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Computational Study on the pK_a Shifts in Proline Induced by Hydrogen-Bond-Donating Cocatalysts

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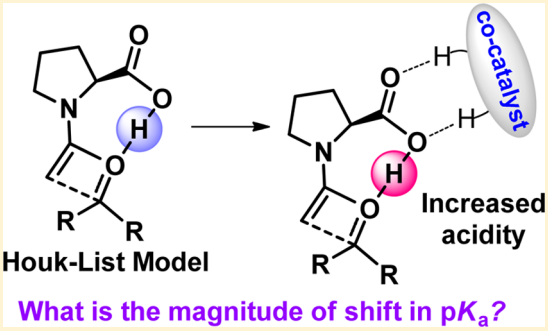
Supporting Information

ABSTRACT: The pK_a shifts of proline induced by a family of hydrogen-bond-donating cocatalysts were computationally evaluated with the M06-2x/6-311++G(2df, 2p)//B3LYP/6-31+G(d)(SMD) method. The calculation predicted that the acidity of proline could be increased by more than 9 pK_a units in nonpolar solvents (*n*-hexane and toluene) when it assembles with hydrogen-bond-donating cocatalysts, which would contribute to the dramatically enhanced catalytic properties. For hydrogen-bond-donating cocatalysts, their relative abilities to induce the pK_a shifts of proline in the gas phase and common organic solvents were established and were found to be well-correlated with their acidities. The results may aid in future development of modularly designed supramolecular catalysis—the assembly of catalyst species by harnessing multiple weak intermolecular interactions.



INTRODUCTION

Catalysis plays a central role in chemistry as it provides tools for efficiently and selectively making and breaking chemical bonds, which is crucial for converting basic chemicals into useful products for society in a sustainable fashion. In 2000, the discovery of the first proline-catalyzed intermolecular aldol reaction by List, Lerner, and Barbas[1] initiated an explosive growth of research interests in organocatalysis, which is now recognized as the third pillar of asymmetric synthesis standing next to metal and biocatalysis. Among numerous catalysts developed, nature's smallest enzyme, namely, proline, is a remarkable one, and a broad range of C−C or C−heteroatom bond formation reactions have been realized with this wonderful natural product.[2]

Although proline is an exceptionally good catalyst for a variety of reactions in terms of its structural simplicity and easy availability, it exhibits some drawbacks such as poor solubility in nonpolar solvents, a relatively low reactivity, and high catalyst loadings. To avoid these undesired issues, considerable effort has been devoted to the chemical modification of proline in order to obtain catalytic systems both with better solubility in common organic solvents and/or with higher acidity of the directing acid proton.[2]

Recently, organocatalysts self-assembled in situ from precatalysts through noncovalent interactions have received a lot of attention.[3] Compared with traditional organocatalysts, these supramolecular catalysts are very amenable to structure modification, and a library of catalysts can be readily obtained for a high-throughput screening by simply combining the precatalysts. Intriguingly, researchers have shown that the addition of catalytic or substoichiometric amounts of hydrogen-bond-donating cocatalysts such as chiral diols,[4] Schreiner's thiourea,[5] and guanidinium salt[6] could dramatically accelerate the reaction rate and increase the diastereo- and/or enantioselectivity of proline-catalyzed reactions. As examples, in 2005, Shan and Zhou disclosed that the addition of (*S*)-BINOL could significantly improve both the yields and enantioselectivities of proline-catalyzed direct asymmetric aldol reactions (Scheme 1A).[4] To explain the enhanced chiral inductive ability of proline, the authors proposed a supramolecular interaction between diol, proline, and reactants in the Houk−List transition state,[7] as shown in Scheme 1. Subsequently, Demir[5] and Rios[5] showed that proline in combination with Schreiner's thiourea could cocatalyze highly stereoselective aldol reactions between cyclohexanones and benzaldehydes (Scheme 1B). To justify the enhanced catalytic activity and enantioselectivity, it was proposed that proline first forms a host−guest supramolecular assembly with Schreiner's thiourea, and this new proline−thiourea complex could have enhanced acidity of carboxyl group and better solubility. More recently, Amo et al. demonstrated that guanidinium salt could act as an excellent hydrogen-bond-donating cocatalyst for proline-catalyzed direct asymmetric aldol reactions (Scheme 1C).[6] Compared to the chemical modification of proline, the approach through adding hydrogen-bond-donating cocatalysts to interact with proline-forming supramolecular catalysts is a very attractive strategy due to its simplicity, economy, and effectiveness.

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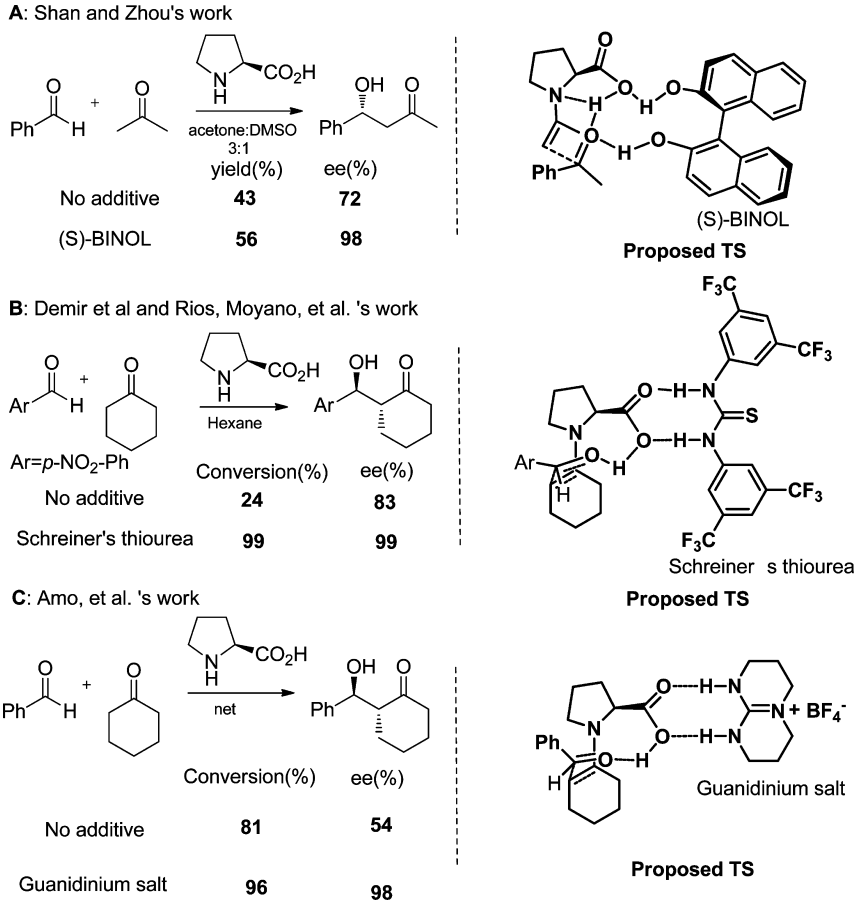
Scheme 1. Proline-Catalyzed Direct Aldol Reactions in the Absence and Presence of Hydrogen-Bond-Donating Cocatalysts Together with Corresponding Proposed Transition States



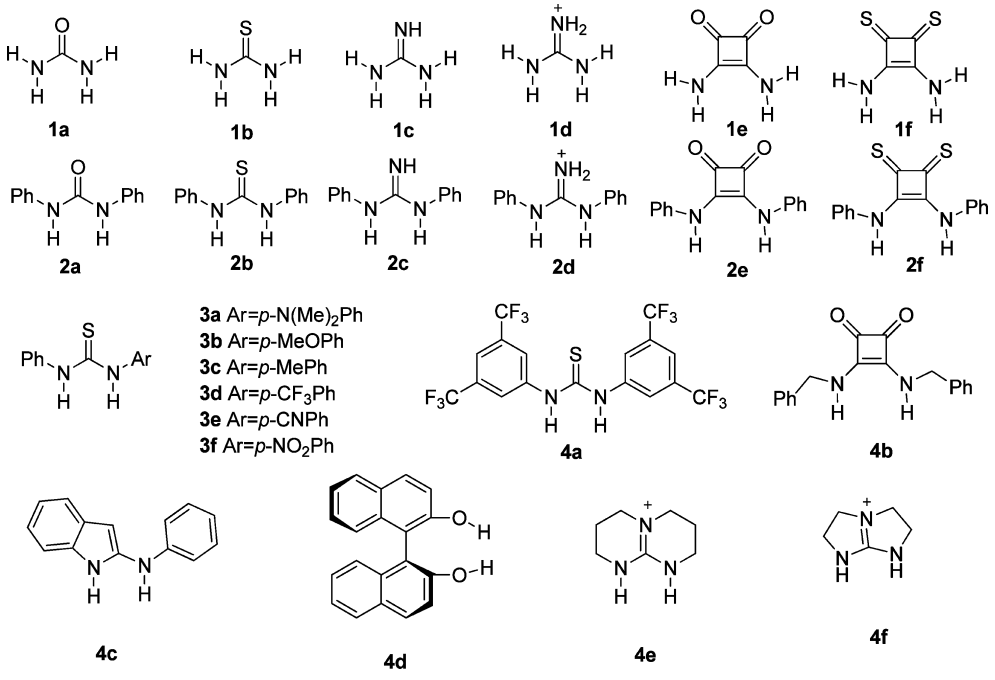


Figure 1. Hydrogen-bond-donating cocatalysts examined.

Although a full-bodied mechanistic picture of the role played by these hydrogen-bond-donating cocatalysts in the reactions is not clear, the significant improvement of activity and/or selectivity of proline is believed to be mainly due to the formation of proline/cocatalyst supramolecular complexes,[4−6] in which the acidity of the carboxyl group in proline is increased

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Table 1. Calculated pK_a Shifting Scales for Hydrogen-Bond-Donating Cocatalysts Using the M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d)(SMD) Method

	pK_a shift					
cocatalysts	gas phase	*n*-hexane	toluene	dichloromethane	acetone	acetonitrile
1a	14.6	10.0	8.9	4.7	4.5	4.0
1b	19.1	13.6	12.2	7.1	6.9	6.3
1c	13.0	9.1	8.1	4.4	4.5	3.9
1d	70.3	41.3	34.6	14.7	11.8	10.1
1e	22.1	14.9	13.1	6.9	6.2	5.5
1f	26.9	19.1	17.1	9.8	9.1	8.2
2a	21.5	14.3	12.5	6.6	6.3	5.6
2b	22.6	15.1	13.3	7.0	6.6	5.9
2c	20.4	13.7	12.2	6.7	6.6	5.9
2d	67.2	40.2	33.8	15.0	12.3	10.7
2e	27.0	18.5	16.4	9.1	8.4	7.5
2f	28.6	19.5	17.3	9.3	8.7	7.7
3a	21.4	13.8	12.1	6.2	5.9	5.2
3b	22.1	14.4	12.6	6.3	5.9	5.2
3c	22.8	15.2	13.4	7.2	6.8	6.1
3d	25.3	16.7	14.6	7.4	6.8	6.0
3e	26.6	17.6	15.4	7.7	7.0	6.2
3f	27.0	17.8	15.5	7.6	6.9	6.0
4a	31.2	24.3	18.1	9.3	8.5	7.5
4b	24.6	16.4	14.3	7.6	6.8	6.1
4c	17.6	10.5	9.0	3.5	3.3	2.7
4d	19.6	13.8	12.5	8.2	8.5	7.9
4e	65.2	38.1	31.7	12.9	10.1	8.5
4f	67.5	39.5	33.0	13.8	10.9	9.3

by hydrogen-bond-donating cocatalysts. Thus, quantitative information of the ability of hydrogen-bond-donating cocatalysts to change the acidity of proline is of great value for a better understanding of this kind of cooperative catalysis.

On the other hand, asymmetric cooperative Brønsted acid catalysis with a combination of achiral Brønsted acids and chiral (thio)urea catalysts developed by Jacobsen and co-workers has been proved to be an efficient methodology to realize a number of enantioselective reactions.[8] Although the main strategy of the hydrogen-bond-donating cooperatively catalytic system was considered to belong to the asymmetric ion-pairing catalysis domain, the quantitative pK_a shift study of a related catalysis system should be helpful for the understanding of the recognition ability on the corresponding anion by hydrogen-bond-donating compounds. Moreover, pK_a shifts resulting from host−guest inclusion are also well-documented in biological systems,[9] which lead to the modification of the chemical reactivity of guests. The corresponding study of the quantitative data of pK_a shifts is an important goal in the understanding and mimicking of enzymatic activity.[10]

In connection with our ongoing project on the investigation of organocatalysis from the perspective of physical organic chemistry,[11] herein, we wish to report the results of our theoretical studies of the shifts in pK_a of proline induced by a variety of hydrogen-bond-donating cocatalysts. The knowledge of these calculations is of great value for providing important clues for more definitive study of structure−activity trends and guide more rational design of new dual organocatalytic systems.

RESULTS AND DISCUSSION

General Information. In the past several years, hydrogen-bond donors such as (thio)urea,[12] guanidinium ion,[13] and squaramide[14] were common structural motifs in molecular recognition and organocatalysis. Some of them have been shown to be good cocatalysts for proline-catalyzed reactions.[4−6] The enhanced catalytic properties of proline may mainly be due to the formation of proline/cocatalyst supramolecular complexes, which leads to an increase in the acidity of the directing acid proton. Thus, the most common hydrogen-bond donors (Figure 1), including (thio)urea, guanidinium ion, and squaramide, were considered in this study. Meanwhile, other hydrogen-bond donors such as (*S*)-BINOL and thiosquaramide have also been examined for deep comparison and analysis. Thus, pK_a shifting scales can be established.

Calculation Method. Over the past 2 decades, considerable effort has been made to develop theoretical protocols to calculate pK_a constants to complement experimental techniques.[15−17] At present, the pK_a values of organic acids in the gas phase and in organic solvents can be calculated with similar or greater accuracy than those obtained experimentally. For example, Pliego et al. calculated the pK_a values of organic acids in DMSO with a root mean square error of 2.2 pK_a units.[17b] Guo et al. developed several PCM-based protocols for the calculation of pK_a values of organc acids in DMSO and MeCN with a precision of around 1.7 and 1.0 pK_a units, respectively.[17d−g] Wang et al. calculated pK_a values for a variety of organic acids using a proton exchange method in nonaqueous solvents, achieving a precision of less than 1.0 pK_a units.[17h] Recently, Trummal and co-workers applied the IEF-PCM method to calculate the pK_a values of organic acids in 1,2-dichloroethane with a mean unsigned error of about 0.6 pK_a units.[17m] Most recently, our study showed that the M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d)(SMD) method could predict (O−H) pK_a with a precision of about 0.5 pK_a units.[11i] In the present study, this method was thus chosen for the

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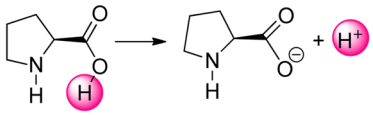
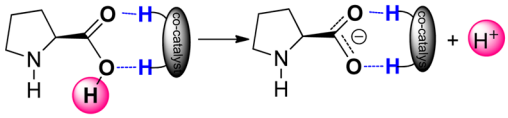
calculation of pK_a shifts of proline induced by a family of hydrogen-bond-donating cocatalysts, as shown in Figure 1.

To calculate the pK_a shifts, the following two processes are considered. First, the pK_a of proline, in the absence of hydrogen-bond-donating cocatalyst, can be calculated according to eqs 1 and 2, where ΔG is the total change in free energy associated with the deprotonation process of proline. Similarly, the pK_a of the supramolecular complexes forming from hydrogen-bond-donating cocatalysts and proline can be evaluated according to eqs 3 and 4.[18] Therefore, the pK_a shifts of proline induced by hydrogen-donating cocatalysts can be calculated according to eq 5. Since nonpolar or low-polar solvents were usually used as a medium for proline/cocatalyst-promoted reactions, the pK_a shifts of proline induced by hydrogen-bond-donating cocatalysts were evaluated in the gas phase, *n*-hexane, toluene, dichloromethane, acetone, and acetonitrile.



$$pK_a(\text{proline}) = \Delta G_1/RT\ln(10) \qquad \text{eq. 2}$$



$$pK_a(\text{complex}) = \Delta G_2/RT\ln(10) \qquad \text{eq. 4}$$

$$pK_a\,(Shift) = pK_a(1) - pK_a(2) = (\Delta G_1 - \Delta G_2)/RT\ln(10) \qquad \text{eq. 5}$$

Calculated pK_a Shifting Abilities of Hydrogen-Bond Donors for Proline. The calculated pK_a shifts of proline induced by hydrogen-bond-donating cocatalysts in different medium are presented in Table 1. From the data, it is clear that the magnitude of pK_a shifts of proline induced by hydrogen-bond-donating cocatalysts is largely dependent on the polarity of solvents. Increasing the polarity of the solvent leads to a decrease in the value of pK_a shifts (Figure 2); for example,

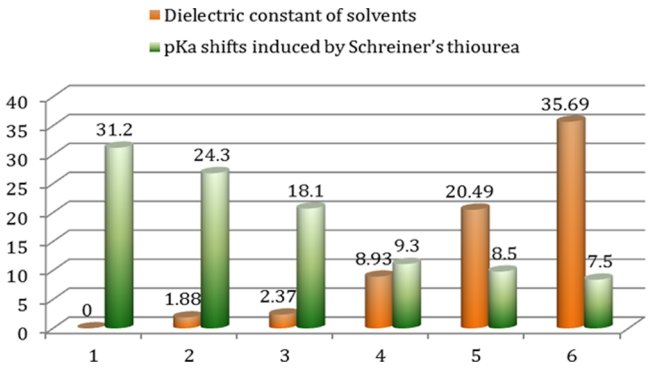


Figure 2. Schreiner's thiourea-induced pK_a shifts in different medium.

Schreiner's thiourea can increase the acidity of proline by 18.1 pK_a units in nonpolar toluene, while it only increases the acidity of proline by 7.5 pK_a units in high-polar acetonitrile. This is in good agreement with Demir et al.'s experimental observation that the efficiency and selectivity were remarkably enhanced when switched to nonpolar solvent from polar solvents.[5a] Also, this would explain why nonpolar solvents are better than polar solvents for proline/cocatalyst-mediated reactions.[5] As the nonpolar toluene was most commonly used as the solvent for proline/cocatalyst-promoted reactions, we will mainly focus on the results in toluene in the following discussion.

Among these hydrogen-bond-donating cocatalysts investigated, guanidiniums (**1d**, **2d**, **4e**, and **4f**) were found to induce the largest pK_a shifts of proline. The calculation predicted that guanidinium ion **1d** could enhance the acidity of proline by as large as 34.6 pK_a units in toluene. Even in polar solvent acetone, the acidity of proline could be increased by 10.1 pK_a units when it assembled with guanidinium ion **4e**. Such an enhancement of the acidity of proline would at least partially account for the enhanced catalytic properties of proline for the aldol reactions.[6] The ability to induce the pK_a shifts of proline for Schreiner's thiourea was predicted to be about 13 pK_a units weaker than that of guanidinium **4e**. The (*S*)-BINOL used by Shan and Zhou[4] was found to induce the pK_a shift of proline by 12.5 and 7.9 pK_a units in toluene and acetonitrile, respectively.[19] Generally, for these parent hydrogen-bond-donating cocatalysts, namely, from **1a** to **1f** (and from **2a** to **2f**), their abilities to inducing the pK_a shifts of proline in the gas phase and nonpolar solvents (*n*-hexane and toluene) are as follows: **1(2)d** (guanidinium) > **1(2)f** [(thio)squaramide] > **1(2)e** (squaramide) > **1(2)b** (thio)urea >**1(2)a** urea > **1(2)c** guanidine. This suggests that (thio)squaramide might also be a potential cocatalyst besides guanidinium ions and thiourea. A similar result had also been observed by Wheeler through their very recent study of the performance of (thio)squaramide and (thio)urea-derived aminocatalysts within the context of Diels–Alder cycloadditions of nitrostyrene and anthracene.[20] Their computations reveal that thiosquaramides engage in stronger hydrogen bonds than squaramide, urea, and thiourea. Therefore, we have confidence to predict that thiosquaramide and corresponding derivatives should be explored as potential hydrogen-bond-donating organocatalysts in the near future.

Having established the ability to induce pK_a shifts of proline for parent hydrogen-bond-donating cocatalysts, we now turn our attention to substituent effects (from **3a**–**3f**). Interestingly, it was found that pK_a shifts calculated in the gas phase can be well-correlated with the Hammett constants σ_p (Figure 3). This suggested that, intrinsically, a better hydrogen donor cocatalyst would induce a larger pK_a shift. Indeed, pK_a shifts were found to be well-correlated with the equilibrium acidities of hydrogen donor cocatalysts (Figure 4).[21] In nonpolar toluene (Figure 4) and hexane (Supporting Information Figures S1 and S2), similar correlation could be obtained. As a result of four CF_3 substitutions, Schreiner's thiourea **4a** could increase the acidity of proline by 18.1 pK_a units in toluene, which is 4.8 pK_a units larger than that induced by thiourea **2b**. It should be pointed out that solvent effects may override substituent effects as the polarity increases; for example, the pK_a shifts induced by **3c**, **3d**, **3e**, and **3f** were predicted to be almost identical in high-polar acetone and acetonitrile.

Application to the Analysis of Hydrogen-Bond-Donating Cocatalyst-Promoted Aldol Reaction. Although the panoramic mechanism of the studied cocatalysts is not clear, the supramolecular assembly system can be used to explain some phenomena in the mechanism research. For example, Rios found that the cooperatively catalytic system of proline and thiourea appears to be operative only in the presence of the ketone reagent. As a result, the ketone–oxazolidinone intermediate and its equilibration with the "open" zwitterionic structure were both formed. Our theoretical

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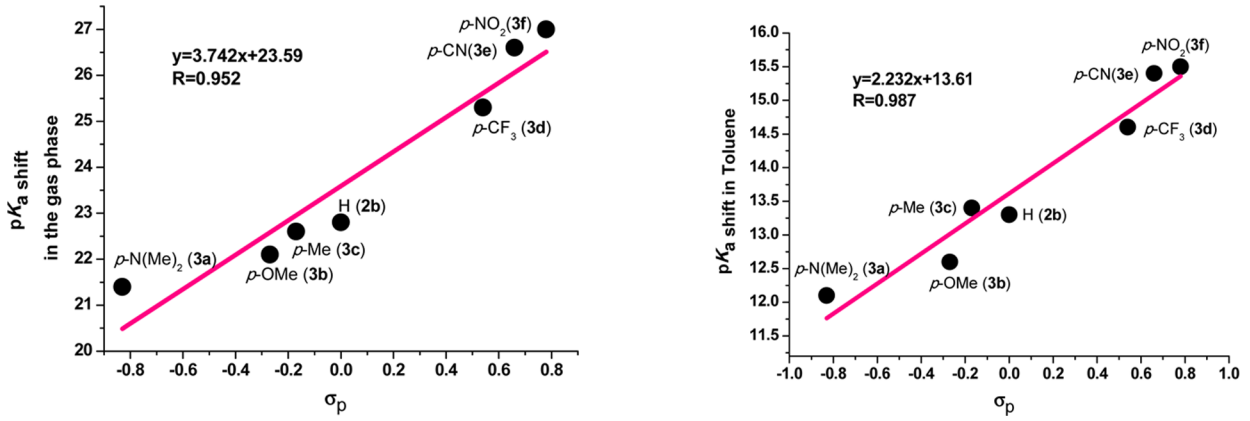

Figure 3. Plot of pK_a shifts of proline in the gas phase and in toluene against the Hammett para-substituents (σ_p).

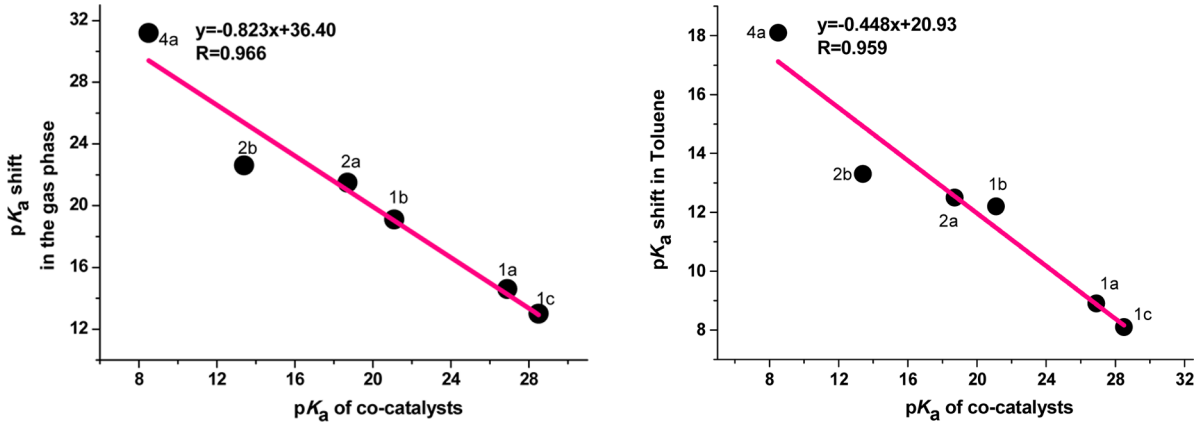

Figure 4. Correlation of pK_a shifts of proline in the gas phase and in toluene with the equilibrium acidities of cocatalysts in DMSO.

calculation can also prove it. As shown in Scheme 2, the initial free energy of oxazolidinone intermediate (**INa**) was predicted to be 11.4 kcal/mol lower than its open zwitterionic counterpart (**INb**). When hydrogen-bond-donating compound thiourea (**2b**) was added in the reaction to conform a host–guest supramolecular assembly system, the energy gap between **INa** and **INb** was decreased to 0.07 kcal/mol. Further increasing the acidity of the hydrogen-bond-donating compound **4a** makes the balance produce the direction of the "open" zwitterionic structure, which is the advantage intermediate of the catalytic activity. The corresponding changes of the bond lengths, which were between hydrogen-bonding donors and intermediates (**INa** and **INb**), were found to relate to the energy gaps. Although we only conducted the simple calculation of the recognition process between hydrogen-bonding donors and intermediates, the trend of the recognition intermediate effect of thiourea was without a doubt in accordance with our obtained pK_a shift rules.

Design and Prediction of New Hydrogen-Bond-Donating Cocatalyst System. Because of the excellent performance of the proline-type supramolecular catalyst, it is easy to think that the strategy may be used for other chiral acid catalytic systems. For a typical example, phosphoric acids,[22] which were considered as the superior small-molecule catalysts, have been proven to be very efficient Brønsted acid catalysts to enable a great number of enantioselective transformations.[23] Although numerous phosphoric-acid-catalyzed highly enantioselective reactions have been reported to date, the relative weak acidity of phosphoric acids[24] limited their application in many catalytic reactions. With an aim to solve this problem, we synthesized many acidic phosphate derivatives, such as *N*-triflyl phosphoramides[25] and bis-sulfur-substituted phosphoric acid.[26] Furthermore, some similar phosphate superacids[27] were also designed and synthesized for the activation of challenging substrates. From a synthetic perspective, the above-mentioned solutions are often more complex and not convenient. It is natural for people to develop better strategies to achieve a more acid phosphate-type catalyst system. Herein, we predicted that the hydrogen-bond-donating cocatalyst between phosphoric acids and hydrogen-bonding donors would be a good solution to this challenge. Therefore, pK_a shift in chiral phosphoric acid induced by guanidinium ion **4f** was calculated as a typical example.

As shown in Scheme 3, phosphoric acid and guanidinium ion can form the self-assembly system through hydrogen binding interactions between guanidinium's two N–H bonds and phosphoric acid's two oxygen atoms. Then the acidity of phosphoric acid was increased by about 23 pK_a units. We summarized that this predicted phosphoric acid-type hydrogen-bond-donating cocatalyst has three clear advantages. First, the recognition of phosphoric acid by a hydrogen-bond donor improves its acidity, which may really enhance the catalytic reaction activity. Second, the changes of structure and steric hindrance induced by the self-assembled catalyst system may help to promote the corresponding chiral induction. Third, a library of catalysts can be readily obtained for high-throughput screening by a simple combination of different phosphoric acids with varied hydrogen-bond-donating compounds. In a word,

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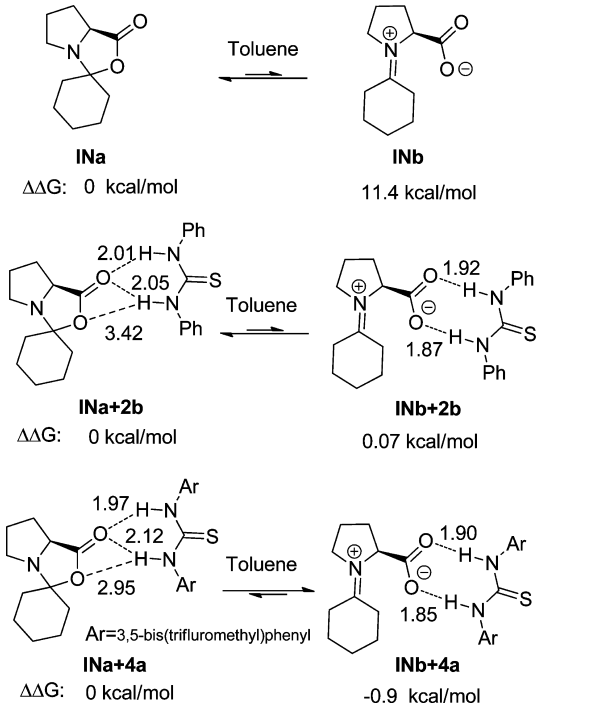
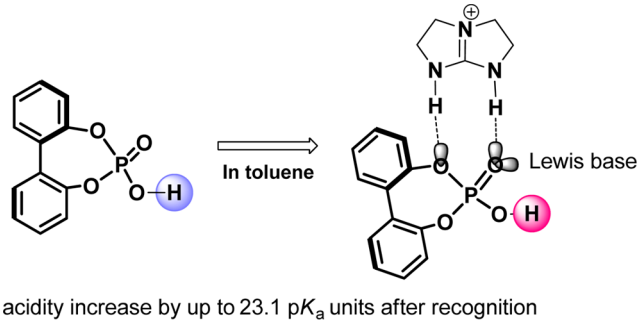
Scheme 2. Relative Free Energies for Seebach's Oxazolidinone Intermediate (INa) and Its Open Zwitterionic Counterpart (INb) in the Absence and Presence of Hydrogen-Bond-Donating Cocatalysts Calculated with the M06-2x/6-311++G(2df,2p)//B3LYP/6-31G(d)(SMD) Method



Scheme 3. Predicted Guanidinium Ion 4f Induced pK_a Shift in Phosphoric Acid in Toluene



the predicted self-assembly system really has the potential to become a novel supramolecular catalyst.

CONCLUSION

In conclusion, the pK_a shifts of proline induced by a variety of hydrogen-bond-donating cocatalysts were computationally evaluated in the gas phase and in common organic solvents. The primary calculated results predicted that the acidity of proline could be increased by more than 9 pK_a units in nonpolar solvents (*n*-hexane and toluene) when it assembles with hydrogen-bond-donating cocatalysts, which might shed light on the dramatically enhanced catalytic activity of proline. Second, the study demonstrated that the pK_a shifts induced by substituted thioureas have linear correlations with the Hammett substituent parameter. Furthermore, pK_a shifts were found to be well-correlated with the equilibrium acidities of hydrogen donor cocatalysts. Finally, as an example of the prediction of a new hydrogen-bond-donating cocatalyst system, pK_a shifts in chiral phosphoric acid induced by guanidinium ion were also discussed. We believe that the data provided in the present study are likely to contribute to a better understanding of proline/cocatalyst catalysis and may aid in future other[28] cocatalyst developments.

COMPUTATIONAL METHODS

All calculations were carried out with the Gaussian 09[29] and Gaussian 03[30] packages. Geometry optimizations were conducted with the B3LYP/6-31+G(d) method. The nature of the stationary points was confirmed by frequency calculations at the same level of theory. Single-point energy calculations were performed at the M06-2x/6-311++G(2df,2p) level of theory with the B3LYP/6-31+G(d) structures. Solvent effects of *n*-hexane, toluene, dichloromethane, acetone, and acetonitrile were estimated using the B3LYP/6-31+G(d)/SMD[31] method with the B3LYP/6-31+G(d) structures.

ASSOCIATED CONTENT

Supporting Information

Figures S1 and S2, Tables S1−S4, and optimized geometries and energies of all computed species. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) List, B.; Lerner, R. A.; Barbas, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395.
(2) (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (c) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (d) Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010**, *39*, 1600. (e) Sunoj, R. B. *Comput. Mol. Sci.* **2011**, *1*, 920. (f) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.
(3) For reviews, see: (a) Meeuwissen, J.; Reek, J. N. H. *Nat. Chem.* **2010**, *2*, 615. (b) Briere, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev.* **2012**, *41*, 1696. (c) Piovesana, S.; Schietroma, D. M. S.; Bella, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 6216. For selected examples, see: (d) Clarke, M. L.; Fuentes, J. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 930. (e) Fuentes, J. A.; Lebl, T.; Slawin, A. M. Z.; Clarke, M. L. *Chem. Sci.* **2011**, *2*, 1997. (f) Uraguchi, D.; Ueki, Y.; Ooi, T. *Science* **2009**, *326*, 120. (g) Uraguchi, D.; Ueki, Y.; Ooi, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 3681. (h) Ohmatsu, K.; Ito, M.; Kunieda, T.; Ooi, T. *J. Am. Chem. Soc.* **2013**, *135*, 590. (i) Uraguchi, D.; Sakaki, S.; Ooi, T. *J. Am. Chem. Soc.* **2007**, *129*, 12392. (j) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088. (k) Xia, A. B.; Xu, D. Q.; Luo, S. P.; Jiang, J. R.; Tang, J.; Wang, Y. F.; Xu, Z. Y. *Chem.—Eur. J.* **2010**, *16*, 801. (l) Yao, Y.; Li, J. L.; Zhou, Q. Q.; Dong, L.; Chen, Y. C. *Chem.—Eur. J.* **2013**, *19*, 9447. (m) Weil, T.; Kotke, M.; Kleiner, C. M.; Schreiner, P. R. *Org. Lett.* **2008**, *10*, 1513. (n) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464. (o) Jones, C. R.; Pantos, G. D.;

Morrison, A. J.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7391. (p) Shi, Y. L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129. (q) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779. (r) Rueping, M.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7832. (s) Probst, N.; Madarasz, A.; Valkonen, A.; Papai, I.; Rissanen, K.; Neuvonen, A.; Pihko, P. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8495. (t) Muramulla, S.; Ma, J. A.; Zhao, J. C. G. *Adv. Synth. Catal.* **2013**, *355*, 1260. (u) Sinha, D.; Perera, S.; Zhao, J. C. G. *Chem.—Eur. J.* **2013**, *19*, 6976. (v) Sinha, D.; Mandal, T.; Gogoi, S.; Goldman, J. J.; Zhao, J. C. G. *Chin. J. Chem.* **2012**, *30*, 2624. (w) Muramulla, S.; Zhao, C. G. *Tetrahedron. Lett.* **2011**, *52*, 3905. (x) Tang, H. Y.; Zhao, G. F.; Zhou, Z. H.; Gao, P.; He, L. N.; Tang, C. C. *Eur. J. Org. Chem.* **2008**, 126. (y) Mandal, T.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714. (z) Perera, S.; Sinha, D.; Rana, N. K.; Van, T. D.; Zhao, J. C. *J. Org. Chem.* **2013**, *78*, 10947.

(4) Zhou, Y.; Shan, Z. X. *J. Org. Chem.* **2006**, *71*, 9510.

(5) (a) Reis, O.; Eymur, S.; Reis, B.; Demir, A. S. *Chem. Commun.* **2009**, 1088. (b) Demir, A. S.; Eymur, S. *Tetrahedron: Asymmetry* **2010**, *21*, 405. (c) Demir, A. S.; Eymur, S. *Tetrahedron: Asymmetry* **2010**, *21*, 112. (d) Demir, A. S.; Basceken, S. *Tetrahedron Lett.* **2013**, *54*, 5677. (e) Demir, A. S.; Basceken, S. *Tetrahedron: Asymmetry* **2013**, *24*, 515. (f) Companyó, X.; Valero, G.; Crovetto, L.; Moyano, A.; Rios, R. *Chem.—Eur. J.* **2009**, *15*, 6564. (g) Companyo, X.; Viciano, M.; Rios, R. *Mini-Rev. Org. Chem.* **2010**, *7*, 1. (h) El-Hamdouni, N.; Companyo, X.; Rios, R.; Moyano, A. *Chem.—Eur. J.* **2010**, *16*, 1142.

(6) (a) Martínez-Castañeda, Á.; Poladura, B.; Rodríguez-Solla, H.; Concellón, C.; del Amo, V. *Org. Lett.* **2011**, *13*, 3032. (b) Martinez-Castaneda, A.; Poladura, B.; Rodriguez-Solla, P. H.; Concellon, C.; del Amo, V. *Chem.—Eur. J.* **2012**, *18*, 5188. (c) Martinez-Castaneda, A.; Rodriguez-Solla, H.; Concellon, C.; del Amo, V. *J. Org. Chem.* **2012**, *77*, 10375.

(7) (a) Bahmanyar, S.; Houk, K. N. *Org. Lett.* **2003**, *5*, 1249. (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (c) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (d) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H. Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558.

(8) (a) Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2009**, *11*, 887. (b) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (c) Beck, E. M.; Hyde, A. M.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 4260. (d) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. *Org. Lett.* **2011**, *13*, 5564. (e) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578. (f) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817. (g) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891.

(9) (a) Honig, B. N.; Nicholls, A. *Science* **1995**, *268*, 1144. (b) Matulis, D.; Bloomfield, V. A. *Biophys. Chem.* **2001**, *93*, 37. (c) Bashford, D.; Karplus, M. *Biochemistry* **1990**, *29*, 10219. (d) MacKerell, A. D, Jr.; Sommer, M. S.; Karplus, M. *J. Mol. Biol.* **1995**, *247*, 774. (e) Ha, N. C.; Kim, M. S.; Lee, W. T.; Choi, K. Y.; Oh, B. H. *J. Biol. Chem.* **2000**, *275*, 41100.

(10) (a) Atwood, J. L.; Orr, G. W.; Robinson, K. D.; Hamada, F. *Supramol. Chem.* **1993**, *2*, 309. (b) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997. (c) Marquez, C.; Nau, W. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3155. (d) Zhang, X. Y.; Gramlich, G.; Wang, X. J.; Nau, W. M. *J. Am. Chem. Soc.* **2002**, *124*, 254. (e) Bakirci, H.; Koner, A. L.; Schwarzlose, T.; Nau, W. M. *J. Phys. Chem. B* **2006**, *12*, 4799. (f) Klock, C.; Dsouza, R. N.; Nau, W. M. *Org. Lett.* **2009**, *11*, 2595.

(11) (a) Li, X.; Deng, H.; Zhang, B.; Li, J. Y.; Zhang, L.; Luo, S. Z.; Cheng, J. P. *Chem.—Eur. J.* **2010**, *16*, 450. (b) Fu, N. K.; Zhang, L.; Li, J. Y.; Luo, S. Z.; Cheng, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 11451. (c) Xue, X. S.; Yu, A.; Cai, Y.; Cheng, J. P. *Org. Lett.* **2011**, *13*, 6054. (d) Li, X.; Xue, X. S.; Liu, C.; Wang, B.; Tan, B. X.; Jin, J. L.; Zhang, Y. Y.; Dong, N.; Cheng, J. P. *Org. Biomol. Chem.* **2012**, *10*, 413. (e) Li, X.; Zhang, Y.-Y.; Xue, X.-S.; Jin, J.-L.; Tan, B.-X.; Liu, C.; Dong, N.; Cheng, J.-P. *Eur. J. Org. Chem.* **2012**, 1774. (f) Zhang, L.; Chen, L. J.; Lv, J.; Cheng, J. P.; Luo, S. Z. *Chem.—Asian J.* **2012**, *7*, 2569. (g) Li, X.; Yang, C.; Jin, J. L.; Xue, X. S.; Cheng, J. P. *Chem.—Asian J.* **2013**, *8*, 997. (h) Xue, X. S.; Li, X.; Yu, A.; Yang, C.; Song, C.; Cheng, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 7462. (i) Yang, C.; Xue, X. S.; Jin, J. L.; Li, X.; Cheng, J. P. *J. Org. Chem.* **2013**, *78*, 7076.

(12) (a) Li, A. F.; Wang, J. H.; Wang, F.; Jiang, Y. B. *Chem. Soc. Rev.* **2010**, *39*, 3729. (b) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (c) Zhang, Z. G.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (d) Amendola, V.; Fabbrizzi, L.; Mosca, L. *Chem. Soc. Rev.* **2010**, *39*, 3889.

(13) (a) Blondeau, P.; Segura, M.; Perez-Fernandez, R.; de Mendoza, J. *Chem. Soc. Rev.* **2007**, *36*, 198. (b) Schug, K. A.; Lindner, W. *Chem. Rev.* **2005**, *105*, 67. (c) Selig, P. *Synthesis* **2013**, *45*, 703. (d) Leow, D.; Tan, C. H. *Synlett* **2010**, 1589. (e) Leow, D.; Tan, C. H. *Chem.—Asian J.* **2009**, *4*, 488.

(14) (a) Storer, R. I.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev.* **2011**, *40*, 2330. (b) Aleman, J.; Parra, A.; Jiang, H.; Jorgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 6890.

(15) For selected recent examples of calculating the gas phase acidities, see: (a) Namazian, M.; Coote, M. L. *J. Fluorine Chem.* **2009**, *130*, 621. (b) Meyer, M. M.; Kass, S. R. *J. Phys. Chem. A* **2010**, *114*, 4086. (c) Rayne, S.; Forest, K. *Theor. Chem. Acc.* **2010**, *127*, 697. (d) Liu, M.; Tran, N. T.; Franz, A. K.; Lee, J. K. *J. Org. Chem.* **2011**, *76*, 7186. (e) Bouchoux, G. *Chem. Phys. Lett.* **2011**, *506*, 167. (f) Himmel, D.; Goll, S. K.; Leito, I.; Krossing, I. *Chem.—Eur. J.* **2012**, *18*, 9333.

(16) For reviews on calculating aqueous pK_a constants, see: (a) Ho, J. M.; Coote, M. L. *Theor. Chem. Acc.* **2010**, *125*, 3. (b) Ho, J. M.; Coote, M. L. *WIREs Comput. Mol. Sci.* **2011**, *1*, 649 and references cited therein. For selected recent examples of calculating aqueous pK_a constants, see: (c) Ali-Torres, J.; Rodriguez-Santiago, L.; Sodupe, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 7852. (d) Lee, T. B.; McKee, M. L. *Phys. Chem. Chem. Phys.* **2011**, *13*, 10258. (e) Mariana Rebollar-Zepeda, A.; Campos-Hernandez, T.; Teresa Ramirez-Silva, M.; Rojas-Hernandez, A.; Galano, A. *J. Chem. Theory Comput.* **2011**, *7*, 2528. (f) Mangold, M.; Rolland, L.; Costanzo, F.; Sprik, M.; Sulpizi, M.; Blumberger, J. *J. Chem. Theory Comput.* **2011**, *7*, 1951. (g) Zhang, S. M. *J. Comput. Chem.* **2012**, *33*, 517. (h) Ghalami-Choobar, B.; Dezhampanah, H.; Nikparsa, P.; Ghiami-Shomami, A. *Int. J. Quantum Chem.* **2012**, *112*, 2275. (i) Keith, J. A.; Carter, E. A. *J. Chem. Theory Comput.* **2012**, *8*, 3187. (j) Sutton, C. C. R.; Franks, G. V.; da Silva, G. *J. Phys. Chem. B* **2012**, *116*, 11999. (k) Chen, Y. L.; Doltsinis, N. L.; Hider, R. C.; Barlow, D. J. *J. Phys. Chem. Lett.* **2012**, *3*, 2980. (l) Uddin, N.; Choi, T. H. C.; Choi, C. H. *J. Phys. Chem. B* **2013**, *117*, 6269. (m) Ali-Torres, J.; Rodriguez-Santiago, L.; Sodupe, M. *Phys. Chem. Chem. Phys.* **2011**, *13*, 7852. (n) Mariana Rebollar-Zepeda, A.; Campos-Hernandez, T.; Teresa Ramirez-Silva, M.; Rojas-Hernandez, A.; Galano, A. *J. Chem. Theory Comput.* **2011**, *7*, 2528. (o) Rebollar-Zepeda, A. M.; Galano, A. *Int. J. Quantum Chem.* **2012**, *112*, 3449. (p) Cunningham, I. D.; Bhaila, K.; Povey, D. C. *Comput. Theor. Chem.* **2013**, *1019*, 55. (q) Abramson, R. A.; Baldridge, K. K. *J. Chem. Theory Comput.* **2013**, *9*, 1027. (r) Gupta, M.; da Silva, E. F.; Svendsen, H. F. *J. Chem. Theory Comput.* **2013**, *9*, 5021.

(17) For examples of calculating pK_a values in organic solvents, see: (a) Kovacevic, B.; Maksic, Z. B. *Org. Lett.* **2001**, *3*, 1523. (b) Almerindo, G. I.; Tondo, D. W.; Pliego, J. R. *J. Phys. Chem. A* **2004**, *108*, 166. (c) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 8717. (d) Fu, Y.; Liu, L.; Li, R. C.; Liu, R.; Guo, Q. X. *J. Am. Chem. Soc.* **2004**, *126*, 814. (e) Li, J. N.; Fu, Y.; Liu, L.; Guo, Q. X. *Tetrahedron* **2006**, *62*, 11801. (f) Li, J. N.; Liu, L.; Fu, Y.; Guo, Q. X. *Tetrahedron* **2006**, *62*, 4453. (g) Fu, Y.; Wang, H. J.; Chong, S. S.; Guo, Q. X.; Liu, L. *J. Org. Chem.* **2009**, *74*, 810. (h) Ding, F. Z.; Smith, J. M.; Wang, H. B. *J. Org. Chem.* **2009**, *74*, 2679. (i) Martin, D.; Illa, O.; Baceiredo, A.; Bertrand, G.; Ortuno, R. M.; Branchadell, V. *J. Org. Chem.* **2005**, *70*, 5671. (j) Trummal, A.; Rummel, A.; Lippmaa, E.; Burk, P.; Koppel, I. A. *J. Phys. Chem. A* **2009**, *113*, 6206. (k) Huang, X. Y.; Wang, H. J.; Shi, J. *J. Phys. Chem. A* **2010**, *114*, 1068. (l) Trummal, A.; Rummel, A.; Lippmaa, E.; Koppel, I.; Koppel, I. A. *J. Phys. Chem. A* **2011**, *115*, 6641. (m) Lipping, L.; Kuett, A.; Kaupmees, K.; Koppel, I.; Burk, P.; Leito, I.; Koppel, I. A. *J. Phys. Chem. A* **2011**, *115*, 10335. (n) Raamat, E.; Kaupmees, K.; Ovsjannikov, G.; Trummal, A.; Kutt, A.; Saame, J.; Koppel, I.; Kaljurand, I.; Lipping, L.; Rodima, T.; Pihl, V.; Koppel, I. A.; Letio, I. *J.*

Phys. Org. Chem. **2013**, *26*, 162. (o) Yu, H. Z; Yang, Y. M.; Zhang, L.; Dang, Z. M.; Hu, G. H. *J. Phys. Chem. A* **2014**, DOI: 10.1021/jp410274n. For a recent study of calculating pK_a values in ionic liquid, see: (p) Xue, X. S.; Yang, C.; Li, X.; Cheng, J. P. *Org. Chem. Front.* **2014**, DOI: 10.1039/C3QO00070B.

(18) It should be noted that the apparent pK_a of the supramolecular complexes that formed from hydrogen-bond-donating cocatalysts and proline should depend on the value of the equilibrium constants for complex formation. For detailed discussion of hydrogen-bonding interactions between hydrogen-bond-donating cocatalysts and proline and its conjugate base anion and corresponding equilibrium constants, please see Supporting Information Tables S1−S4.

(19) It should be pointed out that the proposed TS of (*S*)-BINOL by Zhou and Shan is different from other hydrogen-bond-donating cocatalysts.

(20) Lu, T.; Wheeler, S. E. *Chem.—Eur. J.* **2013**, *19*, 15141.

(21) (a) Li, X.; Deng, H.; Luo, S.; Cheng, J. P. *Eur. J. Org. Chem.* **2008**, 4350. (b) Jakab, G.; Tancon, C.; Zhang, Z. G.; Lippert, K. M.; Schreiner, P. R. *Org. Lett.* **2012**, *14*, 1724.

(22) (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. (b) Terada, D. U. A. M. *J. Am. Chem. Soc.* **2004**, *126*, 535.

(23) For selected reviews, see: (a) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395. (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (c) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262. (d) Rueping, M.; Nachtsheim, B. J.; Ieawsuwan, W.; Atodiresei, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 6706. (e) Yu, J.; Shi, F.; Gong, L.-Z. *Acc. Chem. Res.* **2011**, *44*, 1156. (f) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nat. Chem.* **2012**, *4*, 603. (g) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518. (h) Scheffler, U.; Mahrwald, R. *Chem.—Eur. J.* **2013**, *19*, 14346.

(24) (a) Christ, P.; Lindsay, A. G.; Vormittag, S. S.; Neudörfl, J.-M.; Berkessel, A.; O'Donoghue, A. C. *Chem.—Eur. J.* **2011**, *17*, 8254. (b) Kaupmees, K.; Tolstoluzhsky, N.; Raja, S.; Rueping, M.; Leito, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 11569.

(25) Yamamoto, D. N. A. H. *J. Am. Chem. Soc.* **2006**, *128*, 9626.

(26) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245.

(27) (a) García-García, P.; Lay, F.; García-García, P.; Rabalakos, C.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 4363. (b) Treskow, M.; Neudörfl, J.; Giernoth, R. *Eur. J. Org. Chem.* **2009**, 3693. (c) Berkessel, A.; Christ, P.; Leconte, N.; Neudörfl, J. M.; Schäfer, M. *Eur. J. Org. Chem.* **2010**, 5165. (d) Momiyama, N.; Yamamoto, H. *J. Am .Chem. Soc.* **2005**, *127*, 1080. (e) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (f) Zhou, W.; Xu, L.-W.; Li, L.; Yang, L.; Xia, C.-G. *Eur. J. Org. Chem.* **2006**, *2006*, 5225. (g) Hatano, M.; Maki, T.; Moriyama, K.; Arinobe, M.; Ishihara, K. *J. Am. Chem. Soc.* **2008**, *130*, 16858. (h) Vellalath, S.; Čorić, I.; List, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 9749.

(28) (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080. (b) Hashimoto, T.; Hirose, M.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 7556. (c) Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 10054. (d) Hashimoto, T.; Kimura, H.; Maruoka, K. *Tetrahedron: Asymmetry* **2010**, *21*, 1187. (e) Hashimoto, T.; Kimura, H.; Maruoka, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 6844. (f) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642. (g) Hashimoto, T.; Isobe, S.; Callens, C. K. A.; Maruoka, K. *Tetrahedron* **2012**, *68*, 7630. (h) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 7279. (i) Chang, M.; Nisha, M.; Diana, X. S.; Daniel, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 14084.

(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, N. J.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision B.01; Gaussian, Inc.: Wallingford, CT, 2009.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03*, revision C.01; Gaussian, Inc.: Wallingford, CT, 2004.

(31) Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2009**, *113*, 6378.