

# Asymmetric autocatalytic Mannich reaction in the presence of water and its implication in prebiotic chemistry†

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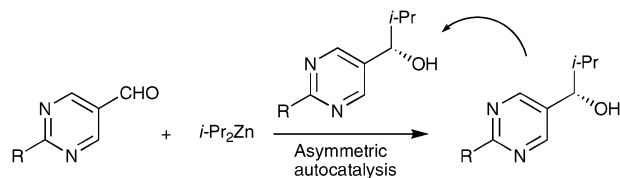
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**An enantioselective process in which the chiral Mannich product acts as a catalyst for its own replication was observed to occur under various conditions in the presence of water.**

The origin of homochirality of biomolecules, such as L-amino acids and D-sugars, remains an intriguing question for scientists.<sup>1</sup> Thus asymmetric autoinductive and autocatalytic reactions may hold significant clues to the generation and propagation of optical activity on Earth. In a catalytic enantioselective autoinductive mechanism the chiral product may participate in a product–catalyst complex that serves as an improved catalyst for the reaction. Wynberg *et al.* described the first example of such enantioselective autoinductive reactions during their studies of organolithium addition to aldehydes.<sup>2</sup> Danda *et al.* also observed autoinductive effects in the formation of chiral cyanhydrines in the presence of a cyclic dipeptide as catalyst. This was evidenced by adding a small amount of the enantioenriched product to the cyclic dipeptide (with low ee) at the beginning of the reaction.<sup>3</sup> More recently, mechanistic investigations by Blackmond *et al.*, invoking a proline-product species, revealed a temporal increase of the enantiomeric excess of the product of the proline mediated aminoxylation and amination of aldehydes.<sup>4</sup> Furthermore, several Diels–Alder reactions were found to be autoinduced by a cyclic adduct, and a catalytic enantioselective and autoinductive aldol reaction in the presence of Ti<sup>IV</sup>(Binol) complexes was described by Figadère *et al.*<sup>5</sup> Despite this progress, these processes still require non-negligible amounts of chiral catalyst.

The Soai reaction offered the first example of an asymmetric autocatalytic reaction. In such a process the chiral product acts as chiral catalyst for its own production with significant amplification of enantiomeric excess.<sup>6</sup> It is not necessary to separate the product from the catalyst, and the efficiency of the reaction increases as the amount of the catalyst increases without the need of any other chiral compound. The group described asymmetric autocatalysis of pyridyl alkanol and pyrimidyl alkanol; pyridyl alkanol acts as an asymmetric autocatalyst in the enantioselective addition of diisopropylzinc to 3-pyridinecarbaldehyde to afford the same pyridyl alkanol of the same absolute configuration (47% ee) with the initial asymmetric autocatalyst. Chiral 5-pyrimidyl alkanol was found to be the most significant asymmetric autocatalyst (Scheme 1). Whereas, an example of non-enzymatic self-replication has previously been evidenced for asymmetric



**Scheme 1** Autocatalytic strategies for product replication.

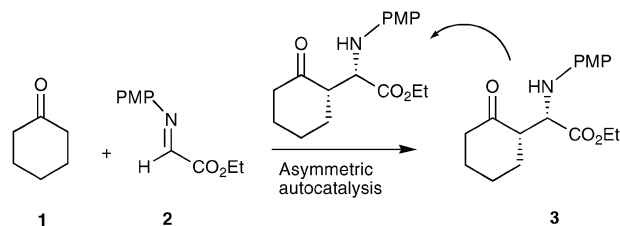
complementary oligonucleotides,<sup>7</sup> recent work has described a non-asymmetric autocatalyzed aldol reaction and competitive nonselective autocatalysis in the Baylis–Hillman reaction.<sup>8</sup>

While the Soai reaction serves as an elegant mechanistic model for the evolution of homochirality, the reaction involves dialkylzinc chemistry that requires an inert atmosphere, and is unlikely to occur in an aqueous prebiotic environment. Thus, the development of a completely new class of organocatalytic reactions,<sup>9</sup> *e.g.* the Mannich reaction,<sup>10</sup> where the product is also the catalyst, was appealing due to the possibility for a nitrogen-containing electrophile to yield an amine nucleophile capable of reproducing itself (Scheme 2).

To make the proposed process relevant to prebiotic chemistry we also undertook an investigation of the hydrophobic effects to provide evidence for the evolution of the biological homochirality in aqueous media. A recent report by Mauksch and Tsogoeva illustrated that a Mannich adduct can act as the catalyst for its own formation from acetone and ethylglyoxylate imine, and thus provided clear evidence for an asymmetric autocatalytic Mannich transformation in non-aqueous media.<sup>11</sup>

Herein, we report our preliminary results in a study of the enantioselective autocatalytic Mannich-type reaction of cyclohexanone with an aldimine in the presence of water.

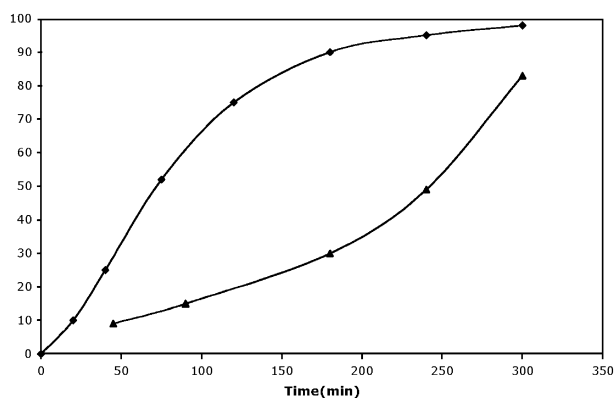
During our studies of the tryptophan catalyzed asymmetric Mannich addition of cyclohexanone **1** to imine **2** in water, we observed an acceleration of the reaction when monitoring the reaction progress. A plot of conversion *versus* time showed the hyperbolic shape indicative of an accelerating reaction rate (Fig. 1, ◆). This behavior suggests a process in which the reaction product either is itself a catalyst or promotes the formation of a more effective catalyst.



**Scheme 2** Asymmetric autocatalytic Mannich reaction.

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**Fig. 1** Fraction conversion vs time for the Mannich reaction carried out with 0.5 M **2**, **2** equiv. **1**, 20 mol% L-Trp in water (◆), and with 10 mol% **3** in CDCl<sub>3</sub> (▲).

To explore the hypothesis of an autocatalytic process, pure *syn*-(2*S*,1'*S*)-**3** was prepared in 98% ee. In our initial experiment cyclohexanone **1** was treated with imine **2** in the presence of freshly prepared (2*S*,1'*S*)-**3** (10 mol%) in CDCl<sub>3</sub>. Indeed, CDCl<sub>3</sub> as solvent makes it possible to monitor the reaction progress *in situ*. This method provides a direct indication of the composition of the reaction mixture and avoids the problems related to work up procedures. Gratifyingly, <sup>1</sup>H NMR studies revealed a smooth reaction with increasing rate (Fig. 1, ▲). The present experiment clearly indicates that we are observing a process in which the chiral **3** operates as a chiral catalyst for its own production.

Under these conditions, however, the Mannich product *syn*-**3** is formed along with an equivalent amount of *anti*-**3**, probably as a consequence of an epimerisation of the newly formed *syn*-**3**, which results in a drop of the enantioselectivity.

Then we turned our attention to the investigation of the factors that could affect the reactivity and the selectivity. A survey of organic solvents indicated that DMF was a suitable solvent in terms of enantioselectivity. In DMF, autocatalysis promoted by 10 mol% of (2*S*,1'*S*)-**3** provided 38% of **3** in an *anti* : *syn* ratio of 37 : 63, and (2*S*,1'*S*)-**3** was isolated in 60% ee (including the catalyst). Although reactions in other organic solvents gave good yields, especially acetonitrile, the enantioselectivity was rather poor (Table 1, entries 2–6). Notably, the *anti*-**3** was isolated with 6 and 3% ee in DMF and DMSO, respectively (entries 2, 3).<sup>12</sup>

Most importantly, a central tenet of the present investigation was to identify an autocatalytic process that can be efficient under aqueous prebiotic conditions. We were pleased to observe that the autocatalytic Mannich reaction also took place in the presence of water and provided better enantioselectivity in a buffer solution at pH7, as revealed in Table 1 (entries 7–9).<sup>13</sup> We, and others, have reported that the organocatalyzed asymmetric aldol reaction could be carried out with excellent enantioselectivity under hydrophobic conditions in water.<sup>14</sup> We reasoned that hydrophobic reactants should associate strongly together in water. However, to promote enantioselectivity in water, buffered conditions are required to minimize general-base catalysis. In accord with our hypothesis, autocatalysis using 20 mol% of (2*S*,1'*S*)-**3** in aqueous media at pH7 provided the product in 59% yield and a dr of 31 : 69 in favor of the *syn* isomer (entry 9). HPLC analysis of *syn*-**3** showed that it had an enantiomeric

**Table 1** Autocatalyzed Mannich reaction under different conditions<sup>a</sup>

Entry	Cat. <b>3</b> (mol %)	Solvent	Time/ h	Yield (%) <sup>b</sup>	dr (%) ( <i>anti</i> : <i>syn</i> ) <sup>c</sup>	ee (%) ( <i>anti</i> : <i>syn</i> ) <sup>d</sup>
1	10	CDCl <sub>3</sub>	8	60	50 : 50	<i>Rac</i>
2	10	DMF	18	38	37 : 63	6 : 60
3	10	DMSO	24	50	53 : 47	3 : 20
4	10	Dioxane	5	49	54 : 46	<3 : 20
5	10	MeCN	24	73	51 : 49	<3 : 16
6	10	THF	24	43	69 : 31	<3 : 20
7	20	Water	5	43	53 : 47	7 : 90
8 <sup>e</sup>	20	Buffer pH5	6	39	46 : 54	3 : 74
9 <sup>f</sup>	20	Buffer pH7	8	59	31 : 69	8 : 92
10 <sup>g</sup>	20	NaCl–water	6	54	36 : 64	<3 : 52
11 <sup>h</sup>	20	PEG–water	6	53	24 : 76	<3 : 60
12 <sup>i</sup>	20	Water	24	41	48 : 52	<3 : 70
13 <sup>i</sup>	20	Buffer pH7	24	35	39 : 61	<3 : 68

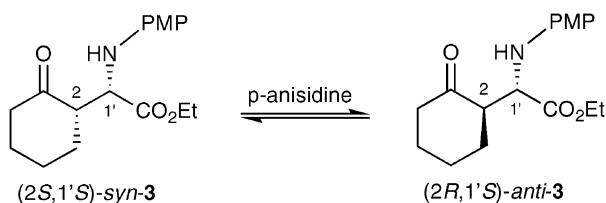
<sup>a</sup> Unless otherwise stated, all reactions were carried out using 1.0 M iminoester and 2.0 M ketone in the presence of 20 mol% catalyst. <sup>b</sup> The yields are for isolated products and after subtraction of the initial asymmetric autocatalyst. <sup>c</sup> Determined by <sup>1</sup>H NMR of the crude product. <sup>d</sup> The ee was determined by chiral HPLC analysis and include the initial catalyst. The enantiomers were assigned by comparison to those obtained with L-proline. nd = ee values below 3%. <sup>e</sup> Titrilot solution at pH5. <sup>f</sup> Phosphate buffer at pH 7.1. <sup>g</sup> NaCl (0.1 M). <sup>h</sup> 30 mol% PEG A400 in water was used. <sup>i</sup> Reactions are performed using a three components protocol with *in situ* formation of the imine.

purity of 92% ee. At the same time, *anti*-**3** was isolated with only 8% ee. In contrast to reactions in organic solvents, water had a significant impact on enantioselectivity—due to solubilisation within the hydrophobic domain of micellar aggregates—and probably by providing hydrogen bonding in the transition state.

To test this hypothesis, we next examined the reaction in micelles. Thus, the presence of PEG, a nonionic surfactant which displays a strong tendency to form micelles in water, led to a relatively greater proportion of the *syn* adduct compared to other aqueous reaction media (entry 11).<sup>15</sup> While the salt-ing-out effect of NaCl led to accelerated reactions, it did not influence considerably the selectivity. The best results were observed for NaCl (0.1 M) with 52% ee (entry 10).<sup>16</sup>

A preliminary investigation into the promotion of aqueous asymmetric autocatalysis in a three components reaction was also undertaken (entries 12, 13).<sup>17</sup> We used a one-pot protocol reacting ethyl glyoxylate, *p*-anisidine, and **1** in the presence of (2*S*,1'*S*)-**3** (20 mol%) as the catalyst. We found that (2*S*,1'*S*)-**3** was capable of promoting the self-production with good enantioselectivity and acceptable yields. However, evaluating the potential of the system is complicated by product epimerization/racemisation under the reaction conditions.

We also were intrigued to observe that longer reaction times had generally a deleterious effect on both diastereo- and enantioselectivity. Indeed, the stereocenter formed in the reaction is expected to be prone to racemization due to the electron-withdrawing substituents attached to it. However, in the present case two chiral centers are involved and increase the difficulty of selectivity control. It is predicted that for asymmetric autocatalysis, even an autocatalyst of very high enantiopurity, capable of replicating itself, will experience erosion of product chirality unless it is sustained by additional reactions (such as the mutual inhibition of enantiomers in the Frank model).<sup>18</sup> Beside this fact



Scheme 3

additional factors may contribute to such erosion of enantioselectivity: (a) competing uncatalyzed reaction pathways *via* enamine or enol intermediates; (b) On the basis of NMR and MS analysis, we noticed that *p*-anisidine was released during the course of the reaction.<sup>19</sup> Thus, *p*-anisidine isomerization<sup>20</sup> of the *syn*-3 product obtained from the *syn*-3-autocatalyzed reaction into *anti*-3 may be considered as a parallel parasitic process (Scheme 3);<sup>21</sup> (c) While, the present results clearly demonstrate that (2*S*,1'*S*)-3 undergoes significant enantioenrichment during autocatalysis, the reaction also produces *anti*-3. It is likely that accumulating enantiopoor *anti*-3 catalyzes the formation of *syn*-3 with lower enantioselectivity.<sup>22</sup> Soai *et al.* have previously reported a similar observation, and the interpretation of the reaction is complicated here by the possibility of a double asymmetric reaction.<sup>23</sup>

Nevertheless, the observation of such an asymmetric autocatalytic organic reaction in the presence of water provides further incentive to evaluate novel small molecules for new considerations in the field of organic autocatalysis, and their implications for autocatalysis in aqueous prebiotic chemistry. Although the high reactivity of such inhomogeneous aqueous reactions is not fully understood, it is quite clear that, beside hydrophobic effects, aqueous hydrogen bonding plays a pivotal role in promoting reactivity.<sup>24</sup>

In summary, we have observed an autocatalyzed asymmetric reaction in an aqueous environment. The Mannich adduct **3** operating as a bifunctional catalyst demonstrated excellent reactivity with good diastereo- and enantioselectivity. Mechanistic investigations of the present process, and the expansion of the reaction scope including the further development of analogous enantioselective systems, are underway.

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  - The *syn*-3 with 98% ee was let to stand in water at rt without any alteration of er or dr after three days. However, upon addition of *p*-anisidine, we observed isomerisation of *syn*-3 into enantiopoor *anti*-3, however, we were not able to assign the enantiomers.
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