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Revisiting the role of acids and hydrogen bond acceptors in enamine formation†

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A systematic investigation into the effects of acids and hydrogen bond acceptors on the reaction rates and equilibria of enamine formation is reported. Acids can accelerate the reaction but do not change the reaction equilibria. In comparison, hydrogen bond acceptors facilitate the enamine formation via their strong hydrogen bonding interaction with the water generated in the reaction.

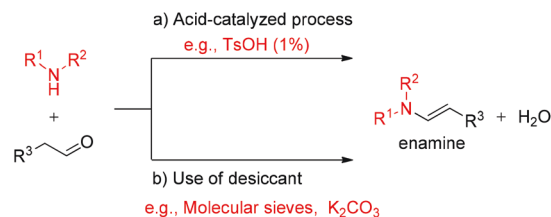
Organo-enamine catalysis is a powerful tool in asymmetric synthesis.^{1,2} The critical step in organo-enamine catalysis is the activation of the carbonyl compound *via* an enamine intermediate using a chiral secondary amine as catalyst.^{2–9} Not surprisingly, research on the structure and reactivity of enamines has been the subject of attention.^{1,2} Selected examples include Seebach and coworkers' work on X-ray structures of enamines,^{10–12} Mayr and coworkers' investigation of structure reactivity relationships,¹³ and Vilarrasa and coworkers' revelation of the influence of the structure of carbonyl compounds²² or secondary amines¹⁹ on the relative thermodynamic stabilities of the resulting enamines. Hitherto missing is a systematic study on the effects of additives such as acids or hydrogen bond acceptors on the reaction rates and equilibria of enamine formation.

There are two standard methods for enamine formation starting from amines and carbonyl compounds (Scheme 1). The most common one is the acid-catalyzed enamine formation. Water removal through azeotropic distillation is often used to complete the reaction (Scheme 1a).^{13,14} Another option is the application of desiccants (Scheme 1b), such as molecular sieves and potassium carbonate for water removal.^{15,16} The effect of acid or base on the reaction is not yet wholly apparent. Understanding their effect as additives or catalysts will help to improve enamine formation and understand the mechanism of organo-enamine catalysis. Our continuing interest in hydrogen bonding effects in organo-enamine catalysis,¹⁷ lead us now to report a systematic investigation on the effect of

acids or hydrogen bonding acceptors on the reaction rates and equilibria of enamine formation.

Since acid catalysts are commonly used in the preparation of enamines, we first investigated the effects of acids of various strengths in *d*-DMSO. It has been generally assumed that acids catalyzed this step and that there is a thermodynamic equilibrium for enamine formation starting from an aldehyde/ketone and a secondary amine.¹⁸ We found that the pK_a of an acid has only a slight influence on the reaction rate and equilibrium. We tested different acids with pK_a ranging from -14 to 7.1 (Fig. 1). As expected, these acid catalysts did not change the equilibrium of enamine formation. Although acid catalysts did accelerate the reaction, strong acids such as *p*-toluene sulfonic acid and TfOH, which are commonly used in enamine formation, are not better catalysts than much weaker acids. Weak acids like nitrophenol and bromoacetic acid enhanced the speed of the reactions, albeit slightly.

We also investigated the consequence of using a stoichiometric amount of acid (Scheme 2). First, we mixed an equimolar amount of cyclohexanone with pyrrolidine in $CDCl_3$ and found that 7% of enamine was formed after the equilibrium was reached (see ESI, section 4.4.2†). When we added an equimolar amount of nitrophenol, the equilibrium shifted, with the formed enamine converting back to the starting materials. This result indicated that the acid–base interaction between



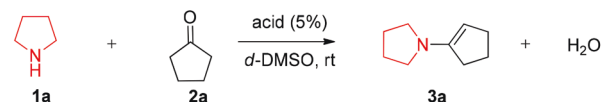
Scheme 1 Various methods for enamine formation.

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Acid	TfOH	TsOH	BrCH ₂ COOH	BzOH	<i>p</i> -NO ₂ PhOH
<i>pK_a</i>	-14	-2.1	2.86	4.2	7.1

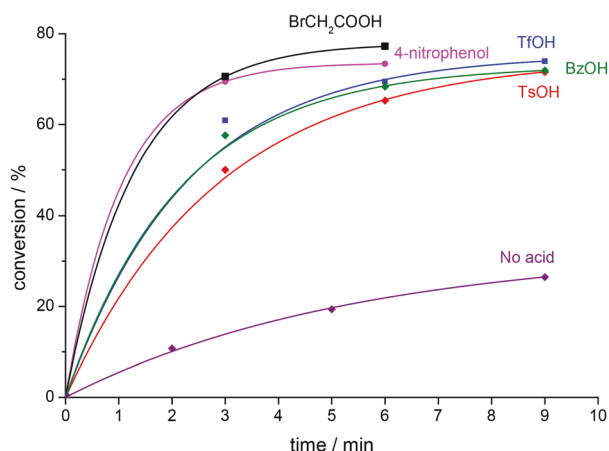
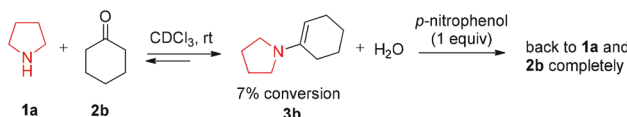


Fig. 1 Effects of acids on the enamine formation.



Scheme 2 Effect of the stoichiometric amount of acid.

pyrrolidine and the added acid was strong enough that it shifted the equilibrium towards the starting materials.

When we utilized a catalytic amount of *p*-toluene sulfonic acid (5%) in different types of solvents, we observed that acids accelerated the reaction but did not change the reaction equilibria, as expected. Interestingly though, solvents rather than acids exert significant effects on reaction rates and equilibria (Fig. 2). The reaction in *d*-DMSO reached equilibrium faster and gave higher conversion compared to reactions in common solvents such as benzene and chloroform. Vilarrasa and other groups described similar results.¹⁹ They ascribed this influence on the polarity and hygroscopic nature of the solvent.

The water generated in the formation of enamine is, as we know, a very good hydrogen bond donor. Moreover, DMSO is a very good hydrogen bond acceptor compared to solvents such as chloroform and benzene. Thus, we believe that the strong hydrogen bonding properties of water and DMSO may play an essential role in the reaction equilibrium. In 2009, Laurence and coworkers reported a comprehensive database of hydrogen-bond basicity (measured by *pK_{BHX}*).²⁰ The *pK_{BHX}* of most compounds is in the range of 1 to 5, where a bigger number indicates higher hydrogen-bond basicity.

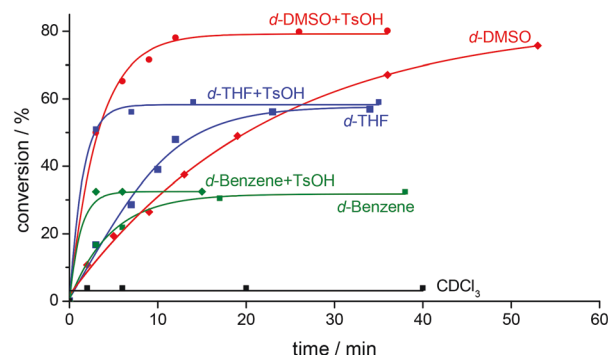
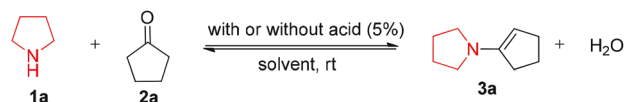
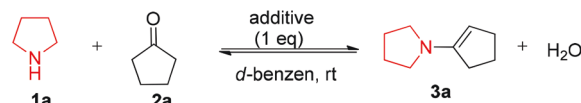


Fig. 2 Acid and solvent effects on rate and equilibrium of enamine formation.

We selected different additives with a bigger *pK_{BHX}* to see if they promoted enamine formation. We examined several good hydrogen bonding acceptors (*pK_{BHX}* > 2.5). We found that pyridine *N*-oxide (PNO, *pK_{BHX}* = 2.72), *N,N'*-dimethylpropyleneurea (DMPU, *pK_{BHX}* = 2.82), hexamethylphosphoramide (HMPA, *pK_{BHX}* = 3.60), DMSO (*pK_{BHX}* = 2.54) accelerated the reaction and shifted the equilibria towards enamine formation (Fig. 3).

We proceeded to investigate the effect of pyridine *N*-oxide (PNO) in a model reaction for enamine formation (Fig. 4). A higher conversion of enamine was obtained when more PNO



HBA	PNO	HMPA	DMSO	DMPU
<i>pK_{BHX}</i>	2.72	3.6	2.54	2.82

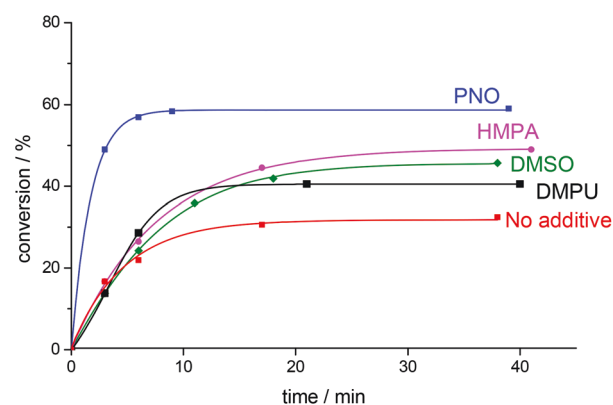


Fig. 3 Different hydrogen bond acceptors' effect on enamine formation reaction rate and equilibrium.

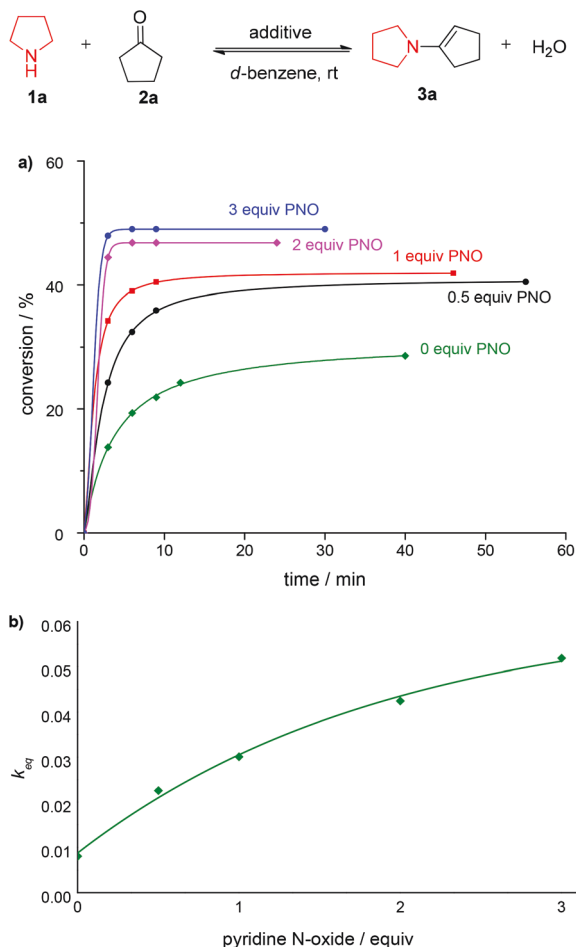


Fig. 4 (a) Effect of hydrogen bond acceptor amount on conversion of enamine formation reaction. (b) Effect of hydrogen bond acceptor amount on enamine formation equilibrium constant.

additive was used (Fig. 4a). The equilibrium constant for the formation of enamine was also calculated and was correlated with different amounts of PNO (Fig. 4b). We found a good correlation between the equilibrium constant for enamine conversion and the number of equivalents of PNO.

The effect of a hydrogen bonding acceptor on a chiral secondary amine was also tested. Jørgensen-Hayashi diarylprolinol silyl ether reagents have been shown to catalyze a variety of bond-forming reactions such as C–C, C–N, C–O, C–S, and C–halogen in high yields with excellent levels of enantioselectivity.^{8,9,21} We selected one Jørgensen-Hayashi catalyst for our enamine formation model reaction (Fig. 5) and observed that the equilibrium constant for this reaction exhibited an almost linear correlation with the amount of pyridine N-oxide.

We then conducted DFT calculations using ω B97X-D (6-31G**) in vacuum to validate the hydrogen bonding effect of hydrogen bond acceptors on enamine formation. The energy difference of hydrogen bonding between a hydrogen bonding acceptor (PNO, or DMPU) and water (Fig. 6, ΔE) was calculated. The results indicated that the energy was reduced after

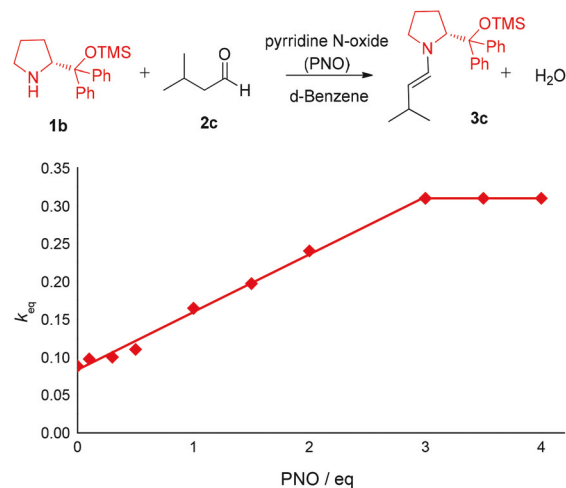


Fig. 5 Correlation of different amounts of PNO and reaction equilibrium constant of diarylprolinol silyl ether chiral enamine formation.

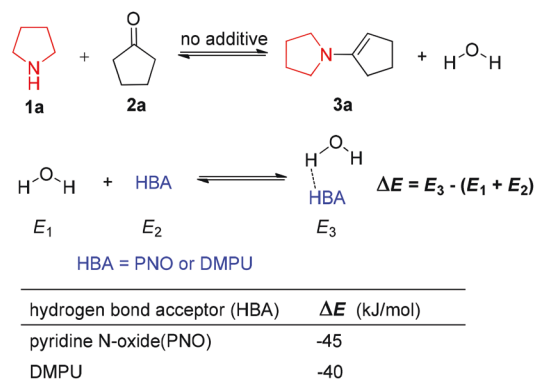
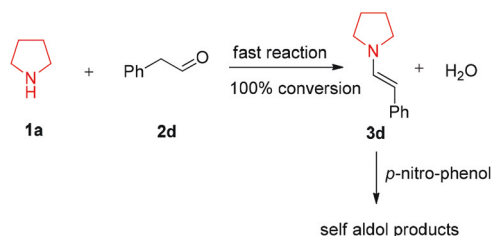


Fig. 6 Hydrogen bonding energies of water with hydrogen bond acceptors (DFT calculation with ω B97X-D-6-31G** in vacuum).

hydrogen bonding. The preferential hydrogen bonding shifts the equilibrium forward towards enamine formation.

Additionally, we investigated the formation of enamine from relatively reactive amines and aldehydes (Scheme 3). The Vilarrasa group has reported the relative thermodynamic stabilities of enamines prepared from different secondary amines and carbonyl compounds.^{19,22} This group showed that pyrrolidines with weak electron-withdrawing substituents on their α position produced the best enamine conversion.¹⁹ The



Scheme 3 Formation of reactive enamines.

Vilarrasa group has also reported a general scale for the tendency of carbonyl groups to form enamines.²² The reactions shown in Scheme 3 were too fast to measure even at low-temperature (−75 °C in THF or DCM, *in situ* NMR and IR). When equimolar amounts of phenylacetaldehyde and pyrrolidine were mixed in CDCl₃, we observed a quantitative amount of enamine (see ESI, section 4.2.1†). Moreover, when we added an equimolar amount of nitrophenol to the reaction mixture, we detected self-aldolization products. Seebach and Hayashi had also witnessed this phenomenon.¹⁸

Our studies indicate that although acids can accelerate enamine formation, this acceleration is not significant. Because acid may shift the equilibrium towards the starting material or induce a self-aldol reaction, we do not believe that the use of acids as catalysts is compelling or necessary for enamine formation.

In conclusion, we have systematically investigated the effects of acids and hydrogen bond acceptors on the reaction rate and equilibrium of enamine formation. In many cases, strong acids are not necessary for enamine formation. Besides, the use of acids may destabilize enamines. On the other hand, hydrogen bond acceptors like DMSO or pyridine *N*-oxide facilitate the formation of enamine through their strong hydrogen bonding interaction with the water formed in the reaction.

Conflicts of interest

There are no conflicts to declare.

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