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Phosphoric Acid Catalyzed Enantioselective Transfer Hydrogenation of Imines: A Density Functional Theory Study of Reaction Mechanism and the Origins of Enantioselectivity

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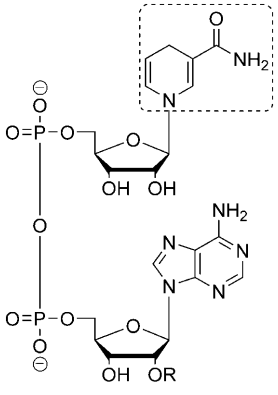
Abstract: The phosphoric acid catalyzed reaction of 1,4-dihydropyridines with *N*-arylimines has been investigated by using density functional theory. We first considered the reaction of acetophenone PMP-imine (PMP = *p*-methoxyphenyl) with the dimethyl Hantzsch ester catalyzed by diphenyl phosphate. Our study showed that, in agreement with what has previously been postulated for other reactions, diphenyl phosphate acts as a Lewis base/Brønsted acid bifunctional catalyst in this transformation, simultaneously activating both reaction partners. The calculations also showed that the hydride transfer transition states for the *E* and *Z* isomers of the iminium ion have comparable energies. This observation turned out to be crucial to the understanding of the enantioselectivity of the process. Our results indicate that when using a chiral 3,3′-disubstituted biaryl phosphoric acid, hydride transfer to the *Re* face of the (*Z*)-iminium is energetically more favorable and is responsible for the enantioselectivity, whereas the corresponding transition states for nucleophilic attack on the two faces of the (*E*)-iminium are virtually degenerate. Moreover, model calculations predict the reversal in enantioselectivity observed in the hydrogenation of 2-arylquinolines, which during the catalytic cycle are converted into (*E*)-iminium ions that lack the flexibility of those derived from acyclic *N*-arylimines. In this respect, the conformational rigidity of the dihydroquinolinium cation imposes an unfavorable binding geometry on the transition state for hydride transfer on the *Re* face and is therefore responsible for the high enantioselectivity.

Keywords: density functional calculations · hydrogenation · imines · organocatalysis · pyridines

Introduction

Nature makes extensive use of the reducing power of 1,4-dihydropyridines. Nicotinamide adenine dinucleotide (NADH), nicotinamide adenine dinucleotide phosphate (NADPH), and their oxidized counterparts NAD^+ and $NADP^+$ are the key cofactors for in vivo oxidoreductions.[1] Since their structural determination, the development of synthetically accessible NAD(P)H mimics has been at the forefront of research in bioorganic chemistry. Throughout the second half of the 20th century many synthetic 1,4-dihydropyridines were employed in the reduction of different functional groups due to their ability to undergo the reversible loss of either one electron and one hydrogen atom (electron transfer mechanism) or alternatively one hydride (hydride transfer mechanism) to yield a stable *N*-alkylpyridinium cation.[2]

The first synthesis of 1,4-dihydropyridines was reported by Hantzsch in 1881[3] and involved the Lewis acid catalyzed condensation of formaldehyde, a β-keto ester (2 equiv), and ammonium acetate, which yielded compounds **1**, known as Hantzsch esters. Even after such a long time, this remains one of the easiest synthetic entries to dihydropyridines. Both Hantzsch esters **1** and *N*-substituted nicotinamides **2** have been extensively used as synthetic models to study the mechanism of NAD(P)H-de-



NADH: R = H
NADPH: R = PO_3^{2-}

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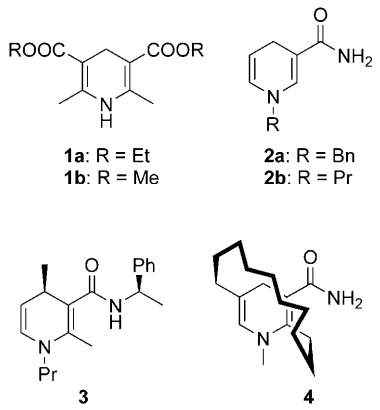
pendent enzymes.[4] Whether NAD(P)H reacts according to a radical or a hydride transfer mechanism has been at the center of scientific debate for many years. Today, there is still no universal consensus about this issue.

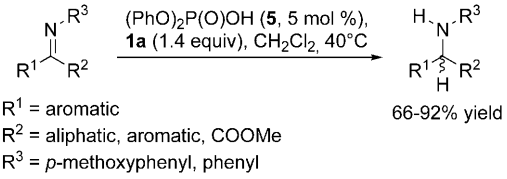


Attempts to reproduce the enantioselectivity observed in enzymatic reductions employing NAD(P)H as cofactors led chemists to design and synthesize enantiomerically pure chiral dihydropyridines to be used as stoichiometric asymmetric reducing agents. Successful examples of this class of compound range from nicotinamide **3**,[5] featuring one stereogenic center on the amide part of the molecule and another one on C4, to more sophisticated miniaturized enzyme mimics such as dihydropyridine **4**,[6] which has a cyclic aliphatic chain with the dual role of mimicking the hydrophobic enzyme binding pocket and of inducing asymmetry in the hydride transfer reaction. Both compounds gave excellent enantiomeric excesses in the reduction of ketones such as methyl benzoylformate (97 and 99%, respectively).

In 1989, Singh and Batra reported up to 62% *ee* in the reduction of *N*-arylimines with ester **1b** in the presence of the hydrochlorides of α-amino acids, with (*S*)-cysteine giving the best results.[7] To the best of our knowledge, this was the first example of an enantioselective catalytic transfer hydrogenation using Hantzsch esters.

The last decade witnessed the explosion of asymmetric organocatalysis, which in a very short time has emerged from a laboratory curiosity to a well-established discipline of organic chemistry. This ignited a new wave of research into the use of 1,4-dihydropyridines as reducing agents, this time more with the aim of developing synthetically useful and environmentally friendly procedures rather than gaining mechanistic insights into biochemical processes.[8]

List[9] and MacMillan[10] and their co-workers independently reported protocols for the enantioselective conjugate reduction of α,β-unsaturated aldehydes using chiral imidazolinone catalysts. Rueping et al. screened different Brønsted acids as catalysts for the reduction of PMP-ketimines (PMP = *p*-methoxyphenyl) with Hantzsch esters: the best results were obtained with 5 mol% diphenyl phosphate in dichloromethane (Scheme 1).[11] This result paved the way for the development of the phosphoric acid catalyzed enantioselective transfer hydrogenation of imines, which is the object of this study.



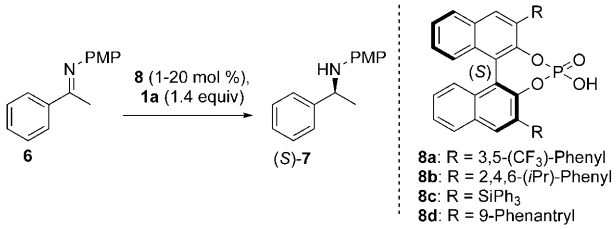
Scheme 1. Diphenyl phosphate catalyzed transfer hydrogenation of *N*-arylimines with Hantzsch ester **1a** as the hydride source.

Although known for a long time, chiral phosphoric acids have only recently been recognized as powerful asymmetric catalysts. In 2004 Akiyama and Terada and their co-workers independently reported asymmetric organocatalytic Mannich reactions (involving silyl enol ethers[12] and acetyl acetone,[13] respectively) catalyzed by 3,3′-disubstituted 1,1′-binaphthol (BINOL)-derived phosphoric acids. Since then a plethora of phosphoric acid catalyzed enantioselective reactions have been reported, mainly involving nucleophilic addition to imines.[14]

As a natural follow-up to their initial results with diphenyl phosphate, Rueping et al. next evaluated several enantiomerically pure BINOL-derived phosphoric acids as enantioselective catalysts for the same transformation: catalyst **8a** promoted the transfer hydrogenation in up to 84% enantiomeric excess (Table 1).[15] In the same year, List and coworkers independently reported that the use of catalyst **8b** in toluene allowed a 20-fold reduction in catalyst loading whilst retaining acceptable reaction times and, most importantly, improving the enantiomeric excesses (up to 93%).[16]

The next step to making this procedure an even more attractive synthetic tool for the preparation of enantiomerically enriched amines was to avoid preliminary preparation of the Schiff bases, thereby expanding the scope of this reac-

Table 1. Comparison of the organocatalytic transfer hydrogenation protocols.



Ref.	Conditions	Preformed imine	In situ imine
[15]	*ent*-**8a** (20 mol%), **1a** (1.4 equiv), benzene, 60°C	76% yield, −74% *ee*	not reported
[16]	**8b** (1 mol%), **1a** (1.4 equiv), toluene, 35°C	96% yield, 88% *ee*	92% yield, 88% *ee*
[19]	*ent*-**8c** (10 mol%), **1a** (1.2 equiv), benzene, 40°C	not reported	87% yield, −94% *ee*

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tion to aliphatic ketimines, the instability of which prevents straightforward isolation, as in the case of aromatic ones. The Brønsted acid catalyzed reductive amination of aldehydes employing a Hantzsch ester as the hydride donor was first reported by Singh and Sharma in 1979.[17] More recently, this reaction was reinvestigated by Menche and co-workers, who replaced glacial acetic acid (solvent and catalyst in the original protocol) with substoichiometric amounts of thiourea and expanded the scope of this transformation to ketones.[18] In their publication on the enantioselective transfer hydrogenation of PMP-imines,[16] List and co-workers showed for one example that comparable results could be obtained by generating the imine in situ rather than by using a preformed imine, thus by just mixing the ketone and *p*-anisidine for 9 h in the presence of molecular sieves at room temperature before adding the catalyst and Hantzsch ester and warming the reaction mixture to 35 °C. Shortly after, MacMillan and co-workers reported a thorough investigation of a similar reaction, replacing the 3,3′-aromatic substituents with even bulkier triphenylsilyl groups, which resulted in improved enantioselectivities.[19] Remarkably, the reaction provided high levels of asymmetric induction even with challenging substrates such as imines derived from 2-butanone (83 % *ee*). A summary of these three methodologies for the transfer hydrogenation of the PMP-imine derived from acetophenone is given in Table 1.

Following these exciting results, the use of phosphoric acid catalysis in combination with Hantzsch esters for the reduction of C=N bonds was explored in depth, including protocols for the enantioselective transfer hydrogenation of α-imino esters,[20] quinolines,[21] benzoxazines,[22] benzothiazines,[22] and benzoxazinones.[22] Despite the impressive efforts devoted to the experiment-driven development of novel synthetic methodologies using this successful reagent/catalyst combination, very little attention has been devoted to the elucidation of the exact mechanism of this intriguing class of reactions. A detailed understanding of both reaction mechanism and reasons for enantioselectivity would be very helpful for further advances in asymmetric organocatalytic hydrogenation.

Herein, we present a density functional theory study of the mechanism of the phosphoric acid catalyzed hydride transfer of Hantzsch esters to *N*-aryl imines. The key factors contributing to the enantioselectivity of this process are discussed for both PMP-ketimines and 2-arylquinolines.

Computational Methods

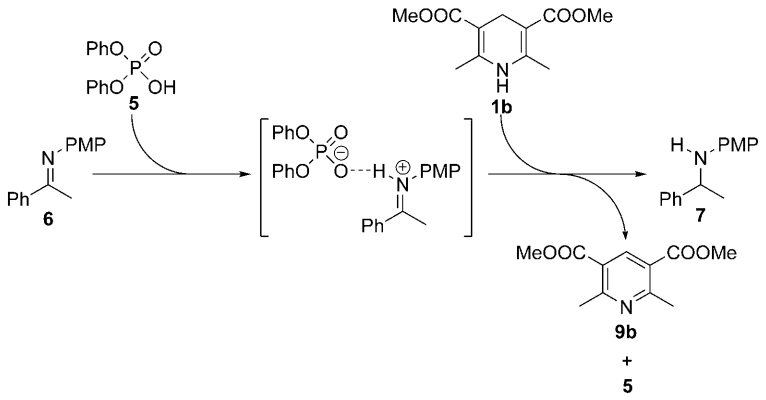
All calculations were performed by using the B3LYP hybrid density functional[23] as implemented in the Gaussian 03 package.[24] Geometry optimizations were carried out at the 6-31G(d,p) level of theory. Final energies were calculated by using a larger basis set, 6-311+G(2d,2p). The effect of solvation was taken into account by performing single-point calculations on the optimized structures using the CPCM polarizable continuum model[25] with toluene ($\varepsilon = 2.379$) as the solvent and by adding the resulting value to the final energies. For the mechanistic study with diphenyl phosphate as the catalyst, all structures (=91 atoms) were verified as being either minima or transition states by vibrational analysis at the same level of theory as the optimization. In these cases, the final energies were corrected for zero-point vibrational effects. On the other hand, the size of the models employed to study the enantioselectivity (123–127 atoms) rendered frequency calculations prohibitive. When diphenyl phosphate was used as the catalyst, the impact of the zero-point vibrational corrections on the relative energies of the transition states for hydride transfer was less than 1 kcal mol^{-1}. We therefore chose to ignore this correction in the modeling of the enantioselective reaction, which consists of a comparison of diastereomeric transition states for the same transformation. The overall adequacy of the chosen computational protocol has previously been established in numerous studies on organocatalytic reactions.[26]

Results and Discussion

Mechanism of the diphenyl phosphate catalyzed reaction: As shown by Rueping et al., compound **1a** does not react spontaneously with *N*-arylimines in the absence of a Brønsted acid, even at elevated temperatures.[11] We will therefore exclusively focus on the acid-catalyzed process, depicted in Scheme 2.

The first step is the protonation of the imine, which results in the formation of an iminium/phosphate ion pair. The calculations show that this step is substantially thermoneutral and very fast, with an estimated barrier of only around 1.0–1.5 kcal mol^{-1}.[27]

In the vast majority of publications describing acid-catalyzed addition to imines (therefore presumably involving the formation of an iminium ion), it is generally assumed that the (*E*)-iminium is the one undergoing nucleophilic attack. At room temperature, the NMR spectrum of imine **6** shows only one set of peaks corresponding to the *E* isomer.[28] This result is compatible with the calculated energy difference between *E* and *Z* isomers being slightly higher than 2 kcal mol^{-1} (Scheme 3).



Scheme 2. Transfer hydrogenation of imine **6**.

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Nevertheless, the interconversion of the *N*-arylimines is fast in the presence of a Brønsted acid, even at room temperature.[29] The mechanism of imine isomerization may involve acid-catalyzed tautomerization to the enamine, rotation along the C=N bond of the iminium, or the reversible attack of a nucleophilic species (such as the conjugated base of catalyst **5**) on the imine moiety leading to a tetrahedral intermediate.[30] Hence, it is sound to assume that the *E* and *Z* forms of imine **6** (and, more importantly, of the forming iminium) can easily interconvert and therefore participate in the reactions studied. This turns out to be important for explaining the stereochemistry of the reaction (see below).

Although in most synthetic protocols compound **1a** is preferred, we chose to model all the transfer hydrogenation reactions by using the Hantzsch dimethyl ester **1b** as the hydride source. In related transformations, the nature of the esters was shown to have virtually no effect on the asymmetric induction.[10,20b]

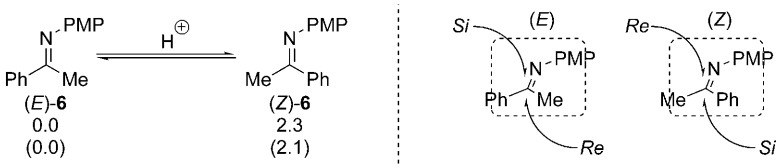
In general, phosphoric acids are regarded as purely Brønsted acid organocatalysts: protonation of a basic site on the substrate leads to an ion-pair complex with increased electrophilicity, which lowers the barrier to nucleophilic attack (in this case hydride transfer). Nevertheless, diaryl phosphates are in every respect bifunctional catalysts. It is somewhat surprising how this aspect of their reactivity has often been overlooked since it was unambiguously established by Akiyama et al. in their seminal publication on the addition of silyl enol ethers to 2-hydroxyphenylimines.[12a] Mechanistic hypotheses involving the interaction of either one or both phosphate oxygen atoms with two reaction partners in the bond-forming transition state were also formulated for other reactions.[31] In the case of the transfer hydrogenation reaction, the amine proton of Hantzsch ester **1b** could engage in a hydrogen bond with the phosphate group. In the transition state for hydride transfer this interaction might become important to stabilize the developing positive charge on the Hantzsch ester nitrogen atom, which would lead to a lowering of the energy barrier. Furthermore, the same proton might subsequently be transferred to the phosphate, thereby regenerating the catalyst and closing the catalytic cycle.

We envisioned three different mechanistic scenarios with respect to the nature of the interactions between the two reaction partners (iminium ion and Hantzsch ester) and the phosphate catalyst in the transition state for the hydride transfer. These are schematically depicted in Scheme 4.

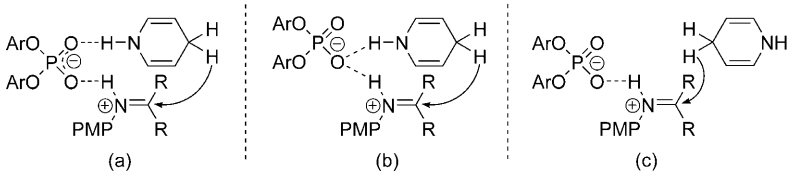
Upon protonation of the imine, both of the oxygen atoms of the resulting phosphate anion become hydrogen-bond acceptors. In what we refer to as a di-coordinated Lewis base/Brønsted acid pathway (di-LBBA, Scheme 4a) one phosphate oxygen atom engages in a hydrogen bond with the iminium whereas the other coordinates to the N–H of the Hantzsch ester. In a mono-coordinated Lewis base/Brønsted acid pathway (mono-LBBA, Scheme 4b) just one phosphate oxygen atom simultaneously forms two hydrogen bonds with the reactants. Finally, in the Brønsted acid pathway (BA, Scheme 4c) there are no hydrogen bonds between the phosphate anion and the Hantzsch ester.

The structures of the calculated transition states for hydride transfer for both LBBA pathways are depicted in Figure 1 (for full-color figures see the Supporting Information). The calculated energies show that the di-LBBA pathway is clearly favored over mono-LBBA by approximately 6 kcal mol^{-1}. Although there are no kinetic data available for this reaction, we consider the calculated overall reaction barrier (18.7 kcal mol^{-1} for the di-LBBA pathway, (*E*)-iminium) compatible with the reaction time and conditions. These results are in very good agreement with the computational study of the phosphoric acid catalyzed Mannich reaction previously reported by Yamanaka, Akiyama, and coworkers who also found a difference of about 6 kcal mol^{-1} between the di- and mono-LBBA pathways (although in their case both hydrogen bonds were established with different sites of the electrophile).[12b]

The small energy difference between the two transition states for the di-LBBA pathway ($\mathbf{TS}_{E1}$ and $\mathbf{TS}_{Z2}$; 0.7 kcal mol^{-1}) suggests that, although hydride transfer to the (*E*)-iminium appears slightly favored, both isomers are suitable substrates for this reaction. This trend is reversed in the two transition states for the mono-LBBA pathway ($\mathbf{TS}_{E3}$ and $\mathbf{TS}_{Z4}$). In the transition states for the mono-LBBA pathway the phosphate oxygen atom that is not directly engaged in hydrogen bonds with the substrates has weak interactions with either one ($\mathbf{TS}_{Z4}$) or two ($\mathbf{TS}_{E3}$) *ortho*-hydrogen atoms



Scheme 3. Calculated energies for the two imine isomers of **6** and stereochemical conventions for nucleophilic addition. Energies are in kcal mol^{-1}; gas-phase energies are given in parentheses.



Scheme 4. Different mechanisms for the hydride transfer reaction. a) Di-coordinated Lewis base/Brønsted acid (di-LBBA) pathway; b) mono-coordinated Lewis base/Brønsted acid (mono-LBBA) pathway; c) Brønsted acid (BA) pathway. For clarity, the Hantzsch ester is depicted as the 1,4-dihydropyridine.

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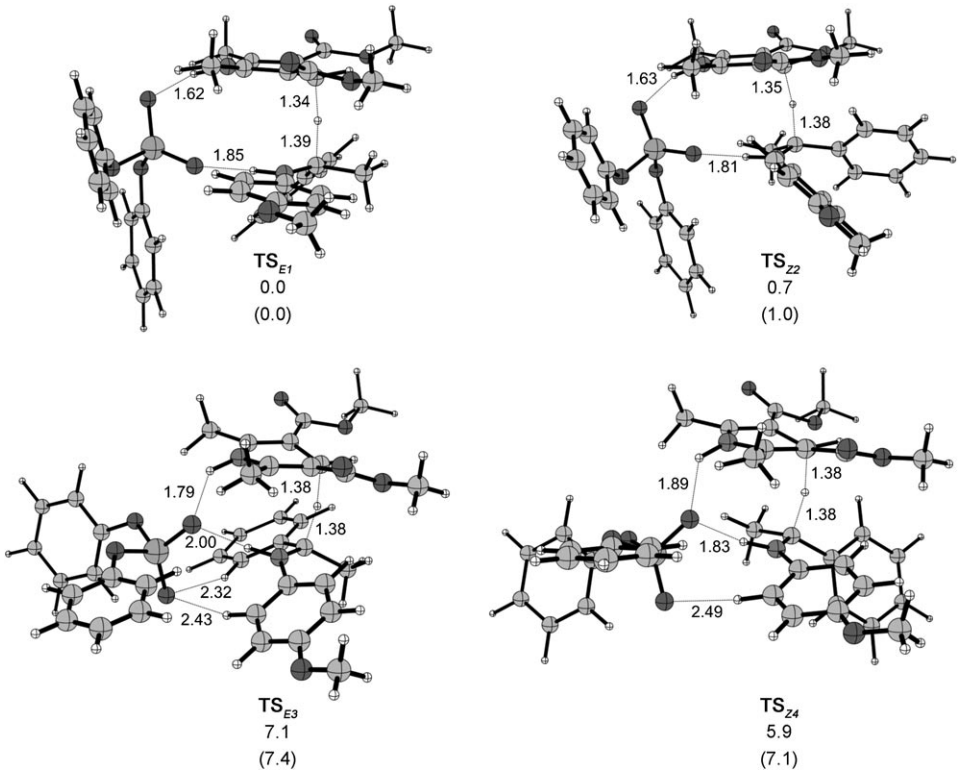


Figure 1. Transition states for the hydride transfer reaction (bifunctional Lewis base/Brønsted acid pathways). All energies are expressed in kcal mol^{-1} relative to **TS$_{E1}$**; gas-phase energies are given in parentheses.

of the phenyl rings of **6**. All attempts to locate alternative mono-LBBA transition states with the above-mentioned oxygen atom on the same side of the Hantzsch ester converged to the di-LBBA transition states, for both the (*E*)- and (*Z*)-iminium.

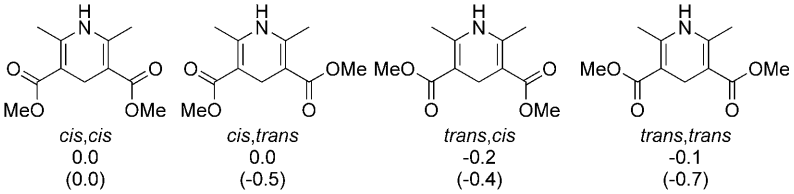
For both pathways the moving hydride is substantially equidistant from C4 of the dihydropyridine and the imine carbon atom. We also note that the hydrogen bond between the phosphate and the dihydropyridine is weaker in the transition states for the mono-LBBA pathway.

Garden et al. proposed that in the reduction of electron-poor olefins the conformation of the ester groups of dihydropyridine **1a** is particularly important for hydride transfer,[32] in agreement with what was previously found for the conformation of the amide group in nicotinamide-mediated reductions.[33]

To assess the magnitude of this effect in our case, starting from **TS$_{E1}$**, we located the transition states corresponding to the other relative *cis*/*trans* orientation of the ester groups (Scheme 5). The energies of these four transition states lie within 0.2 kcal mol^{-1}, which suggests that, for this reaction, ester orientation does not play any significant role. We therefore chose to use a *cis*/*cis* relative orientation for the ester groups in Hantzsch ester **1b** throughout the rest of this study.

As previously mentioned, most of the articles that deal with the reaction under study do not propose a specific interaction between the Hantzsch ester and the phosphoric acid catalyst (Brønsted acid mechanism, Scheme 4c). The transition states for hydride transfer that correspond to this scenario are depicted in Figure 2.

The relative positions of the phosphate group and the Hantzsch ester are opposite in the two pairs of transition states: in **TS$_{E5}$** and **TS$_{Z6}$** there is an *anti* relationship between the two groups, whereas in **TS$_{E7}$** and **TS$_{Z8}$** the dihydropyridine is relatively close to the phosphate oxygen atom not engaged in a hydrogen bond with the iminium.



Scheme 5. Effect of the ester conformation on the energies of the hydride transfer transition state (di-LBBA pathway, (*E*)-imine). All energies are in kcal mol^{-1} relative to **TS$_{E1}$** (*cis*,*cis* in this figure); gas-phase energies are given in parentheses.

All transition states for the Brønsted acid (BA) pathway have a considerably higher energy than those for the di-LBBA pathway (> 10 kcal mol^{-1}). Unlike what was observed in the case of bifunctional catalysis, these four transition states lie late on the reaction coordinate, with the moving hydride being closer to the imine carbon atom. Hydrogen bonds between the iminium and the phosphate are shorter for the BA pathway than for the LBBA ones, in particular for the *Z* isomer of the iminium. We ascribe the high barriers for this pathway to the absence of stabilization of the developing charge on the dihydropyridine nitrogen atom. In two out of four cases (Table 2, entries 6 and 8), during optimization of the reaction product, the resulting pyridinium rotated and transferred a proton to the phosphate, as observed for the LBBA pathways. In the case of the (*E*)-iminiums (Table 2, entries 5 and 7) we could locate a local mini-

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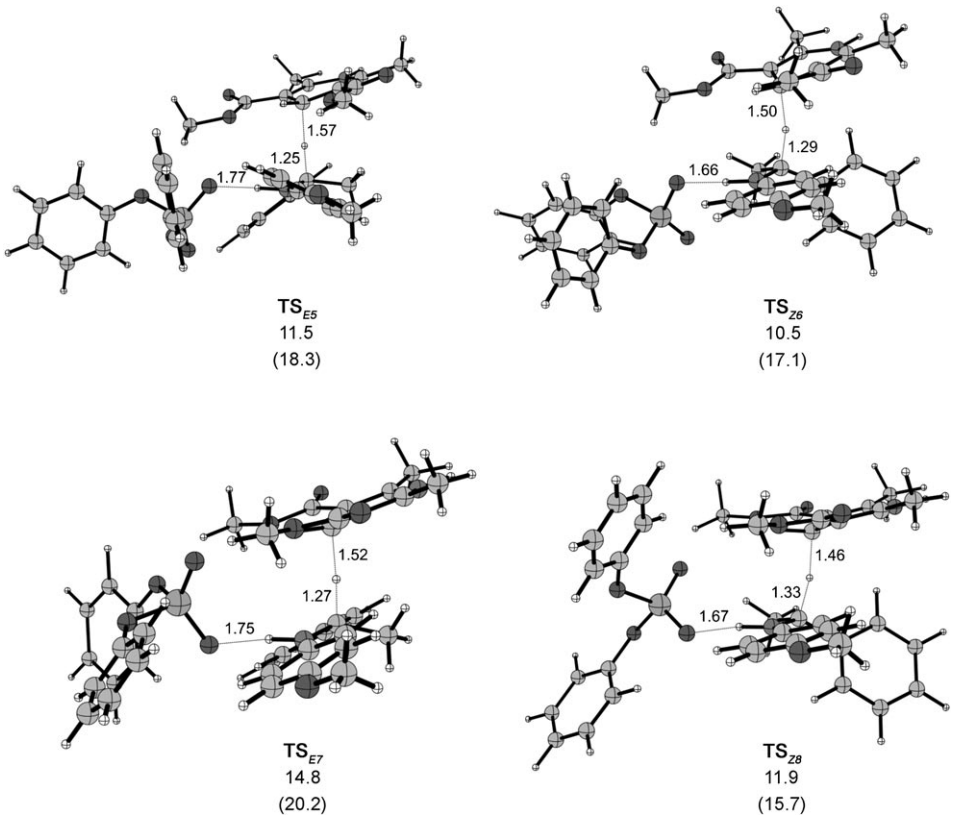
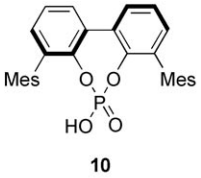


Figure 2. Transition states for the hydride transfer reaction (Brønsted acid pathway). All energies are relative to $\mathbf{TS}_{E1}$; gas-phase energies are given in parentheses.

mum with formal charge separation (hence a phosphate anion and a pyridinium cation). This observation explains the significant discrepancies in energy between the products of this pathway.

Enantioselectivity: The use of any of the catalysts depicted in Table 1 to model the enantioselective hydride transfer would have been prohibitive in terms of computational costs. As previously proposed by Yamanaka, Akiyama, and co-workers, we also considered that replacement of the binaphthyl backbone with a smaller biaryl would not significantly alter the geometry around the reaction center given the strain imposed on the cyclic catalyst by the phosphate linkage between the two phenols.[12b] The presence of large substituents at the 3,3′-positions is a crucial element in BINOL-derived phosphoric acid organocatalysts. We chose the mesityl group due to its bulkiness and close resemblance to the 2,4,6-triisopropylphenyl group employed by List and co-workers.[16] Compound **10** was hence used as the catalyst to model the enantioselective reaction (Figure 3).

Based on our results for the diphenyl phosphate catalyzed reaction, we chose to investigate the hydride transfer to the (*E*)- and (*Z*)-iminium ions derived from compound **6** according to the di-LBBA mechanism.



10

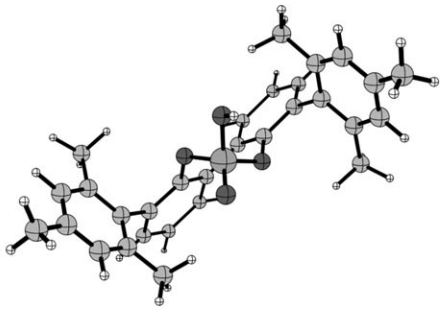


Figure 3. Phosphoric acid **10** used to model the enantioselective hydride transfer reaction (Mes = 2,4,6-trimethylphenyl).

Table 2. Energies for the stationary points in the diphenyl phosphate catalyzed hydride transfer reaction.[a]

Entry	TS name	Pathway	E_{reactant} [kcal mol^{-1}]	E_{TS} [kcal mol^{-1}]	E_{product} [kcal mol^{-1}]
1	$\mathbf{TS}_{E1}$	di-LBBA	0.0 (0.0)	18.7 (19.5)	−8.0 (−8.4)
2	$\mathbf{TS}_{Z2}$	di-LBBA	−0.6 (−0.4)	19.4 (20.5)	−10.8 (−10.8)
3	$\mathbf{TS}_{E3}$	mono-LBBA	−0.7 (1.6)	25.8 (26.9)	−9.9 (−8.8)
4	$\mathbf{TS}_{Z4}$	mono-LBBA	−1.0 (2.2)	24.6 (26.7)	−10.4 (−9.6)
5	$\mathbf{TS}_{E5}$	BA	6.8 (9.1)	33.5 (39.8)	5.4 (6.2)
6	$\mathbf{TS}_{Z6}$	BA	3.7 (8.0)	30.7 (35.2)	−9.3 (−7.7)
7	$\mathbf{TS}_{E7}$	BA	2.8 (7.9)	30.2 (37.9)	5.0 (7.7)
8	$\mathbf{TS}_{Z8}$	BA	4.0 (8.2)	29.2 (38.7)	−12.2 (−10.7)

[a] All energies are given relative to the reactant of the di-coordinated Lewis base/Brønsted acid pathway for the *E* isomer of imine **6**. Gas-phase energies are given in parentheses.

The optimized structures of the two diastereomeric pairs of transition states are shown in Figure 4.

The calculations show that attack on the *Re* face of the (*Z*)-iminium has the lowest energy, lying more than 2 kcal mol^{-1} below all of the other transition states. The two transition states for hydride transfer to the (*E*)-iminium have very similar energies, which suggests that reaction of this isomer with Hantzsch ester **1b** proceeds with no asymmetric induction. Inspection of the geometric parameters for the four transition states highlights some elements that indeed might be responsible for the observed enantioselectivity. First, we note that $\mathbf{TS}_{Z\text{-}(S)}$ has the shortest hydrogen-bond distance be-

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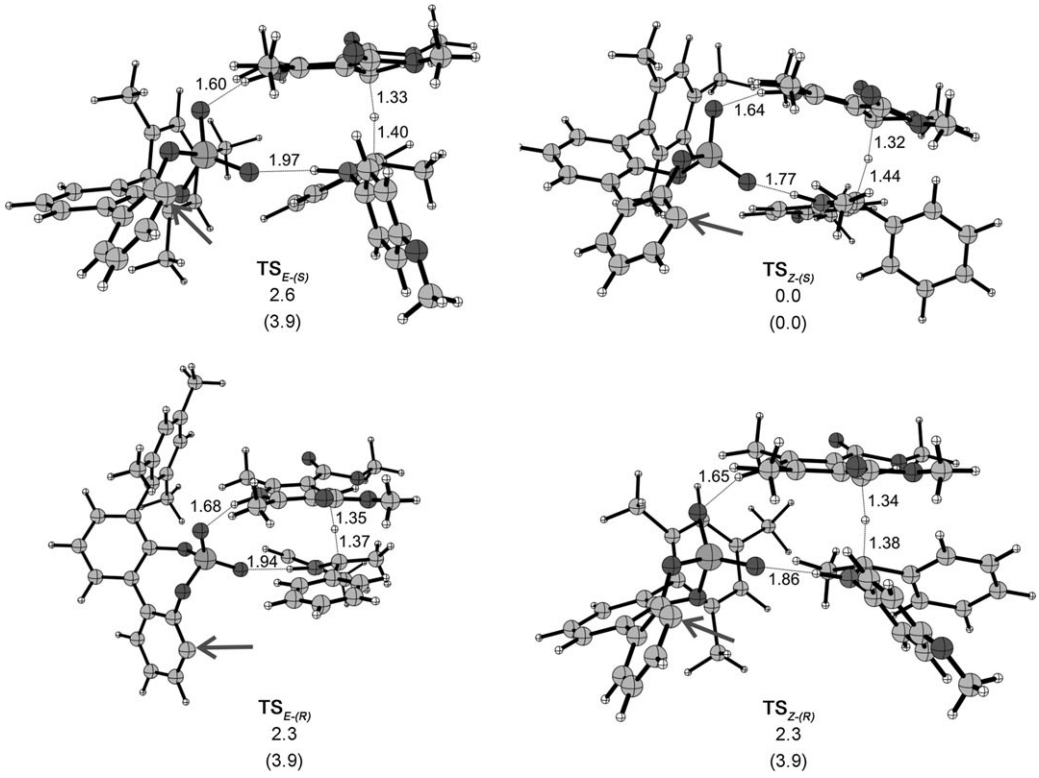

Figure 4. Transition states for the hydride transfer reaction catalyzed by biaryl phosphoric acid **10**. All energies are relative to $\mathbf{TS}_{Z\text{-}(S)}$; gas-phase energies are given in parentheses. For clarity, a mesityl group, corresponding to the carbon atom marked with an arrow, has been removed from all structures.

tween the iminium and the phosphate. The *Z* geometry of the C=N double bond confers more compactness to the iminium ion derived from compound **6**, a factor that appears to be crucial for the species to enter the binding pocket of catalyst **10.** $\mathbf{TS}_{Z\text{-}(S)}$ is the only transition state in which binding of the iminium occurs in an "empty quadrant" (Figure 5), with both phenyl rings being far from the bulky mesityl groups (see the Supporting Information for representation of the quadrants of the other transition states).

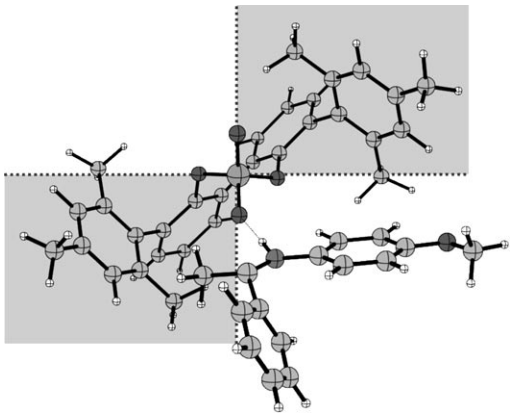

Figure 5. Quadrant representation of $\mathbf{TS}_{Z\text{-}(S)}$ showing the proposed reason for the enantioselectivity. For clarity, the Hantzsch ester has been removed from the picture.

This observation explains both the low energy of $\mathbf{TS}_{Z\text{-}(S)}$ relative to the other transition states and the short distance between the catalyst and the iminium. All other transition states experience some steric repulsion between catalyst and reactants. In $\mathbf{TS}_{Z\text{-}(R)}$ the PMP group is relatively close to one mesityl group. In the two other transition states the more extended (*E*)-iminium cannot approach the phosphate without suffering from steric interactions from one or both mesityl groups. These results hence explain the importance of the bulky substituents at the 3,3′-positions to inducing asymmetry.

As previously mentioned, Rueping et al. extended the phosphoric acid transfer hydrogenation of imines to 2-substituted quinolines.[21] The reaction, which is performed by using slightly more than two equivalents of Hantzsch ester **1a**, is likely to involve hydrogenation of the 3,4 double bond followed by isomerization to yield a dihydroquinoline (not isolated). We reasoned that this postulated intermediate is, in some respects, an *N*-aryl-arylketimine constrained in an *E* geometry (Scheme 6).

Rueping et al. showed that in the presence of phosphoric acid **8d**, many quinolines could be hydrogenated with extremely high enantioselectivity.[21a] Note that, in this case, the sense of asymmetric induction is reversed relative to the reaction with *N*-PMP-imines. For simplicity we employed phosphoric acid **10** to model this reaction too. Hence we used the opposite enantiomer of the catalyst compared with that employed by Rueping and co-workers in their work. To

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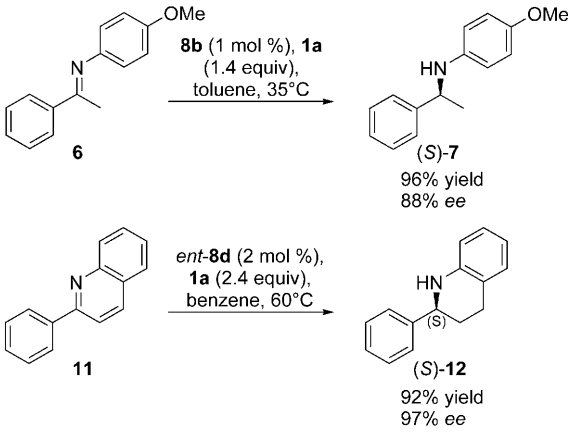

Scheme 6. Reversed enantioselectivity in the hydrogenation of 2-substituted quinoline **11**.

unravel the reasons for this switch in enantioselectivity, we located the transition states for hydride transfer to the 2-aryl-3,4-dihydroquinolinium ion, the intermediate postulated for the hydrogenation of compound **11**. Gratifyingly, also in this case the diastereomeric transition state with the lower energy was also in agreement with experiment (Figure 6).

For the 3,4-dihydroquinolinium, the magnitude of the energy difference (3.6 kcal mol^{-1}) calculated between the transition states leading to opposite enantiomers reflects the higher enantioselectivities observed in the reaction of this class of substrate. Inspection of the geometrically optimized geometries of $\mathbf{TS}_{\mathbf{Q\text{-}(S)}}$ and $\mathbf{TS}_{\mathbf{Q\text{-}(R)}}$ reveals that, again, a tighter iminium···phosphate hydrogen bond corresponds to a lower energy. For these two transition states, however, rationalization of the enantioselectivity in terms of the quadrants rule is not possible. The energy difference is likely to originate from the different binding geometries required to accommodate the two hydrogen bonds between the substrate and catalyst and to place the mobile hydride between the C4 of diester **1b** and the imine carbon atom.

Unlike what was previously observed for PMP-imine **6**, the iminium ion derived from quinoline **11** has a substantially flat geometry because its *N*-aryl group cannot rotate out of the plane of the C=N double bond. As shown by the front view and, more clearly, by the schematic representation (Figure 6b,c), the Hantzsch ester and the dihydroquinolinium ion are practically parallel in both transition states. Although in $\mathbf{TS}_{\mathbf{Q\text{-}(R)}}$ binding of the reactants between the two mesityl groups results in a sandwichlike structure, in $\mathbf{TS}_{\mathbf{Q\text{-}(S)}}$ both the dihydroquinolinium ion and the 2-phenyl ring experience severe steric interactions with the 3,3′-substituents of catalyst **10**.

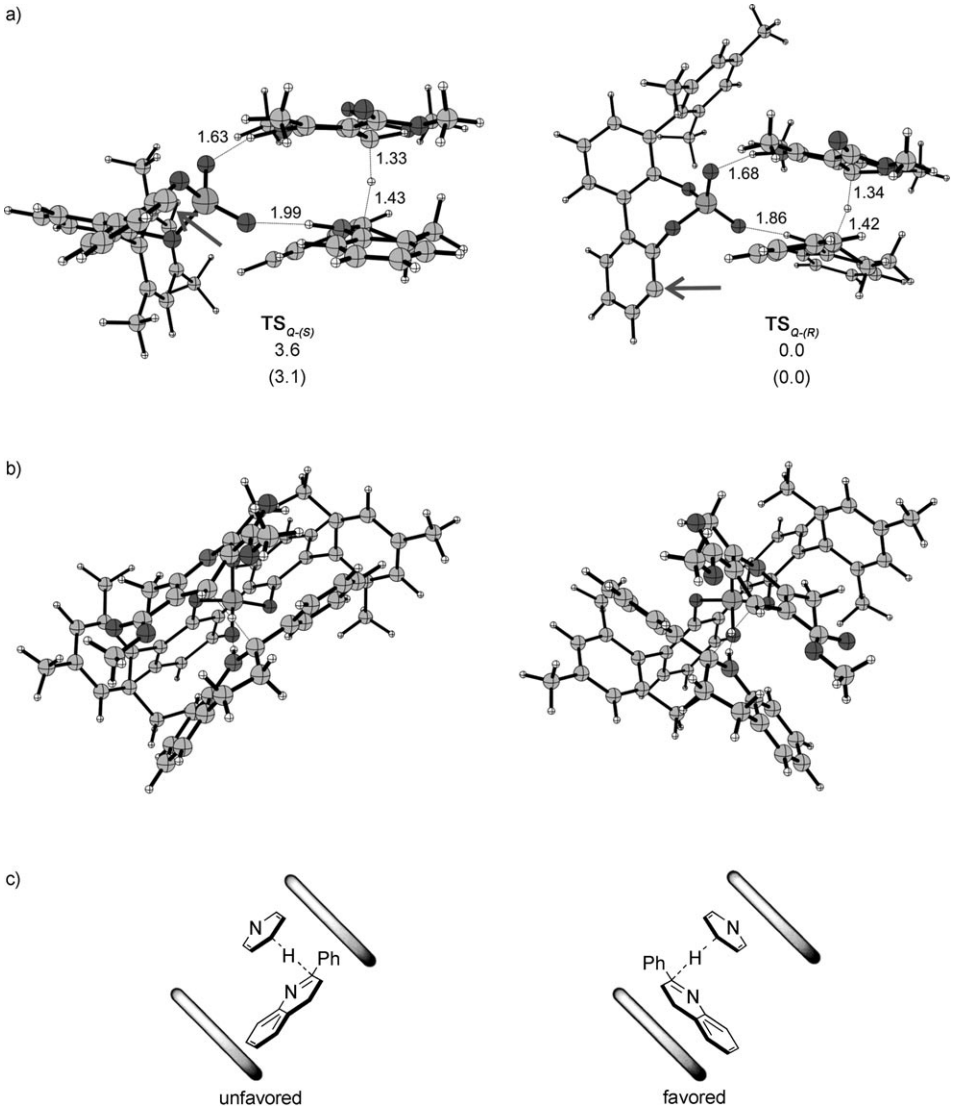

Figure 6. Transition states for the hydride transfer to the 3,4-dihydroquinolinium ion catalyzed by biaryl phosphoric acid **10**. Energies are in kcal mol^{-1}; gas-phase energies are given in parentheses. a) Side view. For clarity, a mesityl group, corresponding to the carbon atom marked with an arrow, has been removed from both structures; b) front view; c) schematic representation of the transition states, the solid bars represent the mesityl groups.

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Summary and Conclusions

We have performed a density functional theory study of the hydride transfer step in the phosphoric acid catalyzed transfer hydrogenation of imines with Hantzsch esters. In the first part we investigated the reaction of an *N*-arylketimine with an achiral phosphoric acid catalyst. The main conclusion of this section is that the diphenyl phosphate functions as a Lewis base/Brønsted acid bifunctional catalyst in this reaction. Simultaneous activation of the reaction partners by hydrogen bonding to both phosphate oxygen atoms (di-LBBA pathway) is crucial to promote the reaction. In this case we calculate the barrier of the reaction to be slightly lower than 20 kcal mol^{-1}, in qualitative agreement with the reported experimental conditions for this transformation. The calculations show that transition state with two hydrogen bonds to the same phosphate oxygen atom (mono-LBBA pathway) or with no hydrogen bonds between the Hantzsch ester and the catalyst (BA pathway) are energetically not viable. We have also shown that hydride transfer to the *E* and *Z* isomers of the iminium ion have comparable energies. Considering that interconversion between these two isomers is presumably fast in the presence of a Brønsted acid, we propose that both participate in the reaction.

We have also investigated the enantioselective transfer hydrogenation promoted by axially chiral phosphoric acids. The computational model reproduces the observed enantioselectivities for the reactions of both *N*-PMP-ketimines and 2-arylquinolines. The steric repulsion between the aryl rings of the iminium and the mesityl groups of the catalyst is ultimately responsible for the enantioselectivity of the reactions. In the case of the *N*-PMP-ketimine, we show that hydride transfer to the *Re* face of the *Z* form of the iminium (which is more compact and fits better in the binding pocket of the catalyst) minimizes these steric interactions. In the case of the 3,4-dihydroquinolinium, the flatness and rigidity of the substrate dictates its interaction with the catalyst pocket. This results in hydride transfer to the *Si* face of the substrate being favored.[34]

These findings will definitely aid the design of new improved catalytic systems for transfer hydrogenation, possibly with multiple interactions between suitable dihydropyridine derivatives and phosphoric acids possessing additional binding sites.

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