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Computational Study on the Acidic Constants of Chiral Brønsted Acids in Dimethyl Sulfoxide

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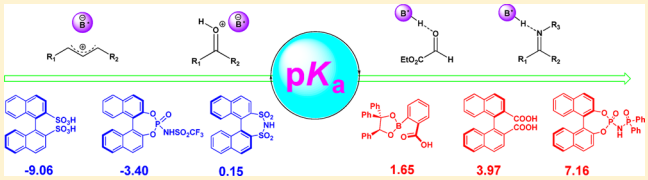
Supporting Information

ABSTRACT: The pK_a values of a series of chiral Brønsted acids, including *N*-triflylphosphoramides, bis(sulfonyl)imides, bis(sulfuryl)imides, dicarboxylic acids, sulfonic acids, and *N*-phosphinyl phosphoramides, were predicted by using the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method in DMSO. The results revealed that the calculated pK_a values ranged from −9.06 to 12.18 for different types of acids. The influence of acidic strength on reactivity and stereoselectivity was discussed using the calculated acidity data. Given that the choice of catalyst with appropriate acidity is the primary condition, several new catalyst candidates were designed by calculating corresponding pK_a values of parent acids.



INTRODUCTION

For centuries, acids and bases have acted as powerful catalysts in countless chemical transformations in chemical and biological processes occurring in nature, in industrial manufacturing, and in the laboratory.[1] In the field of organocatalysis, which is the third pillar in chiral catalyst families, organic Brønsted acids play an important role in a variety of stereospecific C−C and C−X bond formations.[2] Since the chiral phosphoric acids derived from 1,1′-bi-2-naphthol (BINOL) have been introduced into organocatalysis by Akiyama[3] and Terada,[4] the development of strong or super strong Brønsted acids catalysis has been continuously studied and has enabled great progress in the last 10 years.[2−14]

It is well-known that a catalyst with appropriate acidity plays an essential role in the activation of a corresponding substrate. If we look closely into the above-mentioned Brønsted acid catalysts, especially in consideration of acidity, it is not difficult to find that the strategy in which modulating the acidity of chiral catalysts by qualitative analogy with known inorganic or organic acids (Scheme 1) was applied in the design of new Brønsted acid catalysts.[14] Actually, the similar acidity of phosphoric acids to $(EtO)_2P(O)OH$ (pK_a: 1.3 in water)[15] is considered in the initial design of this new class of Brønsted acids by Akiyama.[3] Subsequently, to activate less basic substrates, the strong electron-withdrawing groups were introduced by Yamamoto to develop a strong BINOL-derived acid, *N*-triflylphosphoramides (NTPAs),[7a] considering that pK_a of *N*-triflyl benzamide (11.06 in acetonitrile) is much lower than that of benzoic acid (21.51 in acetonitrile).[16] To further increase the acidity of NTPAs, sulfur- and selenium-substituted NTPAs were synthesized by Yamamoto according to acidic sequence of PhOH (18.0), PhSH (10.3), and PhSeH (7.1) in DMSO.[17] Similarly, Toste[6] applied a dithiophosphoric acid to catalyze the additions of dienes and allenes. List[8a] and Giernoth[8b] developed BINOL-based disulfonimides (BINBAM) according to the stronger acidity of triflymide (Tf_2NH) than that of triflic acid (TfOH). In addition, the Brønsted/Lewis acid-assisted Brønsted acid (BBA, LBA) tactic involved in intermolecular interaction is another strategy used to enhance acidity.[10,14e,18] In this context, several stronger acids, such as aryl glycolic acids,[10a] axially chiral dicarboxylic acids (BINCA),[10b] borylbenzoic acid,[18a] and BINOL-derived disulfonic acid (BINSA),[11b] were successfully applied to a number of asymmetric transformations.

For the purposes of comparing catalytic behaviors and understanding mechanisms of Brønsted acid catalysis, the knowledge of accurate acidities (pK_a) of the acids is highly demanded, which is also helpful in the rational design of new catalysts. In past years, many chemists have devoted themselves to develop various methods to measure pK_a values in molecular/ionic solvents.[19] As a result, the pK_a values of a large number of compounds were determined in water, DMSO, acetonitrile (AN), and other organic solvents,[20] from which many chemical aspects benefit.[21−26] Historically, the studies on equilibrium acidity have led to a series of important discoveries, including the Brønsted relationship,[22] the Hammett equation[23], and the Taft equation.[24] Nowadays, the concept of pK_a has potential application for interpretation of relationships between the acidity of a catalyst and stereoselectivity again.[25−27] Furthermore, as mentioned above, the comparison of acidic differences is a very effective tactic to design new catalysts, to develop new asymmetric reactions, and to diagnose mechanism.[14]

It is not surprising that pK_a values of important molecules, especially widely used organocatalysts, have received significant

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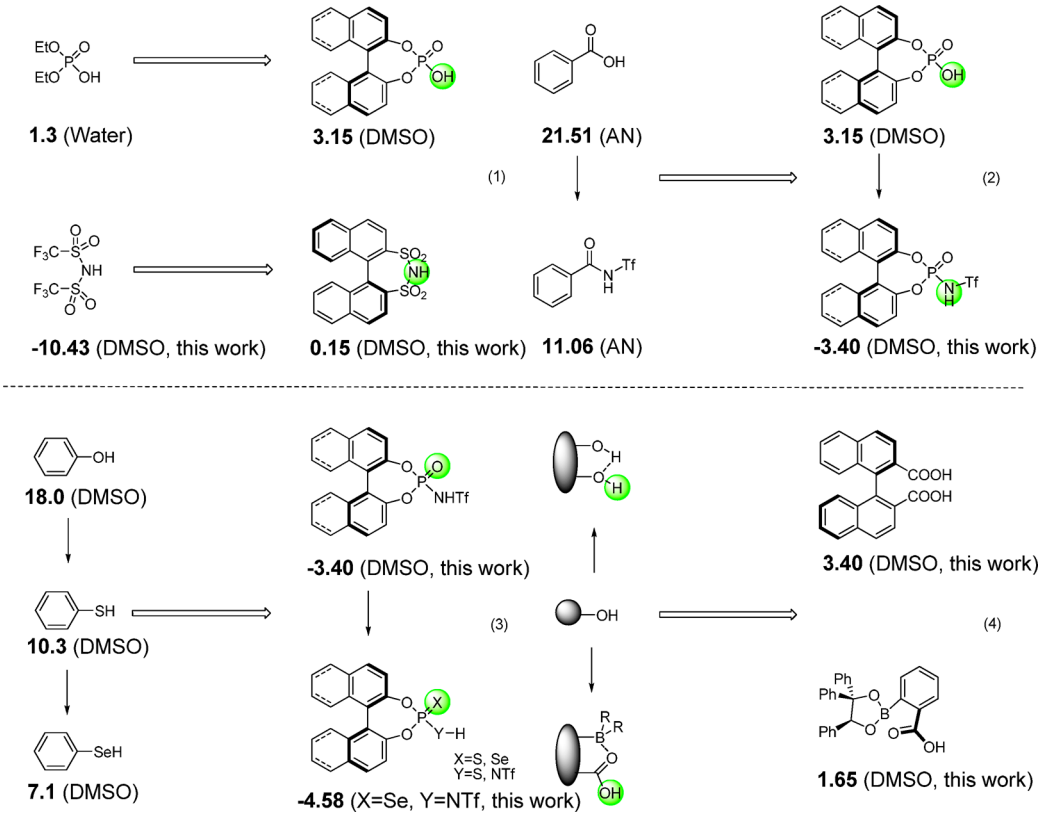
Scheme 1. Development of New Chiral Brønsted Acids by Regulating Acidity



attention.[27−37] In 2007, Cheng established an acidity scale of the *N*-heterocyclic carbine (NHC) precursors, 1,3-dialkylimidazolium salts (pK_a: 19.7−23.4), in DMSO solution.[28] In 2012, Smith and O'Donoghue estimated that the pK_a range of NHC organocatalyst precursors is 16.5−18.5 in aqueous solution by means of kinetic method.[29] Cheng, Luo[27a], and Schreiner[30] reported the determination of popular (thio)urea organocatalysts in DMSO, and they found the pK_a values cover a range from 8 to 20. Mattson developed internal Lewis acid-assisted ureas and determined the pK_a range to be from 7.5 to 16.0.[31] Berkessel and O'Donoghue[32] reported their measurement of chiral Brønsted acid catalysts (e.g., phosphoric acids, 2.63−4.12) in DMSO solution. Seebach[33] synthesized some α, α, α', α'-tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) derived chiral Brønsted acids and reported their pK_as in a mixture of MeO$(CH_2)_2$OH and water. Leito and coworkers reported a number of excellent work on pK_a determination in AN and other organic solvents.[34−37] They have determined many important molecules, such as chiral Brønsted acids,[34] super acids,[35] organosuperbases[36], and triaryl phosphines.[37] Although exciting progress has been achieved, these valuable data sets were determined in various mediums (i.e., DMSO, AN, water), making them somewhat inconvenient for usage. Furthermore, the problem of pK_a measurements for super-strong acids is still another issue, which is worth discussing carefully.[38]

On the other hand, the rapid development of computational chemistry makes the accurate prediction of pK_a values for organic acids in solution a reality.[39−44] Protocols have been developed to account for the solvation effects required for predicting dissociation equilibrium in solution.[42,43] This provided another attractive route for obtaining valuable pK_a values for the molecules concerned.[44]

For a long time, this group has focused on the field of fundamental bond energetics in classic organic solvents, experimentally and theoretically.[19h,27,28,41,45,48] Recently, the research area of physical-organic-oriented organocatalysis has attracted our interest.[40e,46] In the present study, a number of strong Brønsted acids were evaluated for acidic strength through theoretical calculation. By virtue of pK_a values, we would like to reveal the relationship between structure and acidity. Furthermore, the rule of the acidity connected to reaction activity and design of new organocatalyst candidates was also discussed. The results are presented below.

RESULTS AND DISCUSSION

In our recent work,[40e] the acidities of chiral phosphoric acid organocatalysts were calculated with the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method. It was found this method can predict pK_a of (O−H) acids with a precision of about 0.5 pK_a units. For the purpose of setting up a pK_a scale including more chiral Brønsted acids in one specific solvent (e.g., DMSO), we expected this protocol to be suitable for predicting pK_a values of nitrogen acids (N−H) in DMSO. A direct way to verify the reliability of this method is to compare predicted values with experimental data in DMSO. Unfortunately, only limited chiral strong Brønsted acids involving nitrogen acids have been reported.[32,34] Berkessel and O'Donoghue reported only one NTPA pK_a value and two pK_a values for JINGLES in DMSO.[32] Rueping and Leito reported seven NTPA pK_a values and one pK_a for JINGLES in AN.[34] This led us to the idea that converting the pK_a values in AN to pK_a values in DMSO in light of certain rules would be

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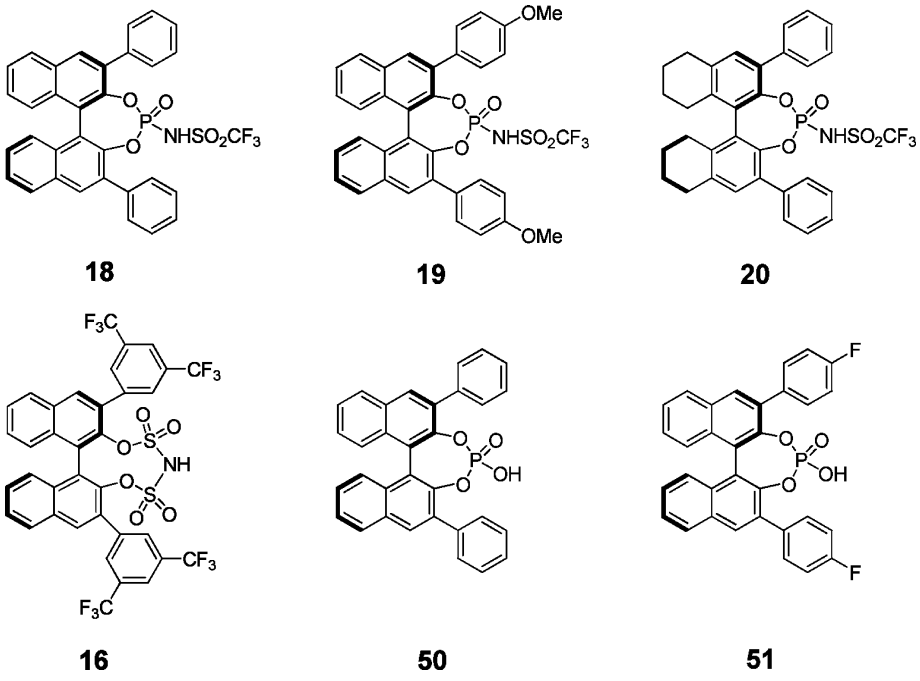

18 19 20

16 50 51

Figure 1. Acids for validation of the calculation method.

helpful. Some previous studies described a linear relationship of the pK_a values between AN and DMSO for weak acids.[16,21,48] For strong acids, it is well-known that medium and leveling effects limit the direct acidity determination of very strong acids (for DMSO, this limitation is around −5).[21] In 2006, Leito determined many neutral acids in AN and found this correlation may extend to strong acids (two acids with pK_a values below zero).[16] To make sure that this relationship is reliable for strong acids, further measurements in both DMSO and AN solutions are necessary. At this stage, three strategies are utilized to ensure reliability of our calculations (Figure 1, Tables 1 and 2). One strategy is to compare calculated pK_a^{DMSO} values with the pK_a values derived from experimental pK_a^{AN} according to the linear correlation for the test chiral acids (Figure 1). The second strategy is to directly calculate pK_a values in AN under identical conditions and to examine the difference between those values and experimental pK_a^{AN} values (Table 1). The last strategy is to calculate several achiral N−H acids in DMSO and AN under identical conditions (Table 2).

Table 1. Performance of SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) Method in pK_a Predictions in DMSO and AN

acid	pK_a^{DMSO} (calcd)[a]	pK_a^{DMSO}[b]	pK_a^{AN} (calcd)[c]	pK_a^{AN} (exptl)[d]
18	**-3.36**	−3.60	**6.04**	6.4
19	**-3.08**	−3.60	**6.31**	6.4
20	**-2.22**	−3.30	**7.13**	6.7
16	**-3.67**	−4.83	**5.54**	5.2
50	**3.33**[e]	2.81	**12.86**	12.7
51	**3.24**[e]	2.61	**12.81**	12.5
MUE[f]	0.7		0.3	

[a]Calculated by SMD/M06-2x/6-311++G (2df,2p)//B3LYP/6-31+G-(d)in DMSO. The solvation free energy of the proton in DMSO is −268.34 kcal/mol.[47] [b]Derived from experimental pK_a values in AN[34] through pK_a(DMSO) = (pK_a(AN) − 9.94)/0.982.[48] [c]Calculated by SMD/M06-2x/6-311++ G(2df,2p)//B3LYP/6-31+G(d)in AN. The solvation free energy of the proton in AN is −255.2 kcal/mol.[49] [d]Experimental data from ref 34. [e]pK_a values from ref 40e. [f]MUE is the mean unsigned error.

Table 2. Performance of SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) Method in pK_a Predictions in DMSO and AN for Achiral N−H Acids

acid	pK_a^{DMSO} (calcd)[a]	pK_a^{DMSO} (exptl)[b]	pK_a^{AN} (calcd)[c]	pK_a^{AN} (exptl)[d]
$TfNH_2$ (**52**)	**9.05**	9.7	**18.42**	
Tf_2NH (**53**)	**-10.43**	2.4	**-0.99**	0.3
$PhSO_2NH_2$ (**54**)	**16.86**	16.1	**26.20**	24.61
$PhSO_2NHTf$ (**55**)	**-3.24**		**6.10**	6.02

[a]Calculated by SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) in DMSO. The solvation free energies of the proton in DMSO is −268.34 kcal/mol.[47] [b]Experimental data for acid **52** and **54** from ref 53; data for acid **53** from ref 50a. [c]Calculated by SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) in AN. The solvation free energy of the proton in AN is −255.2 kcal/mol.[49] [d]Experimental data from refs 35b, 20d, and 16.

As shown in Table 1 (columns 2 and 3), we found that the calculated pK_a values in DMSO by means of the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method are consistent with the derived pK_a values from experimental data in AN for chiral Brønsted acids. The MUE is below 1 pK_a unit. Furthermore, this method also predicted pK_a values for N−H, O−H acids with rather high precision in AN (columns 4 and 5 in Table 1). From Table 2, we can see that the predicted pK_a values of sulfamides in AN were consistent with experiment data. As for pK_a values in DMSO, the predicted pK_a values of weak acids **52** and **54** are in good agreement with the experimental data. The pK_a of strong acid **53** was predicted as −10.43, which is more negative than the experimental value of 2.4. Although pK_a of Tf_2NH was reported to be 2.4 in DMSO according to the literature,[50a] recent studies on super acids in gas and solution phases revealed the acidic strength of Tf_2NH should be more acidic than the above-mentioned value.[35b,50b−d]

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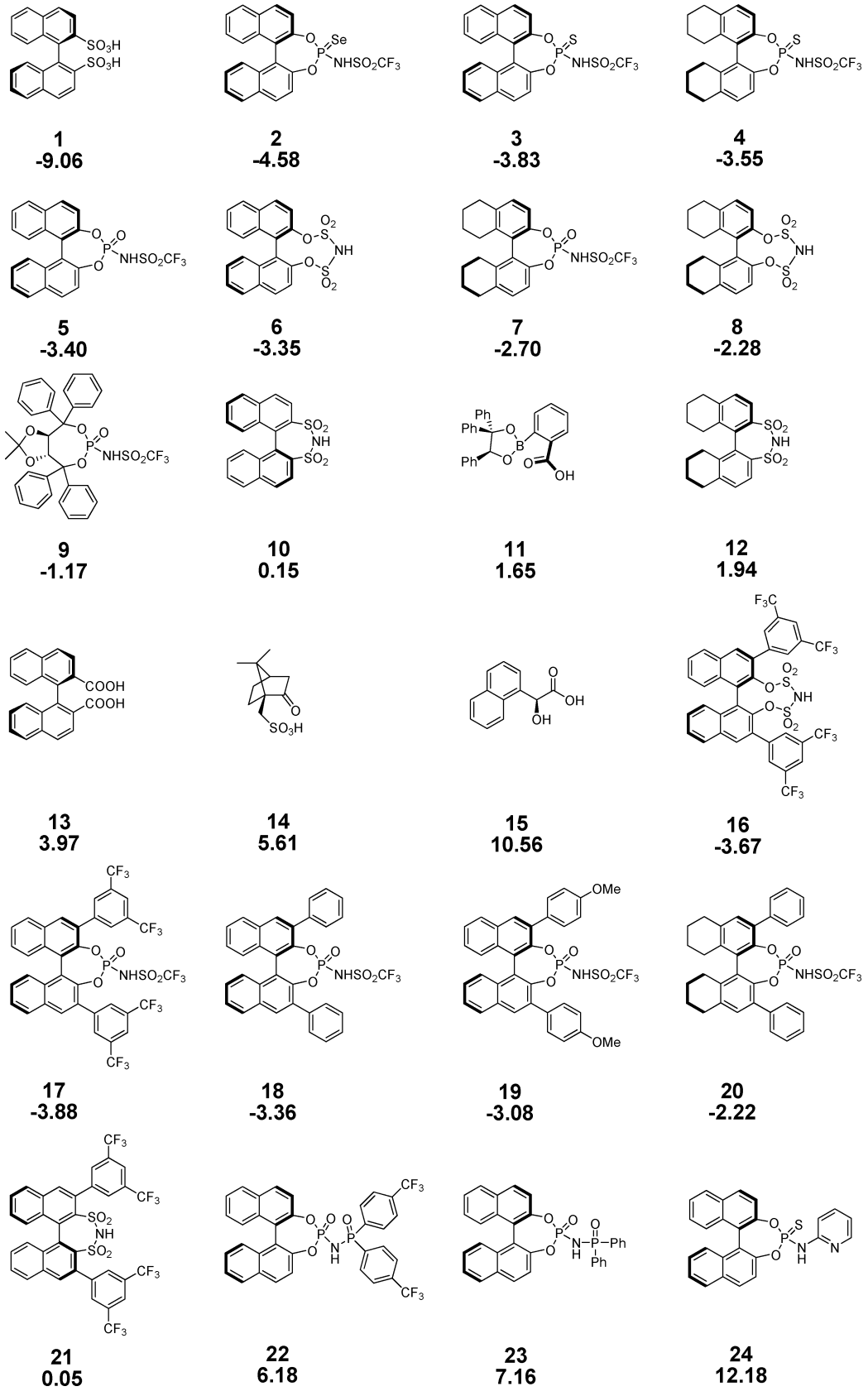

Figure 2. Calculated pK_a values of strong Brønsted acids in DMSO.

The gas-phase acidity of Tf_2NH (286.5 kcal/mol) is stronger than that of Picric acid (302.8 kcal/mol) by 16.3 kcal/mol. Acidity of Tf_2NH (pK_a: 0.3) is stronger than that of Picric acid (11.0) by 10.7 pK_a units in AN. The pK_a of Picric acid is −1.0 in DMSO.[20e] Given the above factors, this value of Tf_2NH should be more negative than that of Picric acid in DMSO.

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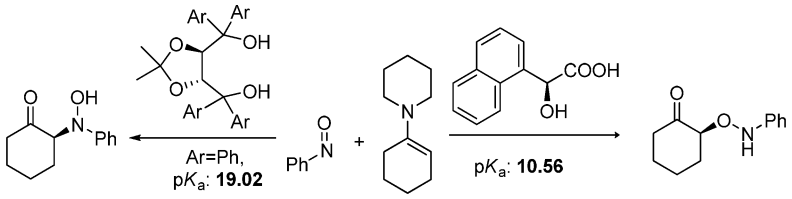
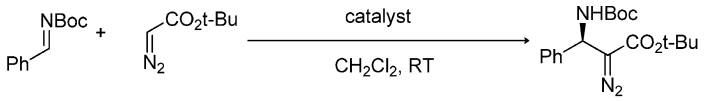
Scheme 2. Effect of Acidity on Regioselectivity in Nitroso Aldol Reaction



Scheme 3. Effect of Acidity on Dicarboxylic Acid-Catalyzed Mannich Reaction



cat			
pK_a	~ 11	3.15	3.97
time	40h	0.5h	40h
yield(%)	3	17 (22, by-product)	41

However, the above-mentioned leveling effects[21] make the direct determination of real acidity for such strong acid in DMSO impossible. The predicted pK_a value (−10.43) should be treated as an extrapolated value, as should pK_a values predicted for some other super acids (e.g., acid **1**) in this study. Though all of the above calculations are mainly based on known pK_a values for relative weak acids (pK_as above zero) in DMSO, this protocol (SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d)) still provided an opportunity to estimate acidity strength for strong acids.

With the established calculation method, the pK_a values of many recently emerged strong chiral Brønsted acids were calculated (Figure 2). In general, the acidities of the calculated acids cover a range from −9.06 to 12.18. The strength sequence is BINSAs (**1**) > NTPAs (**5**) > JINGLEs (**6**) > BINBAMs (**10**) > borylbenzoic acids (**11**) > BINOL-derived phosphoric acids (BPAs) > BINCAs (**13**) > camphorsulfonic acids (CSAs, **14**) > *N*-phosphinyl phosphoramines (NPPAs) (**22**) > glycolic acids (**15**), according to the types of acids. Further inspection of the data from the acids' structures, regardless of phosphoramides, bis(sulfonyl)imides, or bis(sulfuryl)imides, shows that the acidic strength largely depends on the carbon framework, which is consistent with the acidity study of phosphoric acids.[40e] For example, the pK_a values of **5**, **7**, and **9** are −3.40, −2.70, and −1.17, respectively. Another obvious regularity is that the enhanced capacity of the negative charge of the P = X (X = O, S, Se) group leads to more acidic acids; the pK_a values of **5**, **3**, and **2** are −3.40, −3.83, and −4.58, respectively.

Among specific acids, BINSAs were predicted as the strongest acids. For example, the pK_a of nonsubstituted disulfonic acid **1** is −9.06. It is not difficult to find that the intramolecular interactions, such as Lewis acid−base pair and hydrogen bonding, will enhance acidity. The acidity of boronate ester assisted carboxylic acid (**11**, 1.65)[18a,d] is stronger than that of benzoic acid (11.0) by about 9 pK_a units. Similarly, the formation of intramolecular hydrogen bond makes the acidic strength of BINCAs (**13**, 3.97) similar to that of SPINOL-PAs (3.98, pK_a values of phosphoric acids taken from ref 40e, same as below) and biphenyl-2,2′-diol derived PAs (3.58).[51] This phenomenon can also be observed in the case of the glycolic acids (**15**, 10.56), of which the acidic strength is almost two orders of magnitude stronger than that of acetic acid (12.3).

With the obtained complete pK_a values for strong Brønsted acids, the applications of these acids on asymmetric transformations were discussed. Although Rueping and Nachtsheim have made an excellent summary on the achievements of BPAs and NTPAs in asymmetric catalysis from the perspective of modulating the acidity,[14a] it is still worth paying more attention to the topic of the relationship between acidic strength and reaction activity and selectivity. In 2005, Yamamoto described an acidity-dependent regio- and enantioselective nitroso aldol reaction catalyzed by TADDOL and glycolic acid (Scheme 2).[10a] The more acidic glycolic acid (**15**,10.56) coordinates with the nitrogen atom of nitrosobenzene and gives the *O*-adduct, while less acidic TADDOL (**46**, 19.02) interacts with the oxygen atom of nitrosobenzene, leading to the *N*-adduct.

Although carboxylic acids were widely used as reagents or catalysts in organic reactions,[1] the relatively weak acidity of carboxylic acids has restricted their further applications for asymmetric transformations. To solve this problem, Maruoka designed axially chiral dicarboxylic acid (**13**, 3.97), leading the way for intramolecular hydrogen bonds to enhance acidity, and successfully applied them for the asymmetric Mannich reaction of imines and diazoacetates (Scheme 3).[10b] The intermolecular hydrogen bond makes dicarboxylic acid's acidity strong enough to promote this reaction.[51] In fact, 2-naphtholic acid (pK_a

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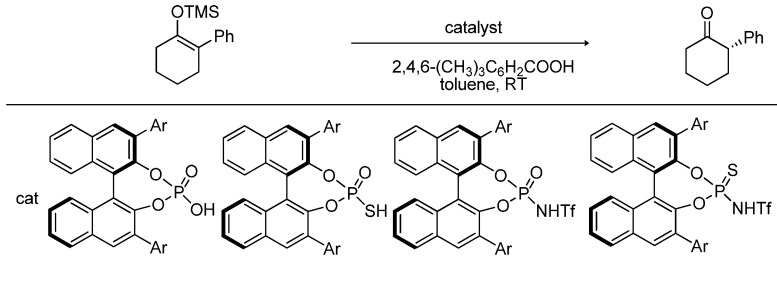
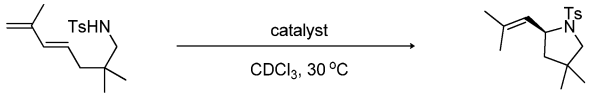
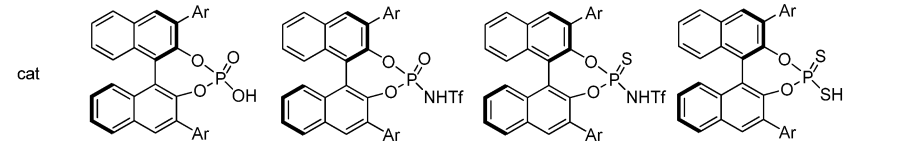
Scheme 4. Effect of Acidity on Protonation Reaction and Hydroamination of Dienes



pK_a	Ar=H, **3.15**	Ar=H, **-3.06**	Ar=H, **-3.40**	Ar=H, **-3.83**	Ar=H, **-4.58**
yield (%)	0	traces	98	97	97
ee (%)	-	-	54	78	72





pK_a	Ar=H, **3.15**	Ar=H, **-3.06**	Ar=H, **-3.83**	Ar=H, **-4.23**
yield (%)	0	0	89	91
ee (%)	-	-	46	41

around 11.0) was found to provide a trace amount of the desired product for relatively weaker acidity. BINOL-PA (3.15) led to more byproduct for relatively stronger acidity.

Another example is the enantioselective protonation of silyl enol ethers reported by Yamamoto in 2008 (Scheme 4).[17] BPA (3.15) and thio-BPA (−3.06) showed no catalytic activity for relatively weak acidity. In contrast, NTPA (**5**, −3.40) catalyzed this reaction smoothly with excellent yield and promising enantioselectivity (98% yield, 54% *ee*). To further increase the acidity, the sulfur and selenium substituted NTPAs (**3**, −3.83; and **2**, −4.58, respectively) were introduced into the acid modification. As expected, both acids gave the desired product in almost quantitative yield and moderate enantioselectivities (78% and 72% *ee*, respectively). Similar results also occurred in the asymmetric hydroamination of dienes developed by Toste in 2011 (Scheme 4).[6] BPA (3.15) and NTPA (**5**, −3.40) cannot catalyze this transformation, whereas highly acidic dithiophosphoric acid (−4.23) and thio-NTPA (**3**, −3.83) catalyzed this challenging reaction with very good yields (91% and 89%, respectively) and promising enantioselectivities (41% and 46% *ee*, respectively).

Although the role of the acidities of catalysts is essential in some cases, it should be noted that the reaction outcomes are also controlled by some other aspects, such as catalyst−substrate interactions, ion-pairing effects, and solvents. The cases about Mukaiyama aldol reaction catalyzed by BINBAM and the acetalization of aldehydes reaction catalyzed by NPPA indicated the efficiencies of these catalysts are not simply a function of Brønsted acidity (Scheme 5). Under identical condition, List found only the disulfonimide (**21**, 0.05) can catalyze the Mukaiyama aldol reaction in very high yield (>99%) and good enantioselectivity (80% *ee*).[8a] The other type acids with strong or weak acidity, such as BPA, NTPA, and BINSA, showed nearly no catalytic activity. In the case of acetalization of aldehydes, NPPAs (**22**, 6.18) exhibited highly enantioselective inducement compared to BPAs (3.15) and NTPAs (−3.06).[12]

Actually, the knowledge of exact acidities of these catalysts is of great help for understanding of present asymmetric catalytic reactions and for designing new catalysts and catalytic systems.[14] On the basis of tuning acidity, we try to design several new catalyst candidates by calculating corresponding pK_a values. The first case involves organocatalysts self-assembled in situ through noncovalent interactions.[52] This fashion is very popular in aldol reactions catalyzed by supermolecular system formed from proline and hydrogen bond donors.[53] However, up to date there is no report about this simple tactic on phosphoric acid catalytic system. In our previous study, pK_a shift of nonsubstituted phosphoric acid in toluene was calculated as a single example.[27b] Herein, we discuss the acidity of complex assembled from biphenyl-2, 2′-diol phosphoric acid and hydrogen bond donors (Figure 3). Given that the acidities of these complexes (**25**, −1.15; **26**, −2.36) are quite close to that of phosphoramides and bis(sulfonyl)imides, they should be utilized as super acids to activate less basic substrates, such as ketones and olefins.

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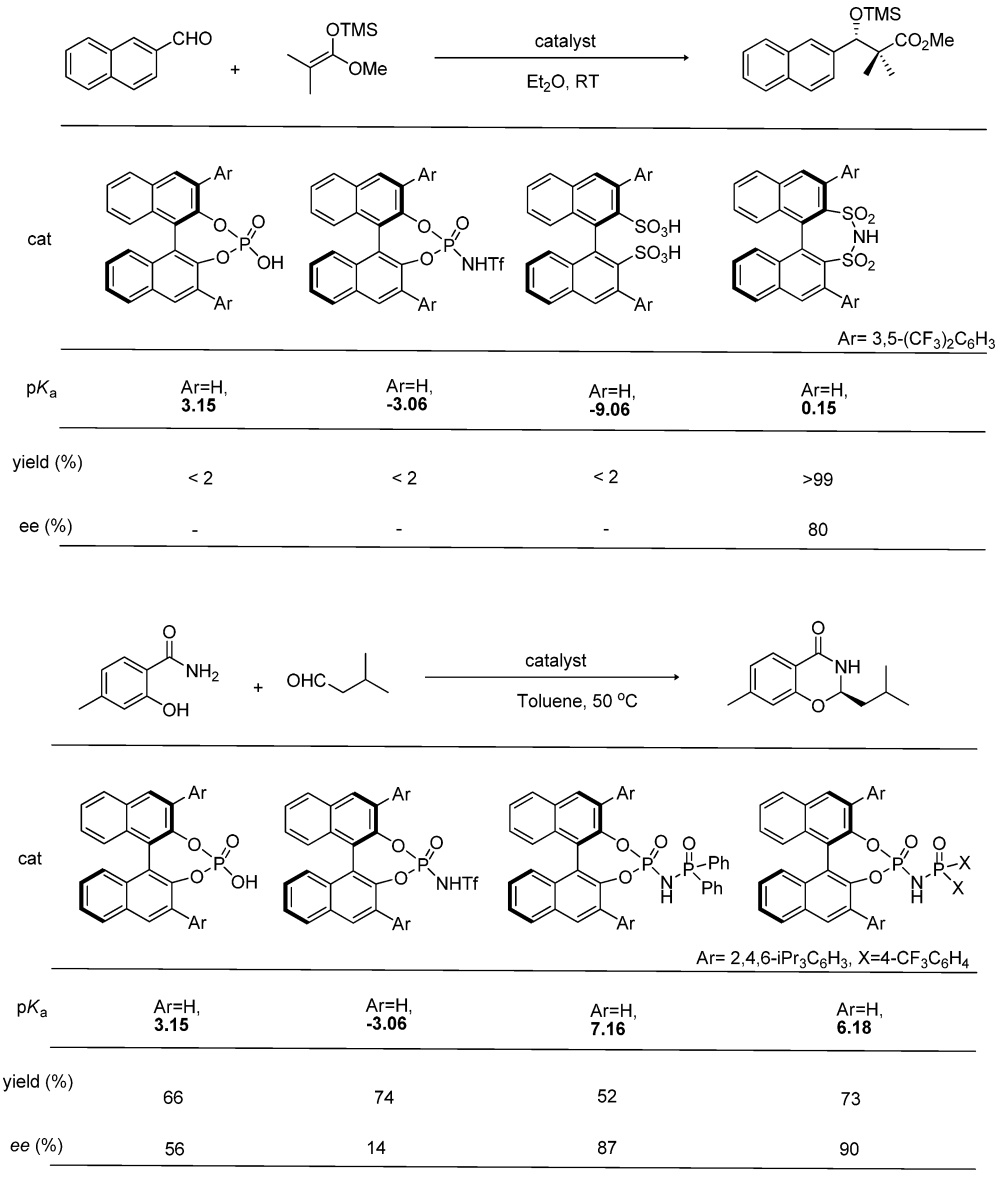
Scheme 5. Effect of Acidity on Mukaiyama Aldol and Acetalization of Aldehydes



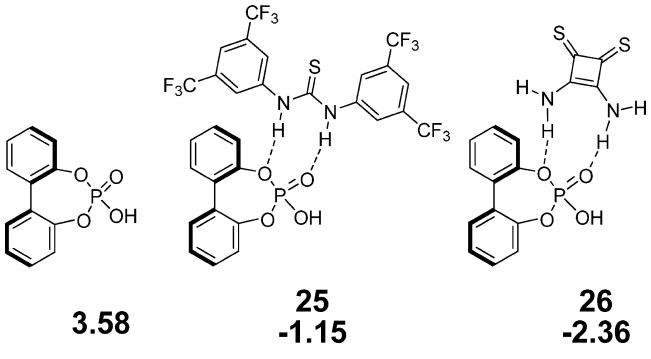


Figure 3. Calculated pK_a values of supermolecular−catalyst system.

The second case focuses on *N*-substituted phosphoramides (NPAs) (Figure 4).[54] Considering multiple modification sites in NPAs, modulating the acidity for NPAs will undoubtedly extend the scope of asymmetric transformations. Interestingly, the acidity of acids **28** (3.47) and **27** (3.76) were predicted to be similar to BINOL-PA (3.15), indicating these types of acids may be utilized to explore some new asymmetric reactions. The acidity of these acids can be further adjusted by introducing election-withdrawing groups to the *N*-substituted position. For example, the pK_a of pentafluorophenyl NPA **40** is 0.47.

Another efficient strategy is aiming at new catalysts with new chiral scaffold and/or new acidic groups. As a result, the designed Brønsted acids and pK_a values of corresponding parent acids are listed in Figure 5. Because phosphoric acids bearing 2,2′-diphenyl-[3,3′-biphenanthrene]-4,4′-diol (VAPOL)[5f] and 1.1′-spirobiindane-7,7′-diol (SPINOL)[5j] have achieved many asymmetric transformations,[2] the designed acids with VAPOL (e.g., **33**, −3.57; **39**, 0.26) and SPINOL (e.g., **32**, −3.76; **34**, −3.34) should be employed in the acid catalyzed reactions. As mentioned above, acidity of *N*-triflyl benzamide is much stronger than that of benzoic acid. Acidities of *N*-triflyl bisbenzamindes with different scaffolds were predicted stronger than those of dicarboxylic acids (e.g., **36**, −2.36; vs **13**, 3.97). According to their different pK_a values, the potential application on asymmetric transformations could be expected. For instance, because of the similar pK_a of

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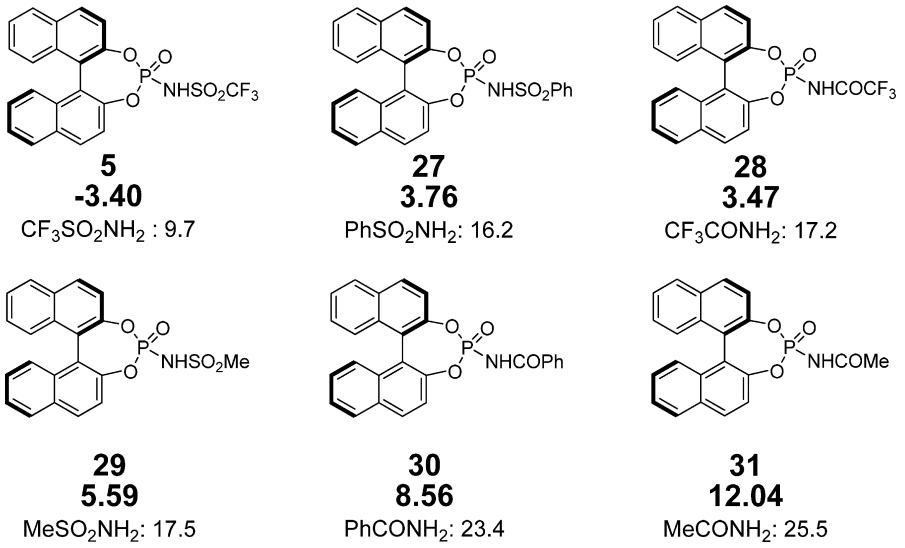

Figure 4. Calculated pK_a values of *N*-substituted phosphoramides in DMSO.

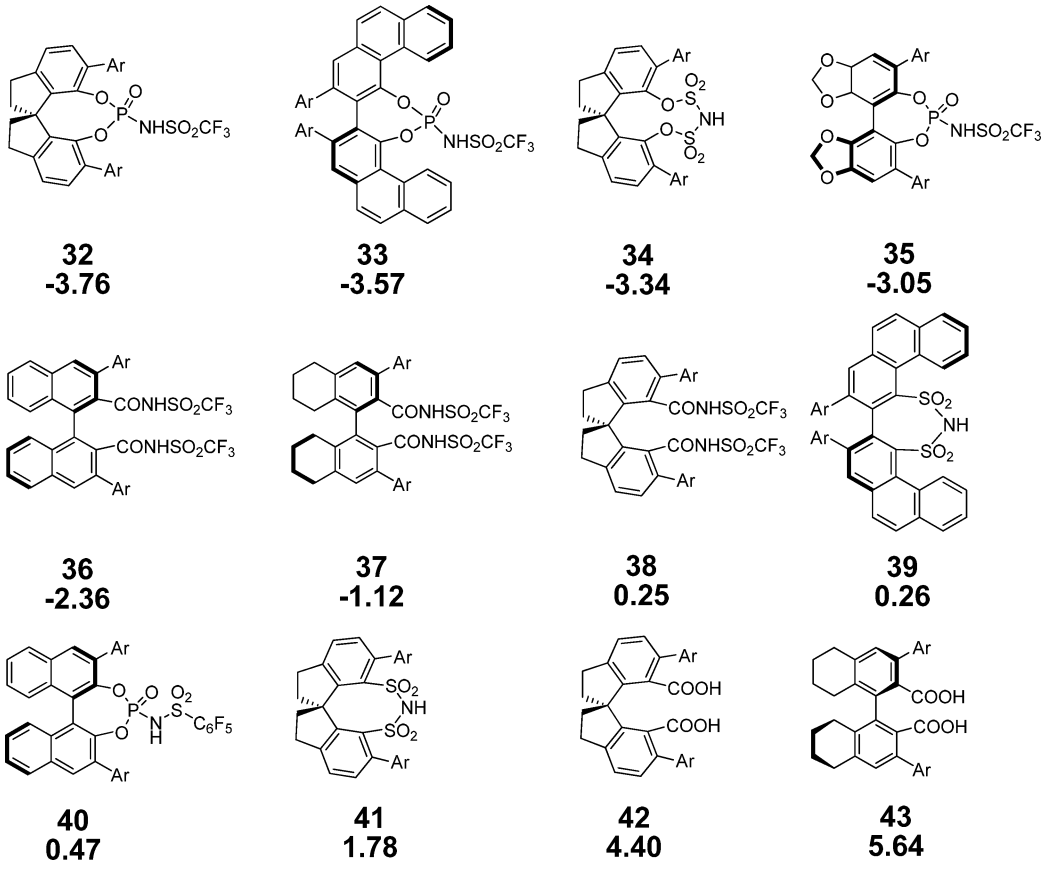

Figure 5. Design of new catalysts and calculated corresponding pK_a values (Ar = H).

bisbenzamides (e.g., **38**, 0.25) to that of acid **10** (0.15), acid **38** may be a catalyst candidate in the reactions promoted by acid **10**. And it can be expected that some new asymmetric chemical transformations may be achieved by employment of these designed acids.

Chiral diols are another widely used class of Brønsted acids.[55,56] Unfortunately, there are limited examples of pK_a values of diols in literature.[32,33,56] It is worth noting that predicting pK_a values of these diols will aid in establishing mechanisms of action and may serve other purposes. Therefore, acidities of some diols (**44**−**49**) were also calculated. As shown in Figure 6, pK_a values of the examined diols ranged from 13.22 to 19.02, which is within the (thio)urea acidity range.[27a,30] It is obvious that the diols' acidities are weaker than those of the corresponding phosphoric acids and *N*-triflylphosphoramides. Upon further inspection of the data, we found that previously reported rules of acidic strength depending on the scaffold, which is disclosed by phosphoric acid studies, were also applicable to diols (**44**−**46**). Furthermore, calculated acidities of organosilanols,[55b−g] which were considered as a new class of

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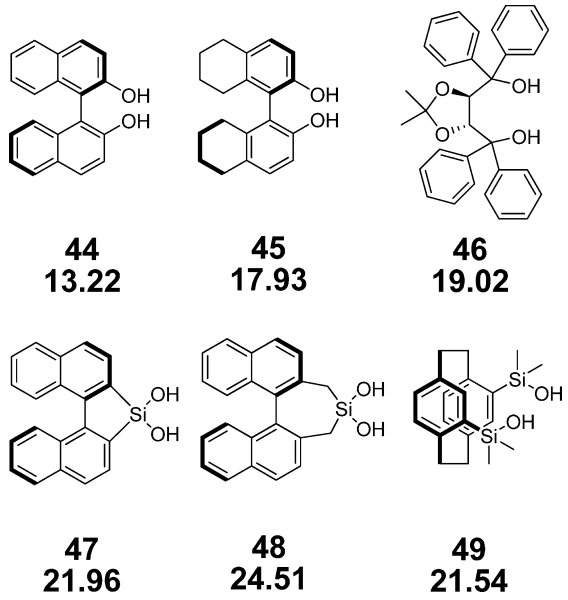


Figure 6. Calculated pK_a values of some chiral diols in DMSO.

hydrogen bond donor catalyst, were 21.96 (**47**), 24.51 (**48**), and 21.54 (**49**), respectively. To the best of our knowledge, this is the first reported case of pK_a values of chiral organosilanediols in organic solvent.[57]

CONCLUSIONS

After we applied the SMD/M06-2x/6-311++G(2df,2p)//B3LYP/6-31+G(d) method, the pK_a values of a set of chiral strong Brønsted acid catalysts in DMSO were predicted. The calculated acidities for different types of acids ranged from −9.06 to 12.18. On the basis of the fact that appropriate acidic strength of catalysts is the primary condition in choosing catalysts, an analysis of the relationship between the acidic strength of catalysts and reaction activity−selectivity was carried out by means of the calculated pK_a values. Inspired by achievements of asymmetric transformations by regulating acidity of catalyst, three tactics based on pK_a predictions were proposed to design new Brønsted acid organocatalysts. In addition, pK_a values of several widely used chiral diols were also predicted with the same calculation protocol. We hope the study of pK_a values of chiral Brønsted acids will be helpful for enriching the catalyst library, developing new catalytic asymmetric reactions, and understanding mechanisms of corresponding Brønsted acids catalyzed reactions.

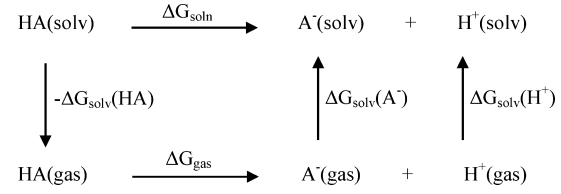
COMPUTATIONAL METHODS

The structures of all species were carried out with the Gaussian 09 packages.[58] Geometry optimizations were conducted at the B3LYP/6-31+G(d) level. The nature of the stationary points was confirmed by frequency calculations at the same level of theory. The solution phase free energy calculations were performed by virtue of SMD model at the M06-2x/6-311++G(2df,2p) level.

The direct method was applied to predict pK_a values (Scheme 6).[59,60]

As shown in Scheme 6, the free energy of acid dissociation in DMSO, ΔG_{soln}, can be obtained through eq 1. Thus, pK_a can be obtained through the thermodynamic relationship (eq 2). In the equations below, asterisks (*) indicate a standard state of 1 mol/L in any phase.[61]

Scheme 6. pK_a Calculation via the Direct Method



$$\Delta G^*_{soln} = \Delta G^*_{gas} + \Delta G^*_{solv}(A^-) + \Delta G^*_{solv}(H^+) - \Delta G^*_{solv}(HA) \quad (1)$$

$$pK_a = \frac{\Delta G^*_{soln}}{RT\ln(10)} \quad (2)$$

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates of optimized structures. 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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