Enamine-based Aldol Organocatalysis in Water: Are They Really ‘All Wet’?


Organocatalysis, the use of organic catalysts instead of metal catalysts to accelerate chemical reactions, is receiving increasing levels of attention in stereoselective chemistry. One of the key advantages of organocatalysis is minimizing the environmental burden by substituting toxic and environmentally unfriendly transition metal catalysts with more benign organic catalysts.

Two prominent studies published in 2006 claimed to take the next step in organocatalysis by using water as the solvent instead of a typical organic solvent, further minimizing the environmental burden of stereoselective aldol catalysis. Upon further examination, we discovered that the claims of these research papers were exaggerated and inaccurate. We found that the reaction mixtures were biphasic (i.e., the reaction occurred in the organic layer and not in the aqueous layer). In one case, one reactant was in significant excess, essentially serving as the solvent, and the reaction mixture contained less water than either reactant.

The correspondence that we published in late 2006 outlined the difference between organocatalysis dissolved in water (i.e., where water is the solvent) and a reaction conducted merely in the presence of water. We provided an example of a truly aqueous organocatalyzed reaction based on research in our laboratory at The Scripps Research Institute that demonstrated that nornicotine, a byproduct of tobacco and minor component in tobacco smoke, is an effective catalyst of aldol reactions using 95% to 100% water as the solvent. Furthermore, density functional calculations and kinetic isotope effect studies indicate that at least one molecule of water is used in the catalytic mechanism.

After the publication of our correspondence in Angewandte Chemie, the conversation shifted to distinguish truly aqueous organocatalysis from biphasic reactions conducted in the presence of water. Researchers started using the terms “on water” and “in the presence of water” to accurately describe biphasic reaction mixtures.