Origins of enantioselectivity in the chiral Brønsted acid catalyzed hydrophosphonylation of imines†

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Received 28th August 2008, Accepted 5th January 2009
First published as an Advance Article on the web 5th February 2009
DOI: 10.1039/b815008g

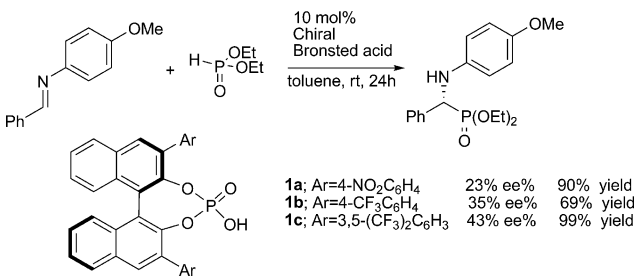
The results of an experimental and ONIOM-based computational investigation of the mechanism and the origins of enantioselectivity in the asymmetric synthesis of α-amino phosphonates by an enantioselective hydrophosphonylation of imines catalyzed by chiral Brønsted acids are reported. It was found that the enantioselectivity observed in the enantioselective hydrophosphonylation of the imine with a benzothiazole moiety was poor. A detailed computational study with a two-layer ONIOM (B3LYP/6–31G(d)/AM1) method on the mechanism of the investigated reaction was carried out to explore the origins of the enantioselectivity. Calculations indicate that the investigated reaction is a two-step process involving proton-transfer and nucleophilic addition, which is the stereo-controlling step. The investigated reaction prefers a di-coordination pathway to a mono-coordination pathway. The different enantioselectivities exhibited by three kinds of catalyst and two kinds of nucleophile were rationalized. Calculations indicate that *si*-facial attack is higher in energy than *re*-facial attack by only 0.1 kcal/mol, which accounts well for the low *ee* value observed in the enantioselective hydrophosphonylation of the imine with a benzothiazole moiety. The energy barrier for phosphonate–phosphite tautomerism catalyzed by chiral Brønsted acid in toluene is only 1.8 kcal/mol, which could explain why the investigated reaction can take place at room temperature.

Introduction

The development of efficient methods of accessing complex chiral molecules with biological activities continues to be one of the most challenging topics in modern synthetic organic chemistry.[1] Although a number of metal-based Lewis acid catalysts have been developed to activate carbon–carbon and carbon–nitrogen double bonds, metal-free chiral organocatalysts, such as chiral Brønsted acids,[2–4] are generally preferred because of their stability toward water and oxygen.

α-Amino phosphonic acids and their derivatives play an important role in chemistry because they often exhibit intriguing biological activities. For example, they can be used as inhibitors of enzymes such as EPSP synthase and HIV protease.[5] Recently, a lot of α-amino phosphonates containing heterocycle moieties, such as thiophene, furan, pyrrole, 1,3,4-thiadiazole, and benzothiazole, were found to possess a wide range of antitumor, antiviral, and antifungal properties and to have been widely used as insecticides and herbicides.[6–12]

Diastereoselective addition of phosphite derivatives to chiral imines,[13] chiral Lewis acid- or chiral Brønsted acid-catalyzed enantioselective addition of phosphites to imines,[14] and other methods[15] have been successfully developed for the preparation of optically active α-amino phosphonates.[16,17] Recently, Akiyama, *et al.* reported a simple and efficient synthetic protocol catalyzed by chiral Brønsted acid **1** to asymmetrically synthesize α-amino phosphonates.[18] α-Amino phosphonates were obtained in moderate yields (Scheme 1). The enantioselectivity could be improved to 90% in cases where diisopropylphosphite was added to imines having *o*-X-C_6H_4-CH=CH substituents at the carbon (where X is an electron-withdrawing group).



Scheme 1

Among the test phosphoric acids **1**, **1a** exhibited the lowest enantioselectivity (23% ee) and **1c** exhibited the highest enantioselectivity (43% ee) and reactivity (99% yield). The enantioselectivity increased when the nucleophile was changed from diethyl phosphonate (43% ee in toluene) to diisopropyl phosphonate (52% ee in *m*-xylene).[18] The study also found that the presence of an *o*-hydroxy moiety decreased the enantioselectivity (88% ee *vs* 39% ee). This indicates that the structures of imine and catalyst play an important role in affecting the reaction's enantioselectivity.

With the information in hand, we proceeded to synthesize enantiopure α-amino phosphonates with heterocycle moieties

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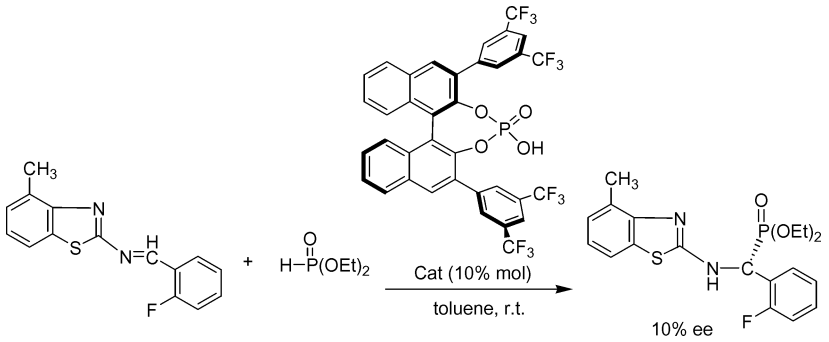
† Electronic supplementary information (ESI) available: Discussion of computational methods; ONIOM evaluation; selected topological parameters at bond critical points in **int1** and **TS4**; optimized structures of the investigated system; Cartesian coordinates of the stationary points discussed in the text. See DOI: 10.1039/b815008g



Scheme 2

to investigate their biological activities. However, we found the enantioselectivity of the chiral Brønsted acid, **1c**, catalyzed enantioselective hydrophosphonylation of imines with a benzothiazole moiety was quite poor (Scheme 2).[19]

This finding motivated us to study the mechanism and the origins of enantioselectivity in the enantioselective hydrophosphonylation of imines catalyzed by chiral Brønsted acids in detail. Recently, Yamanaka, Akiyama *et al.* reported a combined experimental and theoretical study on the chiral Brønsted acid-catalyzed enantioselective Mannich-type reaction of ketene silyl acetals with aldimines.[23] The theoretical study elucidated that the two-point hydrogen bonding interaction resulted in the preference for a di-coordination pathway and the reaction proceeded through protonation followed by nucleophilic attack *via* a nine-membered cyclic TS. It is more important that the origins of enantioselectivity in the nucleophilic addition are well elucidated.[20] On the other hand, theoretical studies of the mechanism of organocatalytic and organometallic reactions have been confirmed to be helpful in understanding reaction results[21] and to give guidance for the future design of new catalysts and new reactions.[22]

Inspired by this, we carried out a detailed computational study on the mechanism of the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine. The present mechanistic study will provide an in-depth understanding of the details of the chiral Brønsted acid-catalyzed C–P bond formation and explain the origins of the low enantioselectivity in the enantioselective hydrophosphonylation of imine with a benzothiazole moiety. The mechanistic insights could also be useful for understanding other Brønsted acid-catalyzed reactions[23] and to guide the design of new chiral Brønsted acids for asymmetric C–O, C–N, and C–P bond formations.[24]

Computational methods

The layer treatment (two-layered ONIOM method) implemented in the Gaussian 98 program package[25] was used to obtain a description of the potential energy surface (PES). The model is divided into a high layer that is treated at the B3LYP/6-31G(d) level of theory[26,27] for the critical bond cleavage atoms and a low layer that is treated with the AM1 method.[28] Selected carbon–oxygen and carbon–carbon bonds were cut and saturated with hydrogen link atoms during the generation of the model subsystem to avoid possible chemical artifacts. Frequency calculations at the same level were performed to confirm each stationary point as either a minimum or a transition structure (TS). Single-point energies in solution were calculated at the B3LYP/D95(d,p) level on the geometries optimized in the gas phase with the conductor-like polarizable continuum model (CPCM) using UAKS radii.[29] The dielectric constant in the CPCM calculations was set to $\varepsilon = 2.379$ to simulate toluene as the solvent medium used in the experiments. The wave function was obtained at the B3LYP/D95(d,p) level for the topological analysis. Topological analysis of the electron densities at bond critical points was performed with the AIM2000 program.[30] In what follows, the discussed energies are relative Gibbs free energies in toluene without zero-point energy correction.

Computational results and discussion

In this section, we will first discuss the mechanism of the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimines and explore the two possible pathways, mono-coordination and di-coordination. Then, we will investigate the substituent effects on the enantioselectivity. Finally, we will explore the origins of the low enantioselectivity in the enantioselective hydrophosphonylation of the imine with a benzothiazole moiety. In addition, we will discuss the phosphonate–phosphite tautomerism catalyzed by chiral Brønsted acid.

Mechanism of the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine

Fig. 1 shows the computed potential energy surfaces for the Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine *via* a di-coordination pathway (two substrates form hydrogen bonds with different oxygen atoms of the Brønsted acid) in solution. The optimized structures involved in this reaction are given in Fig. 2. In the first step of the hydrophosphonylation of the aldimine, the chiral Brønsted acid, aldimine, and diethyl phosphite first form a hydrogen-bond complex **int1**, which is stabilized mainly by three favorable hydrogen bonding interactions and whose stability is also affected by the steric hindrance between the 3,3′-aryl substituents of the Brønsted acid and the substrates. Calculations indicate that (***S*)-int1** is slightly more stable than (***R*)-int1**. In (***R*)-int1**, one strong stabilizing interaction is the O3–H3 · · · O2 hydrogen bonding interaction between the Brønsted acid catalyst and diethyl phosphite, as demonstrated by the H3 · · · O2 distance (1.795 Å) and nearly linear O3–H3 · · · O2 geometry (177.4°). Another stabilizing interaction is the O1–H1 · · · N hydrogen bonding interaction, which is also strong indicated

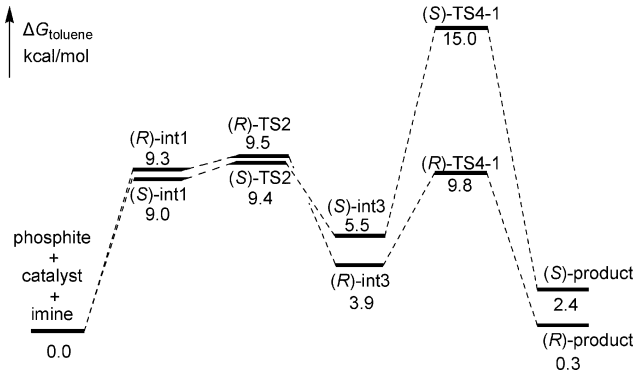


Fig. 1 Potential energy surfaces of the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine by a di-coordination pathway.

by both the H1 · · · N distance (1.460 Å) and O1–H1 · · · N angle (168.2°). The charge density and its Laplacian at the bond critical point between H1 and N are 0.101 and –0.002 au, respectively. The charge density and its Laplacian at the critical point between H3 and O2 (0.034 and 0.106 au) indicate that the O3–H3 · · · O2 interaction is weaker than the O1–H1 · · · N interaction, which is consistent with the distance difference between H3 · · · O2 and H1 · · · N. The large charge density shows that the O1–H1 · · · N hydrogen bond is stronger than normal hydrogen bonds[31] and has some ionic characteristics. The O1–H1 · · · N angle in (***R***)-**int1** deviates from 180° by about 11.8°, which results from the C2–H2 · · · O2 interaction between the Brønsted acid and the aldimine. The topological analyses at the bond critical point show this interaction is a normal hydrogen bond and their charge densities and Laplacians fall into the proposed range of 0.002–0.035 au and 0.014–0.139 au, respectively.[31] The O1–H1 · · · N and O3–H3 · · · O2 interactions in (***S***)-**int1** are stronger than the corresponding ones in (***R***)-**int1**, which is demonstrated by the corresponding hydrogen bond distances (1.440 Å *vs.* 1.460 Å and 1.779 Å *vs.* 1.795 Å). The negative Laplacian at the bond critical point between H1 and N (–0.025 au) indicates that the H1 · · · N interaction is partly covalent in nature.[32] The C4–H4 · · · O2 interaction in (***S***)-**int1** is stronger than the C2–H2 · · · O2 in (***R***)-**int1**, which is demonstrated by the corresponding intermolecular distances (2.266 Å *vs.* 2.337 Å). However, (***S***)-**int1** is only more stable than (***R***)-**int1** by 0.3 kcal/mol, which implies that the steric hindrance may be more significant in (***S***)-**int1**. These complexation processes are endergonic by 9.3 and 9.0 kcal/mol and exothermic by 22.0 and 23.7 kcal/mol in terms of electronic energy, respectively, which is due to the entropy penalty for bringing three molecules together (see ESI).†

Complex **int1** leads to intermediate **int3** *via* a proton-transfer transition structure **TS2**. The protonation of aldimine generates a zwitterionic complex of the iminium salt and is very easy, as demonstrated by the activation free energy (0.2 kcal/mol for (***R***)-**int1** and 0.4 kcal/mol for (***S***)-**int1**). Both intermediates, **int3**, are more stable than the corresponding reactants, **int1**. This is due to the fact that **int3** is more compact than **int1**. For example, the H3 · · · O2 distance in (***S***)-**int3** is shorter than that in (***S***)-**int1**

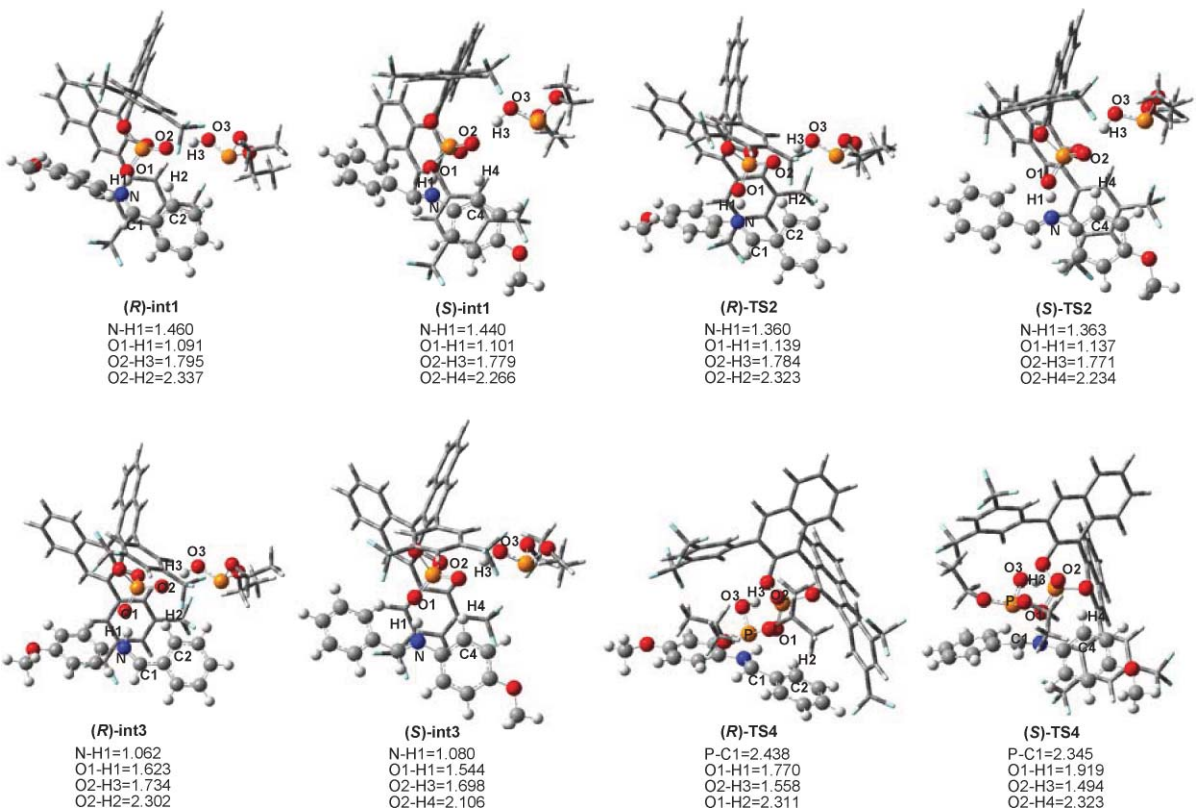
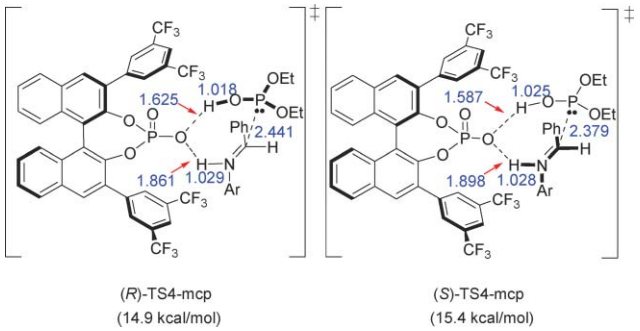


Fig. 2 Optimized structures of the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine by a di-coordination pathway. Bond lengths are in Å.

(1.698 Å *vs.* 1.779 Å). Obviously, the steric hindrance of the 3,3′-aryl substituents also contributes to the stability increase of **int3**. The aldimine moiety in **int3** is flatter than that in **int1**, which results from less steric hindrance. These proton-transfer processes are exergonic by 3.5 and 5.4 kcal/mol, respectively. Though the hydrogen bonding interactions in (***S***)**-int3** are stronger than those in (***R***)**-int3**, calculations show that (***R***)**-int3** is more stable than (***S***)**-int3** by 1.6 kcal/mol. This further indicates that steric factors also contribute toward the energy differences.

Intermediate **int3** evolves to the products *via* a nine-membered transition structure, **TS4**. This transformation is a concerted process involving C–P bond formation and proton-transfer. (***R***)**-TS4** is more stable than its counterpart, (***S***)**-TS4**, by 5.2 kcal/mol. The structural properties allow us to examine the origins of the instability of (***S***)**-TS4** in detail. The shorter H1 ⋯ O1 distance indicates that the N1–H1 ⋯ O1 hydrogen bonding interaction in (***R***)**-TS4** is stronger than that in (***S***)**-TS4**, however, the C3–H3 ⋯ O2 hydrogen-bonding interaction in (***S***)**-TS4** is stronger than that in (***R***)**-TS4**. Furthermore, the electrostatic attraction between the lone pair electrons of the phosphorus atom in dialkyl phosphite and the partly positive carbon atom in the C=N double bond in (***S***)**-TS4** is stronger than that in (***R***)**-TS4**, which is demonstrated by the C–P distances (2.345 Å *vs.* 2.438 Å) and relative large electron density. However, the steric hindrance of the 3,3′-aryl substituents in (***S***)**-TS4** is more significant than that in (***R***)**-TS4**, demonstrated by the aldimine moiety geometries. The steric hindrance of the 3,3′-aryl substituents in (***S***)**-TS4** has forced the aldimine moiety to deviate from the stable planar structure. The benzene ring linking with the N atom is almost parallel to one of the 3,3′-aryl substituents to minimize the steric hindrance, however, the other 3,3′-aryl substituent causes significant steric hindrance with the aldimine and diethyl phosphate. Therefore, (***S***)**-TS4** is less stable than its counterpart, (***R***)**-TS4**. This results in the fact that *re*-facial attack is 5.2 kcal/mol more favored than *si*-facial attack. The predicted ee for the above catalysts should be >99%, however, the experimental ee is only moderate (up to 43%). Although the mismatch between experiment and theory is relatively large, the calculations could well explain the trend of the increase in ee predicted. The use of extended basis sets did not change the trend (see ESI).† The O–H of the diethyl phosphite moiety in (***R***)**-TS4** is 1.027 Å, indicating that proton transfer from the diethyl phosphite moiety to the oxygen of the Brønsted acid occurs later than the C–P bond formation. The shortest distance in **TS4** between two phenyl rings is larger than 4.5 Å, which indicates that the aromatic stacking interaction is very weak. This concerted process requires an activation free energy of 5.9 kcal/mol for *re*-facial attack and 9.5 kcal/mol for *si*-facial attack. The (***S***)**-product** is 2.4 kcal/mol higher in energy than the reactants and the (***R***)**-product** is 0.3 kcal/mol higher in energy than the reactants. So formation of the (***R***)**-product** is both thermodynamically and kinetically favorable.

We also explored the possible mono-coordination (two substrates form hydrogen bonds with the same oxygen atom of the Brønsted acid) pathway. The optimized transition structures of the stereo-controlling step for the Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimines *via* a mono-coordination pathway are shown in Fig. 3. The free energies, required to reach (***R***)**-TS4-mcp** and (***S***)**-TS4-mcp**, are 6.4 and 8.3 kcal/mol respectively, which are greater than that required



(*R*)-TS4-mcp (14.9 kcal/mol) (*S*)-TS4-mcp (15.4 kcal/mol)

Fig. 3 Optimized stereo-controlling transition structures of the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine by a mono-coordination pathway. Bond lengths are in Å.

to reach (***R***)**-TS4** in the di-coordination pathway (5.9 kcal/mol). In addition, (***R***)**-TS4-mcp** and (***S***)**-TS4-mcp** are higher in energy than (***R***)**-TS4** by 4.6 and 1.6 kcal/mol, respectively. This indicates that the di-coordination pathway is more favorable. It is noted that (***R***)**-TS4-mcp** is higher in energy than (***S***)**-TS4-mcp**, which implies that more (***S***)**-product** should be formed instead. This is not consistent with the experimental result. Therefore, the investigated reactions must be carried out *via* the di-coordination pathway, which is similar to the situation observed in the chiral Brønsted acid-catalyzed enantioselective Mannich-type reaction of ketene silyl acetals with aldimines.[19]

Substituent effects on the enantioselectivity of the enantioselective hydrophosphonylation of aldimine

To explore the issue of the enantioselectivity in the present reaction, we compared the transition structures involving the three Brønsted acid catalysts with different 3,3′-aryl substituents used in the experiment. The optimized transition structures and relative stabilities are shown in Fig. 4. The energy difference between *si*-facial attack and *re*-facial attack is as follows: **TS4** > **TS4-2** > **TS4-3**, which indicates that the catalyst **1c** should induce the best enantioselectivity among the three test catalysts. This is in agreement with experimental results. Calculations indicate that the energy difference between the two enantioselective transition structures increased when the nucleophile was changed from diethyl phosphite (5.2 kcal/mol) to diisopropyl phosphite (6.8 kcal/mol), which is also consistent with the experiment. Therefore, the substituent groups in both catalyst and imine affect the enantioselectivities. The sterically repulsive interaction between the 3,3′-substituents of the catalyst and the reaction substrates is sensitive to the nature of the substituents on the aryl group and the dialkyl phosphite, therefore, the highest enantioselectivity was observed when chiral Brønsted acid **1c** and diisopropyl phosphite were used. These results could well explain the origins of enantioselectivity in the enantioselective hydrophosphonylation of aldimine catalyzed by chiral Brønsted acid.[33]

When the origin of the enantioselectivity in the chiral Brønsted acid-catalyzed enantioselective hydrophosphonylation of aldimine was clear, we investigated further why the enantioselectivity of the **1c**-catalyzed enantioselective hydrophosphonylation of imine with a benzothiazole moiety was poor. The optimized transition structures and relative stabilities are shown in Fig. 5. Calculations indicate that (***S***)**-TS4-5** is only 0.1 kcal/mol higher in energy

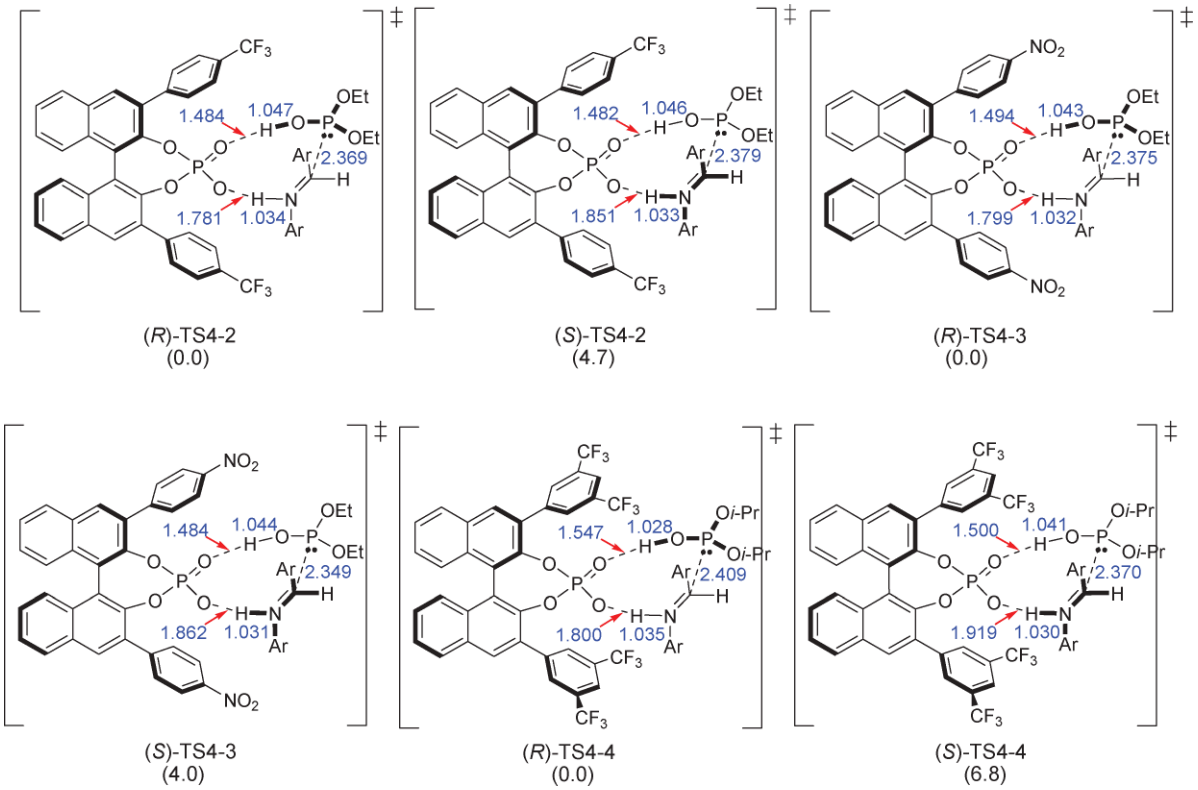


Fig. 4 Optimized selected structures of the chiral Brønsted-acid catalyzed enantioselective hydrophosphonylation of aldimine by a di-coordination pathway. Bond lengths are in Å.

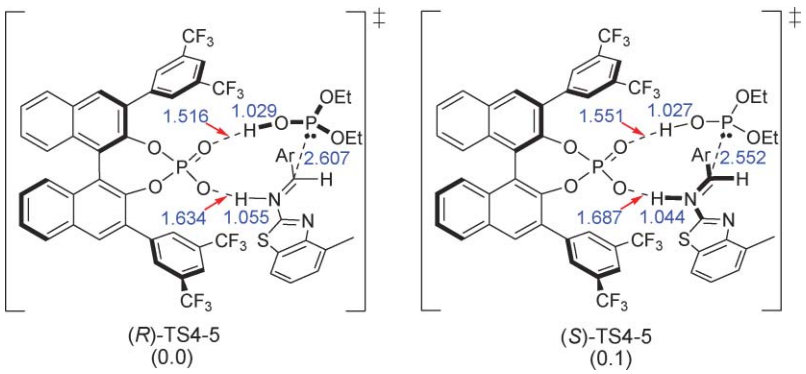


Fig. 5 Optimized stereo-controlling transition states of the chiral Brønsted-acid catalyzed enantioselective hydrophosphonylation of imine with a benzothiazole moiety. Bond lengths are in Å.

than (***R***)-**TS4-5**, which can well account for the fact that the enantioselectivity of the **1c** catalyzed enantioselective hydrophosphonylation of imines with a benzothiazole moiety is poor. The structural properties of (***S***)-**TS4-5** and (***R***)-**TS4-5** were examined to investigate why an energy difference exists between them. The O–H · · · O hydrogen bonding and P–C electrostatic interactions in (***S***)-**TS4-5** are stronger than those in (***R***)-**TS4-5**, which is demonstrated by the corresponding distances. However, the situation is the opposite for the N–H · · · O hydrogen bonding interaction. The sterically repulsive interactions between the 3,3′-substituents of the catalyst and substrates in **TS4-5** are not so significant as those in **TS4**, demonstrated by the imine moiety geometries. The imine moiety in (***S***)-**TS4-5** is almost as planar as that in (***R***)-**TS4-5**, which is probably caused by the relatively small thiazole moiety and no C–H · · · O hydrogen bond being formed between the thiazole moiety and catalyst in (***S***)-**TS4-5**. This indicates that the sterically repulsive interactions between the 3,3′-substituents of the catalyst and substrates in (***S***)-**TS4-5** are not significant, which is not the case for (***S***)-**TS4**. Therefore, the energy difference between *si*-facial attack and *re*-facial attack for **TS4-5** is small and the enantioselectivity of the **1c**-catalyzed enantioselective hydrophosphonylation of imine with a benzothiazole moiety was poor. Further experimental and theoretical investigations are ongoing.

Mechanism of phosphonate–phosphite tautomerism

It is known that phosphonate–phosphite tautomerism exists with the phosphite form as the active nucleophile form and the

phosphonate tautomer as the almost exclusively favored but non-nucleophilic form.[18,34] We found that the investigated reaction could not be carried out at room temperature without Brønsted acid. That is to say, the hydrophosphonylation of imines can take place only if there is phosphite in the reaction and phosphonate–phosphite tautomerism can not be carried out at room temperature without a Brønsted acid catalyst. Furthermore, most one-pot syntheses of α-amino phosphonates have to be carried out under heating conditions. Therefore, we envisioned that the Brønsted acid might be involved in the transition structure of phosphonate–phosphite tautomerism. The optimized transition structures and the energy barriers of the catalyst-free transition structure **TS-tau-1** and the Brønsted acid-catalyzed transition structure **TS-tau-2** are shown in Fig. 6. It can be seen from Fig. 6 that, with its activation free energy of 33.7 kcal/mol, it is difficult for the phosphonate–phosphite tautomerism to take place without catalysis by a Brønsted acid. However, tautomerism catalyzed by a Brønsted acid is likely, with an activation energy of only 1.8 kcal/mol. This could well account for why the hydrophosphonylation of imines catalyzed by Brønsted acid could occur at room temperature or even lower temperature, but hydrophosphonylation of imines without catalyst needs additional energy (heat or microwave).

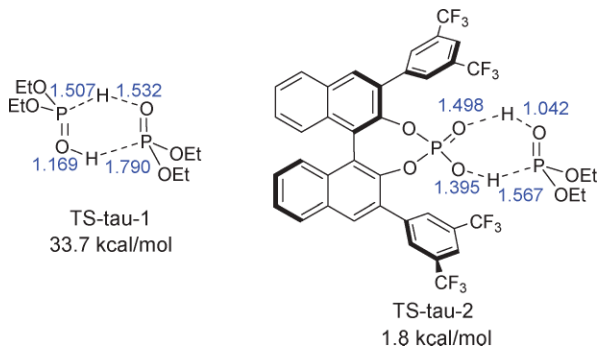


Fig. 6 Optimized structures of TSs for phosphonate–phosphite tautomerism. Bond lengths are in Å.

Conclusions

In this paper, we have reported a joint experimental and computational investigation on the mechanism and the origins of enantioselectivity in the enantioselective hydrophosphonylation of imines catalyzed by chiral Brønsted acids. Calculations indicate that the investigated reaction involves tandem proton transfer and nucleophilic addition. The first proton transfer is very easy with an activation free energy less than 1.0 kcal/mol. The formation of the C–P bond and the second proton-transfer occur in an asynchronous concerted process, which is the stereo-controlling step. Calculations show the di-coordination pathway is favorable. The energy differences between *si*-facial attack and *re*-facial attack are significant for the hydrophosphonylation of aldimine. Calculations indicate that *re*-facial attack of the imine with a benzothiazole moiety is only favorable by 0.1 kcal/mol, which well accounts for the low ee value observed in the enantioselective hydrophosphonylation. The energy barrier for phosphonate–phosphite tautomerism catalyzed by chiral Brønsted acid in toluene is only 1.8 kcal/mol, which can explain why the investigated reaction can be performed at room temperature and the catalyst-free hydrophosphonylation of imine has to be carried out under heating conditions. Further design and synthesis of highly enantiopure α-amino phosphonates with heterocycle moieties are in progress.

Acknowledgements

Supported by the National Science Foundation of China (20802011), the Key Project of Chinese Ministry of Education (208126), the Special Foundation of Government of Guizhou Province (200818), and Talent Project of Guizhou University (2007023).

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