100; 10 (ee%): 12 14 17 26	+
3	11 + 12 →(10 mol% 1a, toluene, 3Å M.S., -35 °C)→ 13	−[c]
4	11 + 12 →(10 mol% 1a, toluene, 3Å M.S., -35 °C)→ 13 — 1a (ee%): 20 40 60 100; 13 (ee%): 12 29 44 46	+[d]
5	14 + 15 →(10 mol% 1a, HEH 16, toluene, 5Å M.S., 50 °C)→ 17	−[c]
6	14 + 15 →(10 mol% 1a, HEH 16, toluene, 5Å M.S., 50 °C)→ 17 — 1a (ee%): 20 40 60 100; 17 (ee%): 23 53 75 85	+[d]

[a] All products have been reported previously.[30–33] [b] The "+" refers to positive NLE and "−" refers to linear effect. [c] The precipitates of phosphoric acid were not removed. [d] The precipitates of phosphoric acid were removed. Bz = benzoyl, M.S. = molecular sieves, PMP = *para*-methoxy-phenyl.

positive nonlinear effect arose from the enhancement of the solution *ee* values by formation of less soluble supramolecular structures of the racemic phosphoric acids through hydrogen bonds formed with crystalline water molecules. The NLE is a general phenomenon that was observed in different phosphoric acid catalyzed reactions with either removal of or in the presence of the racemic solid catalyst. Because pentavalent phosphorus compounds constitute key elements in living systems, particularly in nucleic acids, this finding may be related to the evolution of chirality in biomolecules in the prebiotic environment.

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