Asymmetric aldol reactions catalyzed by tryptophan in water†

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Tryptophan was shown to be able to catalyze direct aldol reactions between various cyclic ketones and aromatic aldehydes in water with high enantioselectivity.

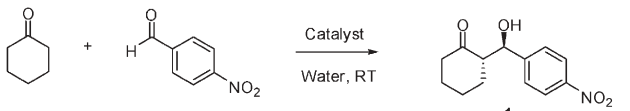
The use of water as a solvent for chemical reactions is of great current interest,[1] mainly due to the low cost, safety and environmentally benign nature of water. Ever since the seminal contributions from Breslow and Grieco in the early 1980s on the positive effects of water on the Diels–Alder reaction,[2] water has gained increasing recognition as a solvent for organic reactions.

In aqueous organic reactions, it is generally assumed that homogeneous solution is essential for an efficient chemical reaction. Therefore, a central theme of aqueous organic chemistry is to promote solubility of reactants and reagents in these reactions. However, some recent discoveries demonstrated that homogeneity is not essential for organic reactions to occur in aqueous media. Sharpless and co-workers reported several examples showing that substantial rate acceleration could be achieved in aqueous suspension, under what they denoted as "on water" conditions.[3] The groups of Takabe, Barbas and Hayashi showed that the direct asymmetric aldol reactions could be carried out with excellent enantioselectivity in water by employing proline-derived organocatalysts.[4] Although the high reactivity of such inhomogeneous aqueous reactions is not fully understood, it is quite clear that hydrophobic effects play a pivotal role in promoting reactivity.[5]

The aldol reaction is one of the most important carbon–carbon bond forming reactions,[6] yielding the β-hydroxy carbonyl structural scaffold which is frequently found in natural product and medicinal agents. In nature, Class I aldolases catalyze highly efficient and enantioselective aldol reactions in water *via* the enamine mechanism. It is highly desirable to develop a chemical system that can mimic the action of aldolase and effect direct aldol reactions in water with excellent stereocontrol. Organocatalysis has experienced a renaissance in recent years.[7] There have been numerous reports on direct, asymmetric aldol reactions catalyzed by proline[8] and its structural analogues[7a,9] that utilize the enamine mechanism. Proline is arguably the most efficient and versatile small organic "enzyme" that catalyzes a wide range of organic transformations.[10] However, the proline-catalyzed aldol reactions can only afford high enantioselectivity in organic solvents. The presence of a large amount of water resulted in the formation of products with low or no enantioselectivity.[11] Although it was shown in List's initial report[8a] that primary and acyclic secondary amino acids failed to catalyze aldol reactions, Cordova and co-workers elegantly demonstrated that acyclic amino acids could effect the direct aldol reaction in DMSO with the addition of water.[12] We reasoned that a hydrophobic amino acid might be an efficient aldol catalyst in aqueous media. It is hypothesized that a hydrophobic catalyst should associate strongly with hydrophobic reactants in water. As a result of optimizing hydrophobic interactions, the transition state may be better defined and high enantioselectivity might be achieved. Herein, we report our preliminary finding that tryptophan is an efficient catalyst for the direct aldol reaction in water.

In our initial screenings, we investigated the catalytic effects of a number of natural amino acids in the direct aldol reactions between cyclohexanone and *p*-nitrobenzaldehyde in water (Table 1). Alanine was not very effective, and only low conversion was achieved after about 4 days (entry 1). Increasing the size of the amino acid side chain led to the improved catalytic effects. Valine, leucine and isoleucine showed improved catalysis, although the rates of the reactions were modest (entries 2–4). While tyrosine was ineffective (entry 5), phenylalanine was a good catalyst, enabling

Table 1 Screening of organocatalysts for the asymmetric aldol reactions of cyclohexanone and *p*-nitrobenzaldehyde in water[a]



1

Entry	Catalyst	Time (h)	Yield[b] (%)	*anti:syn*[c]	ee[d] (%)
1	L-Alanine	109	32	12 : 1	0
2	L-Valine	144	84	4 : 1	65
3	L-Leucine	96	81	3 : 1	79
4	L-Isoleucine	96	67	5 : 1	83
5	L-Tyrosine	28	<5	—	—
6	L-Phenylalanine	48	75	4 : 1	70
7	L-Tryptophan	23	85	4 : 1	86
8	L-Tryptophan methylester	89	57	1.3 : 1	6
9	L-Tryptamine	24	82	1 : 1	0
10[e]	L-Tryptophan	36	82	4 : 1	74
11[f]	L-Tryptophan	36	85	5 : 1	92
12[g]	L-Tryptophan	19	91	5 : 1	96

[a] The reactions were performed with *p*-nitrobenzaldehyde (0.5 mmol), cyclohexanone (2.5 mmol) and catalyst (0.05 mmol) in water (5 mmol) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the products. [d] ee of *anti*-isomer. [e] 0.5 mmol of cyclohexanone was used. [f] 5.0 mol% catalyst was used. [g] 10 mmol of water was used.

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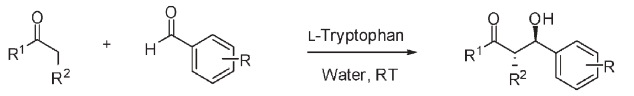
† Electronic supplementary information (ESI) available: experimental details. See DOI: 10.1039/b606154k

Table 2 L-Tryptophan-catalyzed direct aldol reactions of various substrates in water[a]



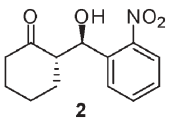
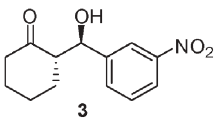
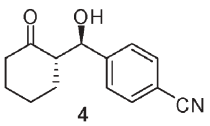
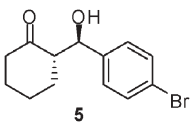
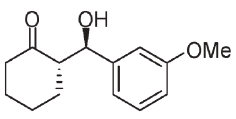
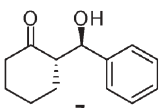
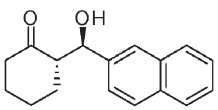
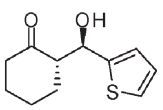
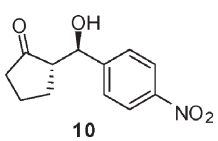
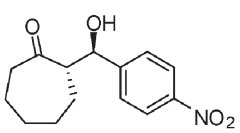
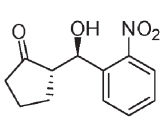
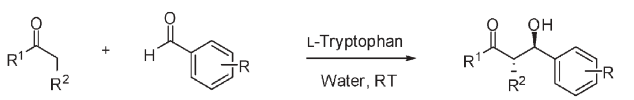
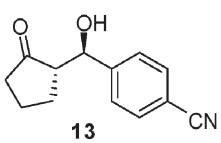
Entry	Product	Time (h)	Yield[c] (%)	*anti:syn*[b]	ee[d] (%)
1	 **2**	24	77	52 : 1	90
2	 **3**	24	79	20 : 1	89
3	 **4**	24	78	6 : 1	88
4	 **5**	96	66	17 : 1	82
5	 **6**	42	42	10 : 1	87
6	 **7**	92	47	78 : 1	89
7	 **9**	24	57	16 : 1	92
8	 **8**	72	49	5 : 1	85
9[e]	 **10**	12	74	1 : 1	78
10	 **11**	24	73	3 : 2	84
11	 **12**	48	99	1 : 4	82

Table 2 L-Tryptophan-catalyzed direct aldol reactions of various substrates in water [a] (*Continued*)



Entry	Product	Time (h)	Yield[c] (%)	*anti:syn*[b]	ee[d] (%)
12	 **13**	20	94	1 : 1	81

[a] The reactions were performed with aldehyde (0.5 mmol), cyclohexanone (2.5 mmol) and tryptophan (0.05 mmol) in water (5 mmol) at room temperature. [b] Determined by ^{1}H NMR analysis of the products. [c] Isolated yield. [d] ee of *anti*-isomer. [e] 5 mmol water was used.

the completion of the reaction in 48 hours (entry 6). Tryptophan was the best catalyst in our trials (entry 7). With 10 mol% tryptophan, the desired aldol product was obtained in an 85% yield with an 86% ee in less than one day.‡ The tryptophan carboxylic acid function seemed to be important for the asymmetric induction, as the tryptophan methyl ester virtually afforded a racemic product (entry 8). Tryptamine also catalyzed the reaction (entry 9). The influence of the substrate ratio, catalyst loading and the water quantity was next examined. Lowering the amount of cyclohexanone resulted in a substantial decrease in the product ee value (entry 10). If only 5 mol% tryptophan was used, the reaction was completed after 36 hours with a slight increase in ee (entry 11). The use of 20 equivalents of water with respect to the aldehyde gave the best result, as the desired aldol product was obtained in excellent yield and with excellent enantiomeric selectivity (entry 12). In a typical aldol reaction that was catalyzed by tryptophan, the reaction mixture was a two phase system where tryptophan was suspended. It is clear that a homogeneous solution is not essential for an efficient reaction to occur.

The scope of such tryptophan-catalyzed direct aldol reactions in water was evaluated with a variety of cyclic ketones and aryl aldehydes (Table 2). Generally, electron-poor aromatic aldehydes are excellent substrates, with the reactions typically going to completion within one day (entries 1 to 3). Less reactive aromatic aldehydes (entries 4 to 7) and a heteroaromatic aldehyde (entry 8) were also suitable—enantioselectivity remained very good, even though longer reaction times were required. The ring size of the cyclic ketones could be varied—both cyclopentanone and cycloheptanone could serve as donors (entries 9 to 12). However, the current method has its limitations, since we were unable to extend it to include simple acyclic ketones and non-aromatic aldehydes. It seems that the hydrophobic nature of the substrates is essential for an efficient reaction to take place. For instance, the direct aldol reaction between acetone and *p*-nitrobenzaldehye in water in the presence of tryptophan did not yield any desired product.

To understand the stereochemical outcome of our reactions, we proposed that the tryptophan-catalyzed aldol reaction occurs *via* the transition state[13] as depicted in Fig. 1, whereby the enamine attacks the aldehyde from the *Re* face, leading to the formation of the major stereoisomer. We believe that the aromatic side chain of

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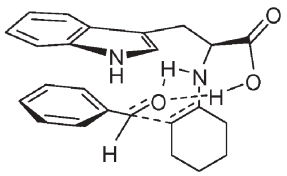

Fig. 1 Proposed transition state model.

tryptophan facilitates the formation of a hydrophobic core with other hydrophobic substrates in water, thus promoting the aldol reaction *in aqua*. The π–π stacking interaction may also be involved in our reactions.

In summary, we demonstrated for the first time that a natural hydrophobic amino acid with a primary amino function could be directly used as an efficient aldol catalyst in aqueous media. The described reactions are highly enantioselective, environmentally benign and operationally simple. We believe that our finding will open up a new avenue for the design of highly effective organocatalysts in water. The further development of relevant catalytic systems and the full extension of the scope of this chemistry are in progress in our laboratory, and will be reported in due course.

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Notes and references

‡ *Typical Procedure for the* L*-tryptophan catalyzed aldol reaction in water:* L-Tryptophan (0.0102 g, 0.05 mmol) was added to a suspension of *p*-nitrobenzaldehyde (0.0755 g, 0.5 mmol), cyclohexanone (0.25 ml, 2.5 mmol) and water (0.18 ml, 10 mmol) at room temperature. The reaction mixture was stirred for 19 hours. The reaction mixture was extracted with dichloromethane several times, and the combined organic extracts were concentrated under the reduced pressure. Flash chromatography on silica gel (ethyl acetate : hexane = 1 : 3) afforded **1** as a yellow solid (0.1137 g, 91%).

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