Organocatalysis

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Enamine-Based Aldol Organocatalysis in Water: Are They Really "All Wet"?**

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Organocatalysis is a burgeoning field of organic synthesis that employs substoichiometric amounts of an organic compound to accelerate a reaction.[1,2] Recent advances in organocatalysis include a wide range of reactions and often enable asymmetric induction in organic solvents. In particular, the aldol reaction is a key C–C bond-forming reaction that has tremendous synthetic utility and is often the platform of choice to examine new organocatalysts. Nature has perfected the stereospecific aldol reaction by using aldolase enzymes. While these enzymes have synthetic utility, they are limited by the lack of large-scale compatibility and typically do not have broad substrate recognition.

There are several examples of small-molecule (MW<600)-organocatalyzed aldol reactions that are capable of asymmetric induction in organic solvents.[1,2] However, from a green chemistry perspective, the use of water instead of organic solvent is preferred to decrease environmental contamination. Therefore, given the synthetic utility of the asymmetric aldol reaction, there is growing interest in the identification of organocatalysts that are capable of efficiently performing this reaction in water. In this context, we note that the first de novo tailored aqueous organocatalysts with high enantioselectivities were catalytic antibodies.[3–5] The importance and utility of these biomacromolecular catalysts cannot be understated, however, alternative small-molecule-organocatalyzed reactions in water with sufficient asymmetric induction would have immense synthetic utility.

Two recent studies, one by Hayashi et al.[6] (catalysts **1**–**4**) and the other by Barbas and co-workers[7] (catalysts **5**–**6**), described asymmetric small-molecule amine catalysts that were proposed to utilize enamine intermediates in water (Figure 1). Reports of small-molecule enamine-based aldol catalysis in water are not limited to these publications and have been scattered throughout the literature over the last several years.[8–12] Furthermore, others have raised the possibility of "prebiotic" relevance; however, to date only organic solvents have been utilized, thus diminishing the strength of this argument.[9,13,14] At first glance, these developments would be significant advances in organocatalysis and green chemistry. However, the reactions are not performed under truly aqueous conditions. While each of these reports depict enamine-catalyzed aldol reactions in varying degrees of an aqueous environment, we focus here on the recent findings of Hayashi and Barbas as representative examples, as these studies directly state their reactions are performed in water. In the spirit of constructive dialogue, we draw attention to particular aspects of developing small-molecule-organocatalyzed asymmetric aldol reactions in water.

It is well established that aldol reactions can be catalyzed by a general base, and small-molecule aqueous catalysts were published as early as 1909.[15] However, to promote enantioselectivity by an enamine-based mechanism in

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[**] Comments to several reports on enamine-based organocatalysis of aldol reactions in water (Refs. [6–12]). We thank Prof. Dale L. Boger for helpful discussions during the preparation of this manuscript.

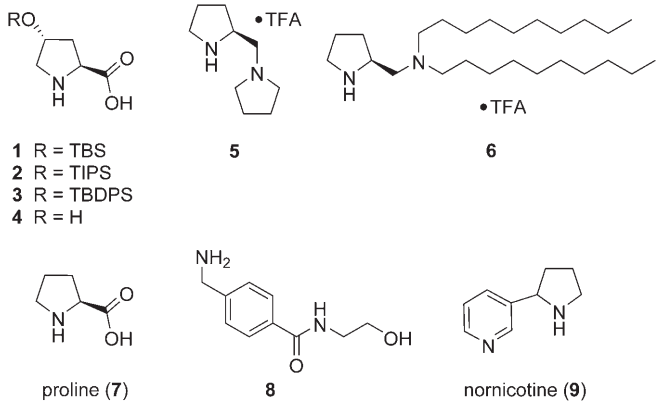

Figure 1. Structures of amine catalysts used in organocatalytic aldol reactions. TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl; TBDPS = *tert*-butyldiphenylsilyl; TFA = trifluoroacetic acid.

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water, general-base catalysis must be minimized. Therefore, buffered conditions are a prerequisite. To our knowledge, the only research groups to have demonstrated small-molecule enamine-based aldol reactions under buffered aqueous conditions are those of Reymond,[16,17] Joyce,[18] and our own.[19] Specifically, Reymond and Chen found that proline (**7**), benzylic amine **8**, and a variety of amino acids can function as catalysts under buffered aqueous conditions, while Joyce and Oberhuber described aldol catalysis on a DNA template using a variety of small-molecule amines, including lysine and putrecine. We reported that nornicotine (**9**), a nicotine metabolite and minor component of tobacco smoke, catalyzes aldol reactions under buffered aqueous conditions (pH 7–8).[19] Modest asymmetric induction was observed by using enantiopure nornicotine (20% *ee*), while no asymmetric induction was reported by Reymond[16,17] or Joyce.[18]

Enamine formation in water is counterintuitive (Figure 2). However, the nornicotine–acetone enamine can be

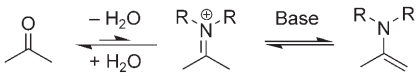

Figure 2. Enamine formation in water.

observed in D_2O by ^1H NMR spectroscopy.[20] In fact, no organic solvent was necessary for enamine formation with nornicotine, although small amounts of DMSO (5%) were used to dissolve the reactants.[19–25] Kinetic analysis verified the presence of least one water molecule at or before the rate-determining step of this reaction,[20] and density functional calculations proposed a two-step model that utilizes a water molecule in each high-energy transition state (Figure 3).[23] With the exception of our own work and that of Reymond[16,17] and Joyce,[18] there is no direct evidence in other reports that enamine catalysis occurs in water.

A fundamental phenomenon overlooked by some researchers is that when a basic compound is placed in non-buffered water, the pH value of the solution will increase. Catalysts **1**–**9** have a primary or secondary amine necessary for enamine-based catalysis and each of

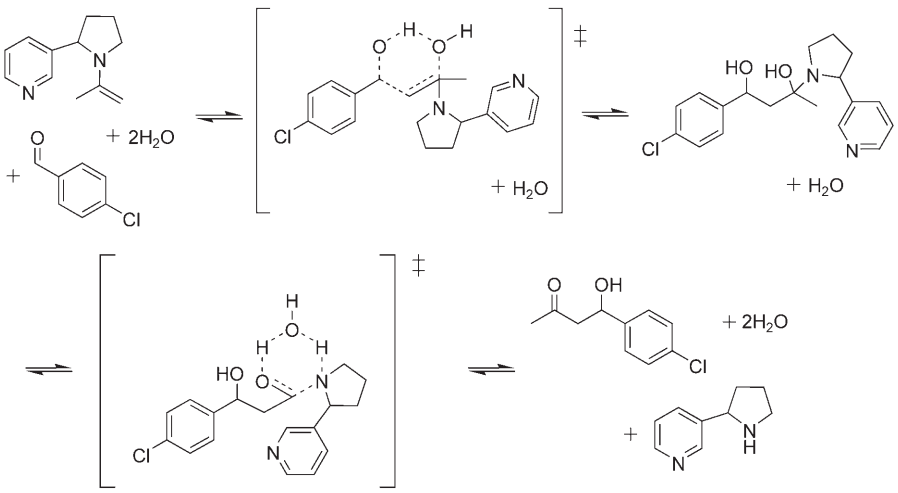

Figure 3. Proposed mechanism for nornicotine-catalyzed aqueous aldol reaction based on density functional calculations and kinetic isotope effect studies.

these amines has $pK_a \approx 11$. If catalysts **5** or **6** are placed in non-buffered water, the pH value of the solution will increase and catalysis of the aldol reaction will in turn be dominated by a general-base mechanism.[26] For example, a typical procedure using catalyst **6**[7] involved 50 μmol of catalyst in 1.0 mL of water (50 mM solution of catalyst). Assuming a pK_a value of 11 for **6**, simple calculations lead to a pH value of 11.8 for the reaction mixture. Catalysis observed for **5** in non-buffered water is also attributable to general-base catalysis. Consequently, it was not until TFA or other strong acids were added that high diastereo- and enantioselectivities were observed, characteristic of an enamine mechanism. Catalysts **1**–**4** include a carboxylic acid in addition to the amine and, therefore, are likely zwitterionic in water. However, Hayashi et al. used approximately the same amount of catalyst (60 μmol) as Barbas and co-workers reported in their study, although in much less water (0.32 mL); in fact, there is less water than either of the reactants (0.6 mL of benzaldehyde and 3.1 mL of cyclohexanone).[6] Given that there is a tenfold excess of cyclohexanone over water, cyclohexanone should be regarded as the solvent or the reaction should be deemed neat with 9% water. With this amount of water, the reaction should not be considered aqueous. Furthermore, from a green chemistry perspective the cyclohexanone waste is essentially organic solvent waste unless the cyclohexanone is easily recycled; therefore, the reaction appears to have little green chemistry benefit.

We would argue that catalysis in any of these reports is not really occurring in water. The solubility of catalysts **1**–**3** and **6** in water at concentrations of 50 mM is expected to be minimal given the large hydrophobic groups that each contain. Furthermore, when compared with the common cationic detergent C_{16}TAB, which has a critical micellar concentration of 1 mM, these amphilic catalysts are likely to form micelles at the concentrations reported. Contrary to the title of the study by Hayashi et al., a few drops of water does not constitute that the reaction is performed in water (see above).[6] Indeed, it is stated that the reaction mixture is biphasic in the discussion. The report by Barbas and co-workers makes note of the limited solubility of catalyst **6** and accurately portrays catalysis, describing the reaction mixture as an emulsion.[7] Yet, these reactions are not truly in water as opposed to being isolated from water.

Conditions for catalyst **6** to provide enantiomeric enrichment requires a stoichometric amount of TFA relative to catalyst **6**. However, the reaction then takes approximately five times longer to reach completion.[7] The increased reaction rate and lack of enantiomeric enrichment without the addition of acid suggests that catalysis in the absence of TFA is dominated by a general-base mechanism. As the addition of a stoichiometric amount of TFA (or any acid) favors the formation of micelles by

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increasing the amphiphilic character of the catalysts, the enantiomeric enrichment observed with the addition of TFA occurs from catalysis in what is accurately described as a "concentrated organic phase", whereby the hydrophobicity of catalyst **6** is concluded to sequester the enamine intermediate and concomitant transition state(s) away from water.[7] The reaction is not really in water and is likely occurring in a micelle, resulting in the exclusion of water and generating a formally biphasic reaction mixture.

These results can be compared to the pioneering study by Breslow and Rideout in which the rate of a Diels–Alder reaction was increased by performing the reaction in water.[27] In that case, hydrophobic molecules are forced into close contact,[28] in contrast to recent amine-catalyzed aldol reactions in which the reactants are excluded from water by the amphiphilic catalyst. Perhaps a more accurate term for these organocatalyzed reactions in concentrated organic phases or micelles would be the "on water" concept recently introduced by Sharpless et al.[29] Nonetheless, the study by Hayashi et al. is not carried out in water and the study by Barbas and co-workers is carried out with an emulsion. Thus, a more accurate description should be used to delineate these systems from truly aqueous systems.

The latest reports of enamine-based aldol reactions in water have prompted us to highlight some aspects in this active topic of research. We do not wish to diminish the significance of the enantiomeric enrichment observed in the reports by Barbas and co-workers and by Hayashi et al., nor do we wish to argue against catalysis occurring in concentrated or isolated organic environments. However, there is a clear distinction between what is described in this work and others where enamine-based catalysis is actually occurring in a buffered milieu.[16–24] Finally, no small-molecule (MW < 600) catalysts have provided synthetically relevant enantioselectivity in aqueous buffered solution—a hallmark of catalytic antibodies and biologically derived catalysts such as enzymes. We recognize the reports of "minimal aldolases",[30–32] yet these polypeptides cannot be considered small molecules. Thus, a clear challenge remains: Can small-molecule catalysts be developed to catalyze reactions in buffered solution with suitable asymmetric induction?

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