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Water: the most versatile and nature's friendly media in asymmetric organocatalyzed direct aldol reactions

Sudipto Bhowmick, Anirban Mondal, Ayndrila Ghosh, Kartick C. Bhowmick *

Division of Organic Synthesis, Department of Chemistry, Visva-Bharati (A Central University), Bolpur, West Bengal 731 235, India

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ABSTRACT

The aldol reaction is an excellent synthetic tool to construct β-hydroxy carbonyl skeletons. The asymmetric version of this reaction has been developed for the synthesis of enantiomerically enriched β-hydroxy carbonyl motifs, which can be extended toward the stereogenic construction of complex polyol architectures. L-Proline and other organic molecules are known to catalyze asymmetric direct aldol reactions in various solvents. Most asymmetric organocatalyzed direct aldol reactions occur in organic media, although some aldol reactions have been carried out in water, either as a co-solvent or additive. The development of highly diastereo- and enantioselective organocatalyzed direct aldol reactions between a wide variety of substrates in water without the contamination of any organic solvent is of great interest. Herein, we discuss organocatalysts based on L-proline, 4-hydroxy-L-proline, simple amino acids, enzymes etc., which have been so far applied in asymmetric aldol reactions in aqueous media. The present review describes the chronological development of asymmetric organocatalyzed aldol reactions in aqueous media considering both 'in water' and 'on water' concepts in each subsection.

Contents

* Corresponding author.
E-mail address: kartickc.bhowmick@visva-bharati.ac.in (K.C. Bhowmick).

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1. Introduction

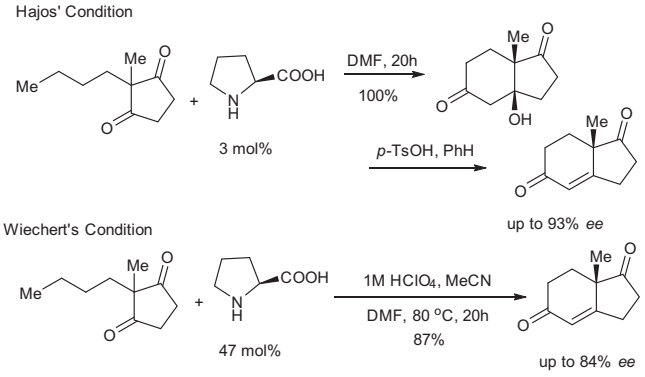
'Water', the only reaction media for all chemical transformations in biological systems, has recently become a frequent choice of solvent.[1] The growing environmental pollution due to exponential use of volatile and harmful organic solvents in chemical industries including agrochemicals, pharmaceuticals, dyes etc. has forced chemists to focus on alternative solvents such as water.[1] Other than environmental issues, water is the safest and least expensive solvent, it also does not require the prerequisite to dry the starting materials before a reaction which will be carried out in aqueous media. With respect to many organic solvents, water possesses a very high dielectric constant and cohesive energy density, resulting in completely new chemical reactivity.[1b,c] Moreover, the appearances of various interactions (hydrophobicity, acidity, hydrogen bonding, polarity etc.,) between the substrates and water molecules have a significant impact on the expected outcome of the selectivity for a product.[1c] It is evident from the literature that the very first organic synthesis urea synthesis in 1828 by Wöhler,[2] and many other named reactions such as Baeyer–Villiger oxidation,[3] the Curtius rearrangement,[4] the Pictet–Spengler reaction,[5] the Sandmeyer reaction,[6] the Wolff-Kischner reduction,[7] and the Hofmann degradation,[8] which we consider to be the foundation of organic synthesis, were first developed in aqueous media. The significant development of organometallic chemistry in the early years of last century has been responsible for the radical transition of the reaction medium from aqueous solvents to organic solvents.[9] The aforementioned multifaceted advantages of water for organic synthesis have long been neglected until the rate acceleration observation by Breslow in a Diels–Alder reaction in 1980, which is very often marked as the turning point of the reverse journey.[10] In addition to the use of water as reaction media, the employment of metal-free organic molecules as catalysts for asymmetric organic synthesis, inspired by the impetus gained through study of type-I aldolase antibodies, has appeared to be a better environmentally benign chemical technology.[11] Organocatalysts are readily available, less toxic, mostly inexpensive, stable to moisture and air, and more importantly show a very broad substrate scope unlike enzymes. However, performing organocatalytic reactions in aqueous media does not necessarily mean an absolutely 'green' chemical technology.[12] Nevertheless, asymmetric organocatalysis in aqueous media, a relatively greener synthetic tool, is gaining an edge over the other available techniques for the synthesis of chiral building blocks which are in ever growing demand for the total synthesis of natural products and for applications in medicinal chemistry.[13] Our present focus of discussion on asymmetric organocatalyzed synthesis in aqueous media is on the aldol reaction, which is the most extensively studied carbon–carbon bond-forming reaction in this area. The present review will describe the chronological development of asymmetric organocatalyzed aldol reactions in aqueous media in each subsection.

2. Enantioselective organocatalytic aldol reactions

The aldol reaction, which was first discovered by Wurtz in 1872, remains an unparallelled synthetic tool to construct the β-hydroxy carbonyl skeletons.[14] The asymmetric version of this reaction has been developed for the construction of enantiomerically enriched β-hydroxy carbonyl motifs, which could be extended toward the stereoselective construction of complex polyol architectures.[15] The aldol reaction is also crucial for the biosynthesis of carbohydrates, keto acids, and some amino acids.[16] L-Proline and other organic molecules are known to catalyze asymmetric direct aldol reactions in various solvents.[17,18] Asymmetric organocatalyzed direct aldol reactions occur in organic media, some of which have been carried out in water, either as the co-solvent or additive.[17] However, the prime objective is to develop highly diastereo- and enantioselective organocatalyzed direct aldol reactions between a wide array of substrates in water without the contamination of any organic solvent, a path which was independently initiated by Barbas et al. and Hayashi et al. in 2006.[19] Herein, we discuss all types of organocatalysts based on L-proline, 4-hydroxy-L-proline, simple amino acids, enzymes etc. which have so far been applied in asymmetric aldol reactions in aqueous media.

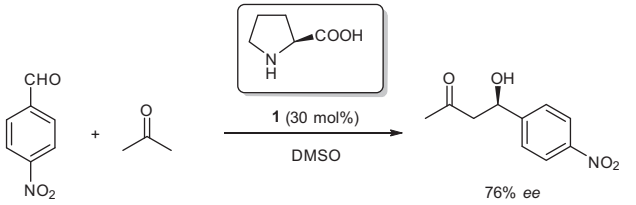
3. Proline catalysts

In the beginning of the 1970s, Hajos et al. and Wiechert et al. independently reported the L-proline catalyzed intramolecular direct aldol reaction in anhydrous DMF (Scheme 1).[20]



Scheme 1.

Three decades later, the first organocatalytic intermolecular direct aldol reaction was reported by List and Barbas in organic media (Scheme 2).[21]



Scheme 2.

When a small amount of water (less than 4 vol %) was added into the reaction mixture the enantiomeric excess of the aldol product was found to be affected negligibly, however 20 vol % water resulted in a substantial decrease in enantioselectivity.[22]

L-Proline **1** catalyzed aldol reactions of acetone or 4-thianone with different aldehydes were accelerated by the addition of (1–10) equiv of water in DMF media and good enantioselectivity was obtained.[23] Pihko et al. demonstrated that an appropriate volume of water in an L-proline catalyzed aldol reaction can remarkably enhance the rate as well as the enantioselectivity, a significant improvement of the work reported by Barbas et al.

In 2010, Sunoj et al. revealed after DFT theoretical studies that among the two models (Houk–List model and Seebach–Eschenmoser model) proposed as the mechanism of L-proline catalyzed intermolecular aldol reaction, the Houk–List transition model involving an enamine intermediate for the stereoselective C–C bond formation was the most accurate model (Schemes 3 and 4).[24]