Chem. Commun., 2008, DOI:10.1039/B716110G (Communication)

Retracted article: First asymmetric autocatalytic Mannich reaction in the presence of water and its implication in prebiotic chemistry†

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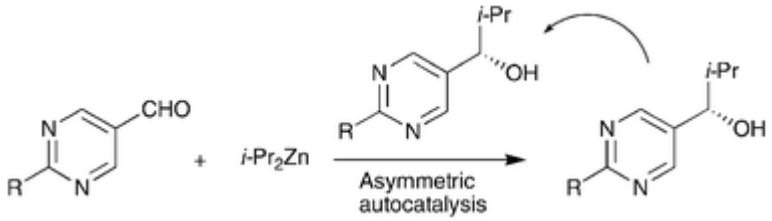
Received (in Cambridge, UK) 18th October 2007, Accepted 21st December 2007

First published on the web 28th January 2008

We, the named authors, hereby wholly retract this Chemical Communication. Signed: Mohamed Amedjkouh and Maria Brandberg, Göteborg, Sweden, February 2008. Retraction endorsed by Sarah Thomas, Editor. Retraction published 28th February 2008

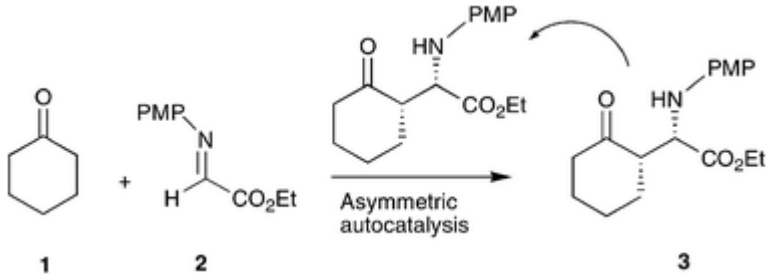
The origin of homochirality of biomolecules, such as L-amino acids and D-sugars, remains an intriguing question for scientists.[1] Thus asymmetric autoinductive and autocatalytic reactions may hold significant clues to the generation and propagation of optical activity on Earth. In a catalytic enantioselective 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.[2] 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.[3] More recently, mechanistic investigations by Blackmond *et al.*, invoking a proline-product species, revealed temporally increasing enantiomeric excess of product in the proline mediated aminoxylation and amination of aldehydes.[4] Furthermore, several Diels–Alder reactions were found to be autoinduced by the cyclic adduct, and a catalytic enantioselective autoinductive aldol reaction in the presence of Ti^{IV}(Binol) complexes was described by Figadère *et al.*[5] Despite this progress, these processes still require non-negligible amounts of chiral catalyst.

The Soai reaction offered the first, and to date the only, example of an asymmetric autocatalytic reaction. In such process the chiral product acts as chiral catalyst for its own production with significant amplification of enantiomeric excess.[6] 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. They found an 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 congifuration (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 complementary oligonucleotides,[7] only a non-asymmetric autocatalyzed aldol reaction has been described recently.[8]



Scheme 1 Autocatalytic strategies for product replication.

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,[9] where the product is also the catalyst, *e.g.* the Mannich reaction,[10] was appealing due to the possibility for a nitrogen-containing electrophile to yield an amine nucleophile capable of reproducing itself (Scheme 2).



Scheme 2 Asymmetric autocatalytic Mannich reaction.

To make the proposed process relevant to the prebiotic chemistry we also undertook an investigation of the hydrophobic effects to provide evidence for the evolution of the biological homochirality in aqueous media. Herein, we report our preliminary results in the first 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.

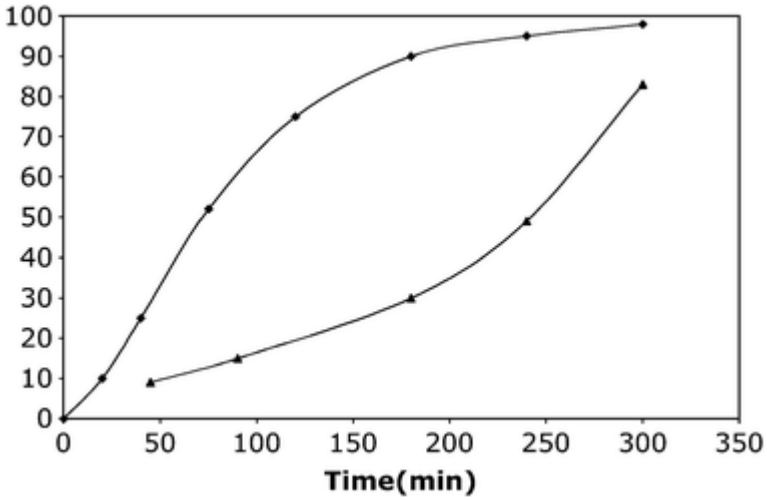


Fig. 1 Fraction conversion *vs.* time for the Mannich reaction carried out with 0.5 M **2**, 2 equiv. **1**, 20 mol% L-Trp in water (◆), and with 10 mol% **3** in $CDCl_3$ (▲).

To explore the hypothesis of an autocatalytic process, pure *syn*-isomer (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 $CDCl_3$. Indeed, $CDCl_3$ 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, ^{1}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 the isomer *anti*-**3**, probably as a consequence of an epimerisation of the newly formed *syn*-**3**, which resulted 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 and 3).[11]

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 buffer solution at pH7, as revealed in Table 1 (entries 7–9).[12] We, and others, have reported that the organocatalyzed asymmetric aldol reaction could be carried out with excellent enantioselectivity under hydrophobic conditions in water.[13] 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 pH 7 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 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.

Table 1 Autocatalyzed Mannich reaction under different conditions[a]

Entry	Cat. 3 (mol %)	Solvent	Time/h	Yield (%)[b]	dr (%) (*anti* : *syn*)[c]	ee (%) (*anti* : *syn*)[d]
1	10	$CDCl_3$	8	60	50 : 50	*rac*
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[e]	20	Buffer pH5	6	39	46 : 54	3 : 74
9[f]	20	Buffer pH7	8	59	31 : 69	8 : 92
10[g]	20	NaCl–water	6	54	36 : 64	<3 : 52
11[h]	20	PEG–water	6	53	24 : 76	<3 : 60
12[i]	20	Water	24	41	48 : 52	<3 : 70
13[f,i]	20	Buffer pH7	24	35	39 : 61	<3 : 68

[a] Unless otherwise stated, all reactions were carried out using 1.0 M iminonester and 2.0 M ketone in the presence of 20 mol% catalyst. [b] The yields are for isolated products and after subtraction of the initial asymmetric autocatalyst. [c] Determined by ^{1}H NMR of the crude product. [d] 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: are for ee values below 3%. [e] Titrisol solution at pH 5. [f] Phosphate buffer at pH 7.1. [g] NaCl (0.1 M). [h] 30 mol% PEG A400 in water was used. [i] Reactions are performed using a three components protocol with *in situ* formation of the imine.

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).[14] While the salting-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).[15]

A preliminary investigation into the promotion of aqueous asymmetric autocatalysis in a three component reaction was also undertaken (entries 12 and 13).[16] 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 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).[17] Beside this fact 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.[18] Thus, *p*-anisidine isomerization[19] 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);[20] (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 formation of syn-**3** with lower enantioselectivity.[21] 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.[22]

Scheme 3

Nevertheless, the observation of such an asymmetric autocatalytic organic reaction in the presence of water provides further incentive to synthesize, characterize, and evaluate novel small molecules for new considerations in the field of organic autocatalysis. This also may have significant implications for autocatalysis in aqueous prebiotic chemistry under hydrophobic conditions. Although the high reactivity of such inhomogeneous aqueous reactions is not fully understood, it is quite clear that, beside hydrophobic effects, hydrogen bonding plays a pivotal role in promoting reactivity.[23]

In summary, we have developed the first autocatalyzed asymmetric reaction in an aqueous environment.[24] The Mannich adduct **3** operating as bifunctional catalyst demonstrated excellent reactivity, diastereo- and enantioselectivity. The ultimate aim is a chemical algorithm enforcing exponential amplification of chirality such as that described by Soai. Mechanistic investigations of the present process, and the expansion of the reaction scope including the further development of analogous enantioselective systems, are underway.

This work was supported by the Swedish Research Council (Veteskapsrådet) and The Royal Society of Arts and Sciences (KVVS).

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14 Similar conditions in the presence of anionic surfactant such as sodium dodecylsulfate (SDS) produced only racemates.

15 For example reaction in NaCl (3.0 M) produced the *syn*-**3** with 44% ee. For discussion on the effects of added salts and their concentrations on reactivity in water see ref. 23c.

16 NMR analysis of the reaction mixture showed a significant equilibrium concentration of the imine **2**.

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18 One referee suggested the use of ethyl glyoxylate in excess to trap the *p*-anisidine. However, we were unable to observe any significant change in the selectivity.

19 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.

20 *p*-Anisidine (pK_a = 5.34) may proceed as in the imidazole (pK_a = 6.95) isomerization of the *anti*-Mannich into *syn*-Mannich as reported by Barbas *et al.*(*a*) S. Mitsumori, H. Zhang, P. H-Y. Cheong, K. N. Houk, F. Tanaka and C. F. Barbas III, *J. Am. Chem. Soc.*, 2006, **128**, 1040; (*b*) see supporting information in ref. 10c. For imidazole isomerisation of aldols see: D. E. Ward, M. Sales and P. Sasmal, *J. Org. Chem.*, 2004, **69**, 4808.

21 A preliminary study showed that *anti*-**3**, isolated from the reaction in DMF, catalyzed the formation of *anti* : *syn***3** (10 : 9) mixture with no measurable selectivity. Work is currently under way to assess the catalytic effect of the enantiomerically pure *anti*-**3**.

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24 *Note added in proof*: Since this manuscript was first submitted for publication, a paper by Mauksch and Tsogoeva has appeared that describes a similar phenomenon with and in non-aqueous acetone, see: M. Mauksch, S. B. Tsogoeva, I. Martynova and S.-W. Wei, *Angew. Chem., Int. Ed.*, 2007, **46**, 393.

Footnote

† Electronic supplementary information (ESI) available: Experimental. See DOI: 10.1039/b716110g