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On the mechanism of stereoselection in direct Mannich reaction catalyzed by BINOL-derived phosphoric acids

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Abstract—Associates between the chiral phosphoric acids and Boc-protected imine were characterized computationally and by NMR; the primary importance of the bulky protecting group in imine for the high enantioselectivity in the direct Mannich reaction is rationalized via the analysis of the stereodiscriminating intermediates.

Asymmetric catalysis by chiral Brønsted acids is a new and actively developing research area.[1] The possibility to achieve high orders of enantioselection in useful organic transformations without applying transition metal catalysis is an attractive goal for the synthetic chemists.[2] Numerous synthetically useful methods for the preparation of non-racemic compounds using chiral Brønsted acids have been already developed.[3] In particular, chiral phosphoric acids proved to be very useful catalyst from the point of view of their catalytic activity and availability.[4–6]

However, mechanistic aspects of these reactions have been studied much less frequently. In 2002 Vachal and Jacobsen via a series of subtle experiments supported by computations concluded that the asymmetric Strecker reaction catalyzed by an urea derivative proceeds via the bifunctional binding of two urea NH protons and the relatively unstable *Z*-isomer of aldimine.[7] This explanation is now widely accepted for rationalizing high orders of enantioselection in the organocatalytic transformations catalyzed by various urea derivatives. On the other hand, the principles of enantioselection in the cases when only one proton per catalyst is available are inevitably much less straightforward, since the chelating association is hardly conceivable, and one must analyze the catalyst–substrate complexes with much more flexible structure. For example, this is the case when the chiral phosphoric acids are used as the Brønsted acids.[4–6] We are not aware of any mechanistic approach to this problem published so far. In this work we report our computational and experimental studies highlighting the important features of the mechanism of stereoselection in the phosphoric acid-catalyzed direct Mannich reaction reported two years ago by one of us (e.g., Eq. 1).[5a]

Preliminary computational analysis showed that the exothermic formation of 1:1 adducts between the catalyst **1** and imine **2a** is sterically controlled by the bulky substituents of the phosphoric acid (Fig. 1).[8]

The imine molecule is capable to accommodate itself only stretching through the non-hindered quadrants; it can do this in two different ways using either of the two otherwise equivalent oxygen atoms (Fig. 1). Besides, the isomerization of more stable *trans*-imine **2a** into its cis-isomer can precede the effective coordination.[7] Hence, we looked computationally for four different configurations of the H-bond associates: two for the *trans*-imine (**4a**,**b**) and two for the *cis*-imine (**4c**,**d**).

Inspection of Figure 2 and Table 1 shows that both *cis*- and *trans*-**2a** can exothermically form associates through the hydrogen bonding. For the *trans*-**2a** we located both possible associates **4a** (Fig. 1A) and **4b** (Fig. 1B), whereas only **4c** (Fig. 1A) is a real minimum for the association of **1** and *cis*-**2a**.[9] Among **4a**–**c** only **4a** is pertinent for the stereospecific nucleophilic attack: whereas one side of the C=N double bond is effectively shielded by one of the biphenyl substituents, another

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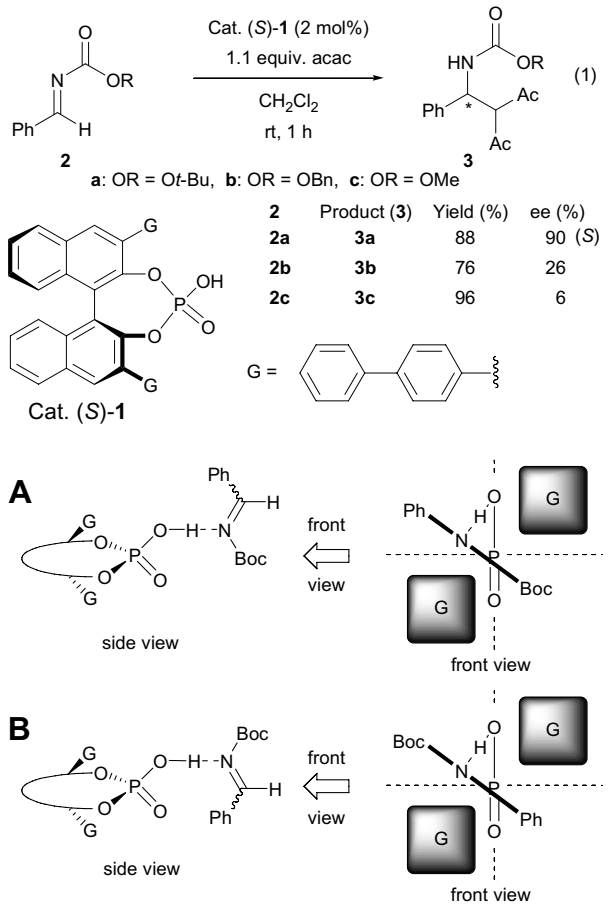

Figure 1. Schematic representation of two possible modes of the hydrogen bond formation between (*S*)-**1** and **2a**. The flat imine molecule is represented as a front-view rod with two non-equal termini.

side is completely open for the approach of the nucleophile. Assuming that the enantioselection occurs via the stereoselective reaction of associate **4a**, one should expect selective formation of *S*-**3a**; that was the sense of enantioselection observed in the catalytic reaction of **2a** with acetylacetone catalyzed by **1**.

The close inspection of other two structures **4b**,**c** showed that the C=N bond of the imine in these associates is approximately equally shielded from both sides of the molecule. Hence, a reaction of nucleophile with either **4b** or **4c** would result in a non-stereospecific reaction, but it must be slower than the reaction of **4a**. If interconversion between **4a**–**c** is fast enough, only **4a** would react, and the whole catalytic transformation would occur stereoselectively due to the effective stereodifferentiation of the prochiral sides of imine in **4a** (Fig. 3).

Inspecting the interatomic distances shown in Table 1, one can conclude that the acidic proton in **4a**–**c** keeps its connection to the chiral phosphoric acid. On the other hand, the significantly low-field moved chemical shifts of the same proton indicate a strong interaction with the nitrogen atom of **2** that must provide the necessary activation of the imine molecule.

Looking more closely at the structure **4a** with clearly differentiated prochiral sides, we have realized the importance of the bulky *t*-Bu substituent of the imine for effective stereoselection. Indeed, the order of hindrance provided to either side of the imine molecule might change dramatically if the free rotation around the hydrogen bond would be possible. In **4a** such free rotation is prevented by close contacts of the *t*-Bu group of the imine with either one or another biphenyl substituent of the phosphoric acid. If this hindrance would be reduced, it must result in dramatic decrease of the order of enantioselection. In order to check, whether this assumption is correct, we have prepared imines **2b** and **2c** differing from **2a** only by the substituent attached to the oxygen atom, and carried out their reactions with acetylacetone catalyzed by **1** (Eq. 1). Indeed, the ee of the product dropped dramatically when the imine **2b** with benzyl substituent was used in the reaction, and the reaction became only slightly stereoselective with the imine **2c**.

Having in hands the computed chemical shifts for the acidic protons in the H-bonded associates (see Table 1) we have looked for the corresponding signals in the low-field region of the ^{1}H NMR spectra of the samples prepared by mixing the substrate with the catalyst.[10] Indeed, we have found a set of signals resonating in the expected spectral region (Fig. 4). The lineshape of these signals demonstrated reversible changes in the temperature interval from 253 to 293 K (Fig. 4) attesting for the reversible interconversion between the species represented by each signal. The doublet splitting observed for the signal with $\delta = 17.2$ was recognized as coupling constant with phosphorus since it kept the same value (6.8 Hz) when recorded at 300 or 600 MHz. All signals shown in Figure 3 immediately disappeared from the spectrum when acetylacetone was added to the sample.[11]

Overall computational and NMR evidence suggests that these signals belong to the H-bonded associates between the catalyst and the substrate. Although the observed chemical shifts are somewhat higher than the computed ones (most probably due to the neglecting the solvent effects), computations correctly predict a very low-field position of the acidic proton involved in the formation of the associates. Besides, the observation of its coupling with phosphorus is in accord with the computed structures.

In conclusion, our experimental and computational results point out that the formation of the simple hydrogen bonded associates between the chiral phosphoric acid and imine is finely regulated via the steric interaction of the catalyst with the substrate. Although intuitively numerous geometries of the H-bonded associates are conceivable, the detailed analysis shows that the possibilities for the effective substrate activation are quite restricted. In particular, in the studied here interaction between **1** and **2a** only the coordination mode achieved in the structure **4a** makes the imine susceptible to the enantioselective nucleophilic attack. The *t*-Bu group of the imine acts like an anchor preventing the free rotation around the hydrogen bond, thus ascertaining the high

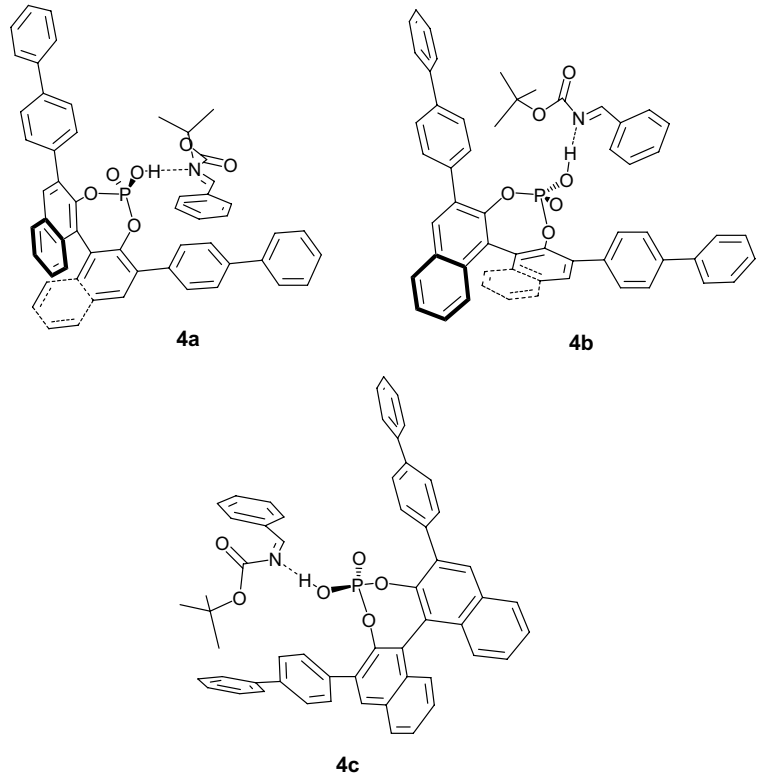

Figure 2. 2D Representation of 3D structures for the optimized geometries (at the B3LYP/6-31G* level of theory) of the H-bonded associates **4a**–**c**.

Table 1. Computational data for the H-bond associates **4a**–**c**[a]

4	Rel. energy (kcal/mol)	Energy of formation (kcal/mol)	Distance N–H (Å)	Distance O–H (Å)	δ(H) calcd[b]
4a	0.0	−16.8[c]	1.67	1.02	13.2
4b	0.8	−16.0[c]	1.65	1.02	13.6
4c	6.9	−15.1[d]	1.65	1.02	12.6

[a] On the B3LYP/6-31G(d, p) level of theory.
[b] Chemical shifts were computed by GIAO method, the absolute shift (σ) of tetramethylsilane (TMS) was used to compute the relative chemical shifts $\delta = \sigma$ reference $- \sigma$ compound.
[c] Relative to (**1a** + *trans*-**2a**).
[d] Relative to (**1a** + *cis*-**2a**).

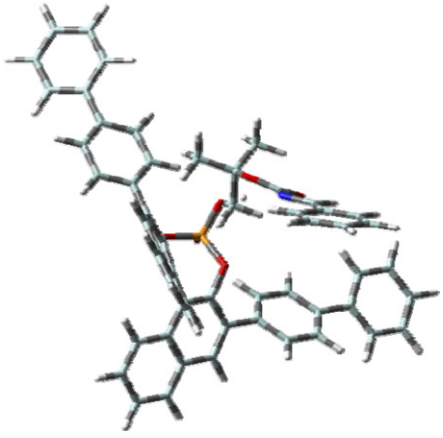

Figure 3. 3D Structure of the associate **4a** showing effective shielding of one side of the prochiral imine molecule.

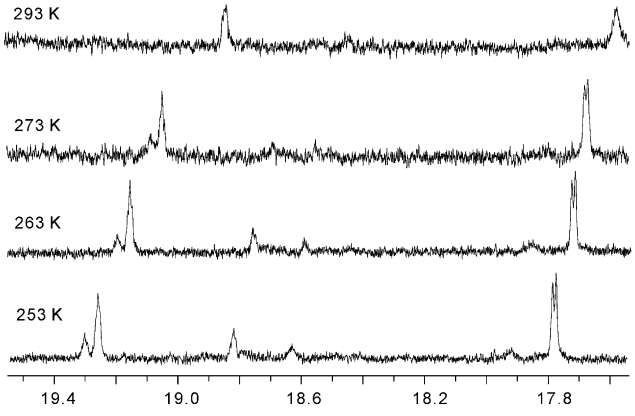

Figure 4. Temperature dependence of the low-field region of the ^{1}H NMR spectra (600 MHz, toluene-d_8) of the samples obtained by addition of **2** (0.1 mmol) to a solution of **1** (0.01 mmol) in dry deuteriotoluene (0.5 mL).

order of the enantioselection. Alternative coordination modes (e.g., **4b**) can lead to a non-stereoselective catalysis if the nucleophilic reagent is small enough. Fast interconversion of the different H-bond associates is required for the successful stereoselection, since the appropriate binding mode is not preferred thermodynamically.[12] This may account for the significant decreasing of the ee's at lower temperatures observed in some of similar reactions.

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Supplementary data

Experimental details, computational details, cartesian coordinates of the computed structures. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.017.

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8. We have also regarded the possibility of 2:1 adducts, and have optimized corresponding structures (see ESI for details). However, the participation of such species in the stereoselective catalytic cycle is excluded since we have found linear dependence of the product ee versus catalyst ee in the reaction of Eq. 1.
9. We also tried to locate another structure corresponding to the coordination of *cis*-**2a** with different chiral phosphoric acid applied for the computations (see ESI for details). However, results were very similar to those for **4a**–**c**: apparently the alternative mode of the *cis*-imine coordination is destabilized due to unfavourable closeness of the *t*-Bu substituent of imine and one of the bulky radicals of the phosphoric acid.
10. The NMR experiments were carried out in toluene-d_8 since it is easier to remove the traces of water from this solvent than from CD_2Cl_2. Carrying out the catalytic reaction in toluene gives essentially the same results as in CH_2Cl_2 (see Ref. 5a).
11. Similarly, a series of signals disappeared from the ^{31}P NMR spectrum. However, we were unable to get any additional information from the ^{31}P NMR due to the low intensity of the corresponding signals.
12. The present analysis demonstrating how the asymmetric pocket for the enantioselective nucleophilic attack is being created opens the door for the computation of transition states involving nucleophile that are necessary to allow more confident conclusions on the mechanism of enantioselection.