JOURNAL OF SYSTEMS CHEMISTRY

REVIEW Open Access

Organoautocatalysis: Challenges for experiment and theory

Svetlana B Tsogoeva

Abstract

Recent reports about enantioselective organoautocatalytic systems, in which small organic molecules assist in their own formation and under conservation of their absolute configuration, are discussed. This process, appearing as a natural extension to non-covalent enantioselective organocatalysis, seems analogous to template-directed self-replication, previously observed in simple organic molecules and holds implications for models on the origin of life.

Review

The idea that molecules could make countless exact copies of themselves offers fascinating prospects in materials science and holds interesting implications for the origin of life on earth. Oparin was the first to realize the importance of self-replication for life processes [1,2]. Self-replication appeared for a long time to be a sole domain of RNA and DNA molecules replicating via enzymatic pathways [3], until the pioneering studies of von Kiedrowski [4-7], who first demonstrated that oligonucleotides could self-replicate even non-enzymatically via template-directed autocatalysis. Self-replication has been also invoked as an integral part of systems chemistry [8,9].

That even much smaller and simpler molecules are capable of exhibiting self-replication, was first shown by Rebek and co-workers for artificial synthetic models (Figure 1) [10,11].

The finding has been much debated. Challenged by Menger et al. [12,13], who argued that the rate enhancement is due to amide-catalysis and not due to template-autocatalysis, Rebek's interpretation of self-replication has been vindicated by Reinhoudt's group later [14]. Since then, a few other scattered reports about self-replicating molecules have appeared in the literature [15-18].

The potential enantioselectivity of the self-replicating autocatalytic process was implied, but has not drawn particular attention at that time.

Correspondence: tsogoeva@chemie.uni-erlangen.de
Department of Chemistry and Pharmacy, Chair of Organic Chemistry I, University of Erlangen-Nuremberg, Henkestrasse 42, 91054 Erlangen, Germany

Asymmetric autocatalysis, a term first introduced by Wynberg, is the process of automultiplication of a chiral compound in which the chiral product acts as a chiral catalyst for its own formation [19]. Catalyst and product possess of the same absolute configuration and are structurally related. The first example for such a process was reported by Soai in 1990, in the irreversible enantioselective addition of dialkylzinc reagents to pyridine-3-carbaldehyde (Figure 2) [20]. Thus, when product of the reaction was used as catalyst at 20 mol% loading and with 86% ee, the newly generated product was isolated in 67% yield and 35% ee. No autoamplification of product enantiomeric excess was observed.

In 1995, Soai reported the ability of a chiral pyrimidyl alkanol to amplify a tiny initial product enantiomeric excess - in the presence of *i*-Pr_2Zn - to almost enantiomeric purity in a sequential batch reaction protocol (Figure 3) [21-23]. This process is highly advantageous, because product and catalyst don't need to be separated after completion of the reaction, allowing required product purity easier to be obtained [22,23].

The Soai reaction is therefore able to generate impressive enantioenrichment from nominally achiral initial conditions, a behaviour unprecedented in stereochemistry, and as an example of true "absolute asymmetric synthesis" in absence of external chiral influences [24]. Soai observed a positive non-linear effect ((+)-NLE) in this reaction [21], indicating the involvement of catalyst aggregation [25]. The reaction is self-accelerating, because the rate-determining step is of the quadratic (or even higher) reaction order in the product concentration, due to formation of a catalytically active homochiral dimeric product Zn-complex (Figure 4)

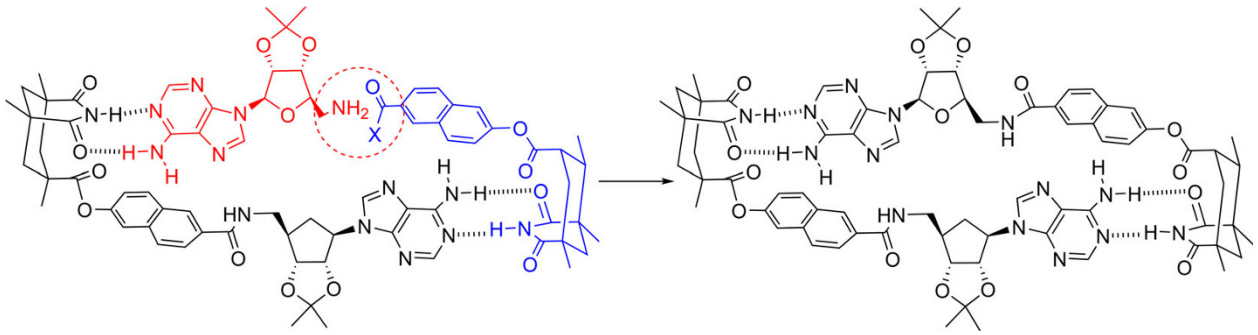

Figure 1 Self-replicating system of Rebek.

[26-28]. As a result, one of the asymmetric autocatalytic product enantiomers is outrun by its antipode, which forms faster.

The first example of asymmetric autocatalysis for an organocatalytic (metal-free) system was reported by Mauksch and Tsogoeva in 2007 for the reversible Mannich reaction of acetone and *N*-PMP-protected α-imino ethyl glyoxylate (Figure 5) [29], followed by demonstration of spontaneous asymmetric amplification under nominally achiral starting conditions for the same reactive system and by the same authors [30,31].

The enantioselectivity observed in the presence of product catalyst is comparable to that obtained with known external catalysts, like proline. The majority of the newly formed product has the same absolute configuration as the initially added product catalyst, which might suggest a template-directed (self-replicating) mechanism. The Mannich product was assumed to bind non-covalently via hydrogen bonds to the reactant, which is attacked by the nucleophile (activated ketone in enol or enamine form) (Figure 6).

This mechanistic proposal has a high appeal, because it is resembling existing mechanistic concepts for classical non-covalent (enantioselective) organocatalysis [32,33]. Further evidence supporting this idea was found by DFT computations, which allowed to locate the transition state structures for this transformation.

In 2002 Philp reported a non-asymmetric experimental example of a minimal self-replicator in the bimolecular reaction A + B → T (also the initiation step): reactant molecules A and B, both bound by secondary interactions (hydrogen bridges) to a product template T, react to give a dimer [T·T] in a template directed synthesis (Figure 7) [16], based on the earlier expectations of von Kiedrowski for related systems [5]. The initially formed product template dimers then could facially release the monomeric autocatalysts through dissociation [5,16].

This mechanism, extended to account for the chirality of the template [31], provides a simple explanation for the observed chiral induction in the organoautocatalytic Mannich reaction: selective transition state structures (where the chiral product template catalyzes formation of new product molecules of the same absolute configuration) may yield homochiral dimers, while antiselective transition state structures (where the product template catalyzes formation of new product with opposite absolute configuration) may yield heterochiral dimers. For the Mannich reaction, the formation of homochiral dimers in the autocatalytic step was indeed

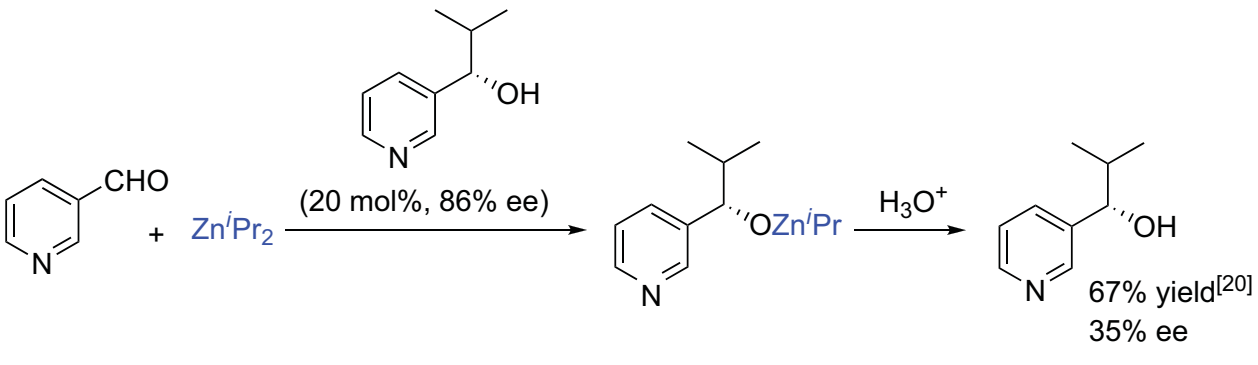

Figure 2 Soai's initial demonstration of an autocatalytic reaction.

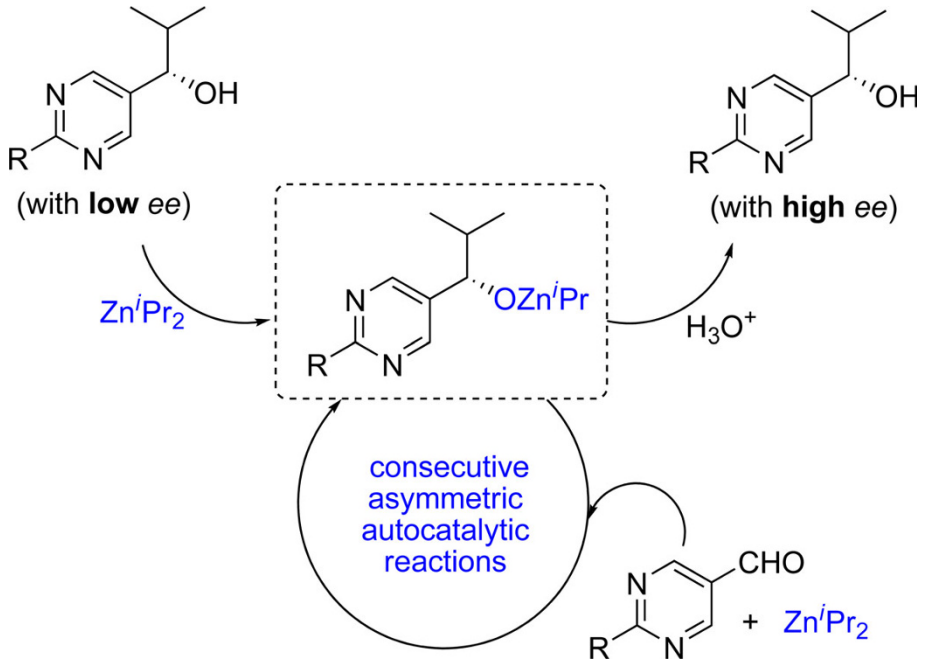

Figure 3 The Soai autocatalytic reaction: a first absolute asymmetric synthesis.

found to be kinetically preferred, in accord with the observed enantioselectivity [29].

Furthermore, such organoautocatalytic reactions should involve merely linear autocatalysis (unlike to Soai's example) in the light of lacking coordination sites at a metal allowing to form multiple catalytic aggregates. Linear autocatalysis alone, though, cannot result in the observed asymmetric amplification [34].

Hence, to explain the unprecedented spontaneous mirror symmetry breaking observed in the Mannich reaction [30], Ribó and co-workers proposed the reversible exergonic formation of a heterochiral dimer of the product autocatalyst [35], resulting in mutual inhibition of autocatalyst formation through reduction of the antipode's concentration - in analogy to the seminal theoretical proposal of such spontaneous asymmetric amplification by Frank in 1953 [36]. However, such thermodynamically stable dimers were not yet located computationally or observed experimentally for this reactive system. As an alternative, recycle kinetics, involving endergonic formation of labile heterochiral dimers which take part in closed reaction loops, was invoked recently to explain the observation of spontaneous mirror symmetry breaking in such formally closed reversible (homogenous) reactive systems [30,37]. Non-equilibrium quasi-steady states might form temporarily in open

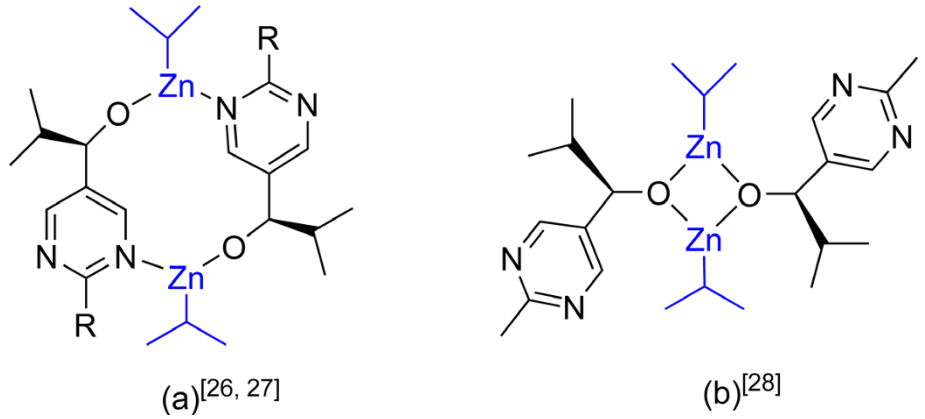

Figure 4 The dominant catalytic species in the Soai reaction.

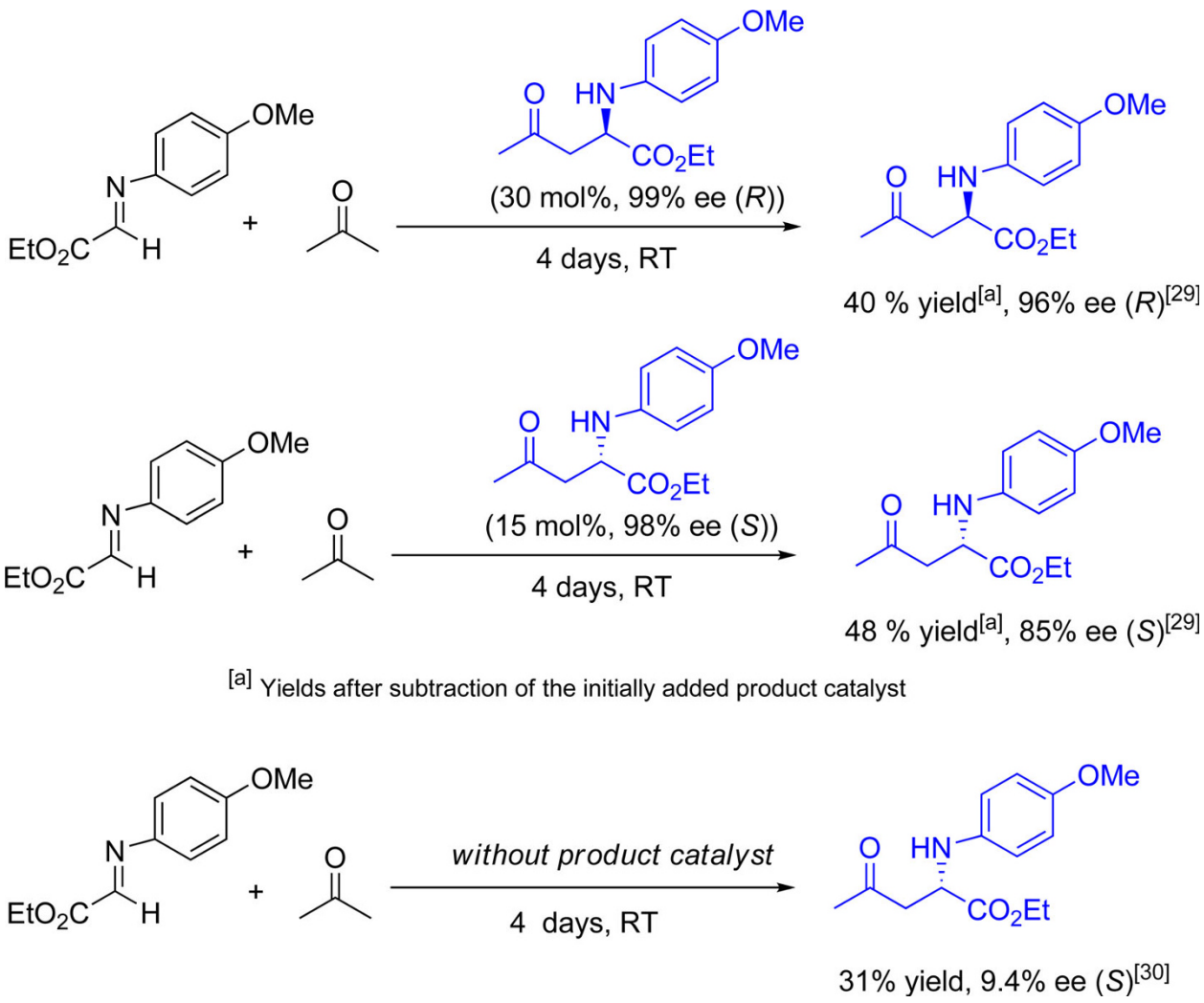

Figure 5 The first asymmetric organoautocatalytic system: Mannich reaction of acetone with *N*-PMP-protected α-imino ethyl glyoxylate.

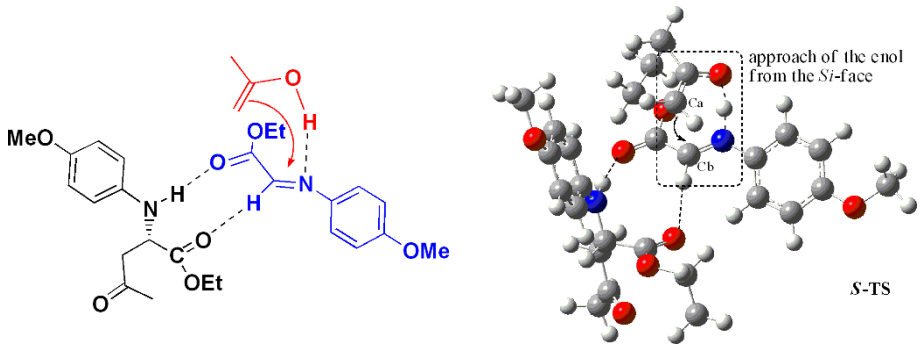

Figure 6 Transition-state structure for the formation of *S* enantiomer of the Mannich product computed at B3LYP/6-31G level [29].

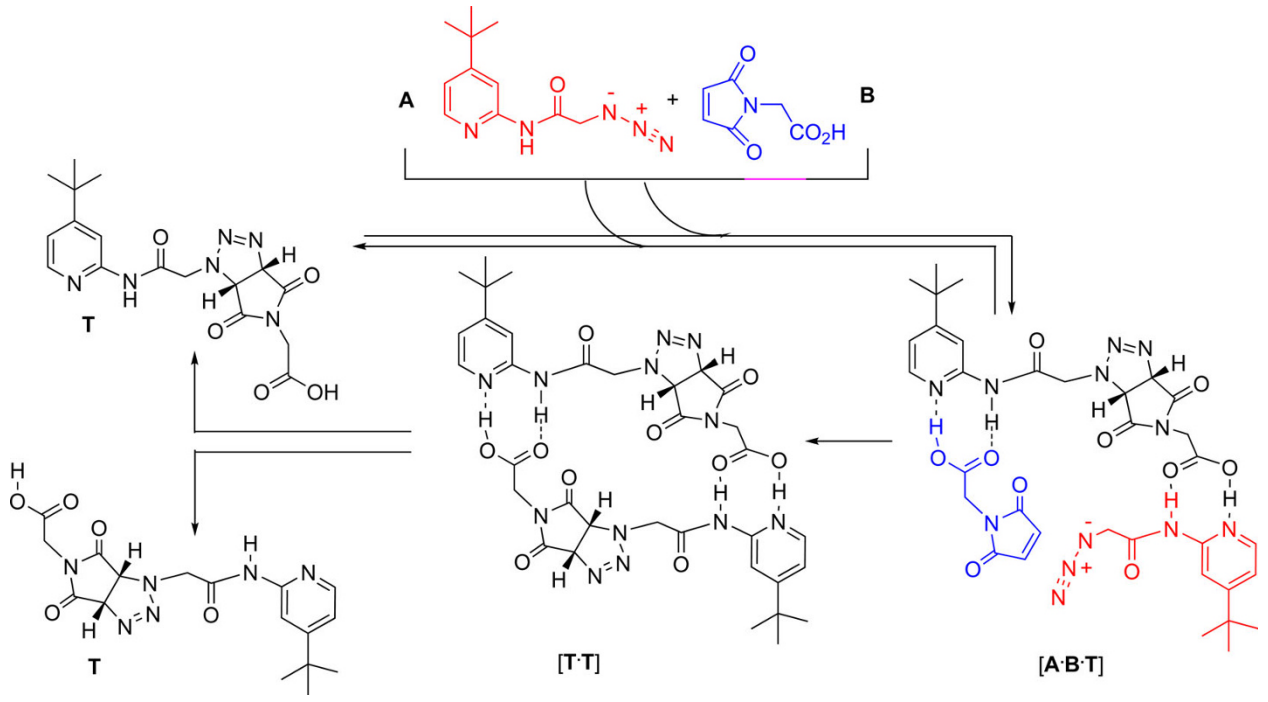

Figure 7 Self-replicating system of Philp.

subsystems of closed systems and with cyclic kinetics [37,38]. A related theoretical model was also forwarded by Plasson and co-workers, wherein it was proposed that a non-spontaneous reactant recycling step could be driven through coupling to an external source of energy [39,40]. This situation might apply to several biochemical reaction cycles, driven e.g. by hydrolysis of energy rich compounds.

The reports of the first example for enantioselective organoautocatalysis has drawn considerable attention. Results for a similar reactive system (Mannich reaction of *N*-PMP-protected α-imino ethyl glyoxylate with cyclohexanone instead of acetone) and in the presence of water were reported in 2008 (Figure 8) [41]. Notably, ^{1}H NMR studies revealed the acceleration of the rate in course of the reaction and in presence of product catalyst. Such rate acceleration is often seen as a hallmark of autocatalytic reactions.

Most recently, Wang and co-workers further reported the enantioselective organoautocatalytic Mannich reaction of isovaleraldehydes to the same *N*-PMP-protected α-imino ethyl glyoxylate and employed both product catalysts and their close mimics (Figure 9) [42]. In addition to the often observed near retention of product enantiomeric excess (99% ee), it was also reported that a noteworthy - fairly significant - change of diastereoselectivity in course of the reaction occurs (autocatalyst with *syn*-configuration provides the formation of *anti* product). To explain, these authors suggested that the *anti* product may be formed faster than the *syn* product under kinetic control.

The generality of asymmetric organoautocatalysis in various organic reactions is conceivable. It might be

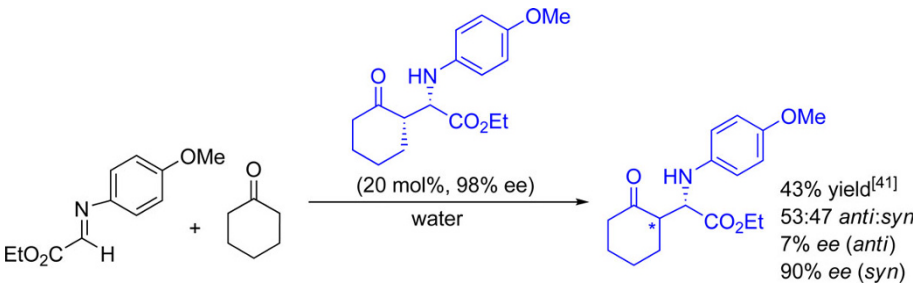

Figure 8 Asymmetric organoautocatalytic Mannich reaction of cyclohexanone with *N*-PMP-protected α-imino ethyl glyoxylate.

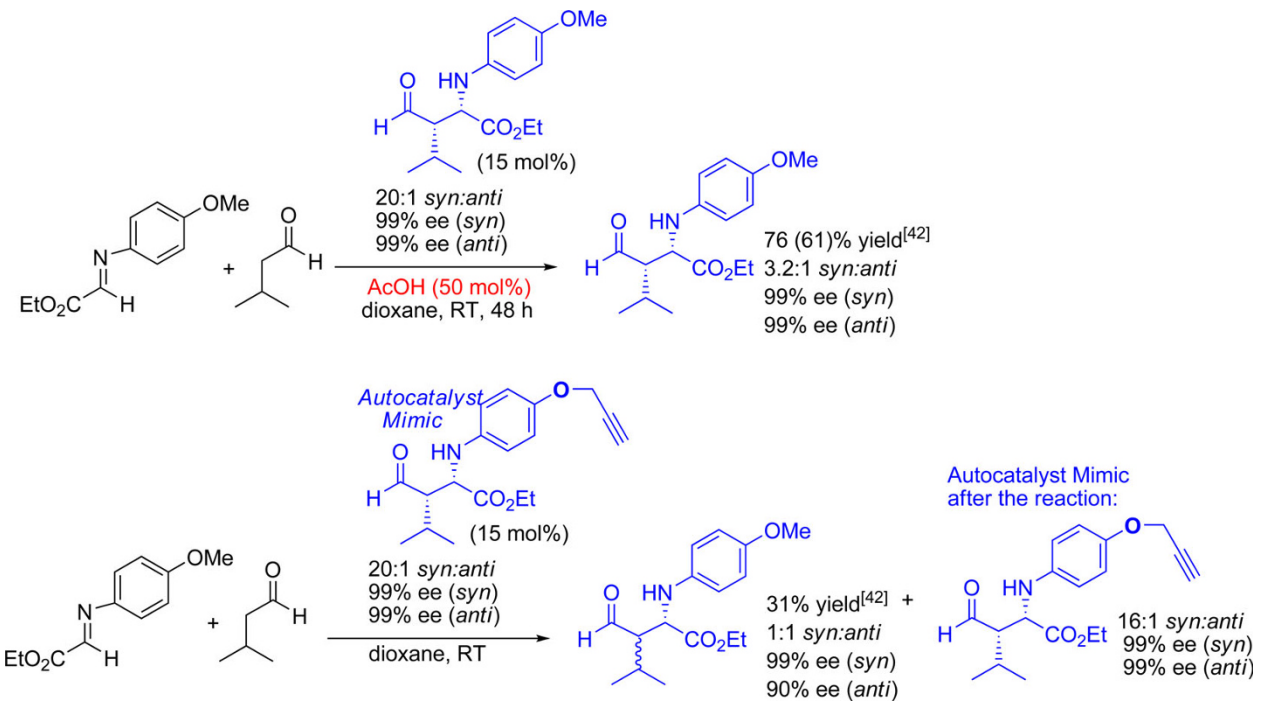

Figure 9 Asymmetric organocatalytic Mannich reaction with autocatalysts and their mimics.

expected, that this phenomenon may be demonstrated for other reactions than the Mannich reaction in the near future.

Seemingly, presumably well-understood organic reactions appear to have much more complicated mechanisms, than previously expected. This poses a challenge for further mechanistic investigations of organoautocatalytic reactions, both experimentally and theoretically. Classical existing mechanistic concepts may not be sufficient to allow yet a full understanding of all the processes involved. There is no doubt, that the further insights gained will be of great value for the synthetic community both in research laboratories and in industry. A further related enticing prospect might be the deeper understanding of the fundamental question of biological homochirality.

Acknowledgements
The author gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft through SPP 1179 "Organocatalysis" and COST Action on Systems Chemistry CM0703.

Received: 18 April 2010 Accepted: 18 August 2010
Published: 18 August 2010

References

1. Oparin AI: **The Origin of Life.** Rabochii, Moscow 1924.
2. Orgel LE: **Molecular replication.** *Nature* 1992, **358**:203-209.
3. Joyce GF: **RNA evolution and the origins of life.** *Nature* 1989, **338**:217-224.
4. von Kiedrowski G: **A Self-Replicating Hexadeoxynucleotide.** *Angew Chem Int Ed* 1986, **25**:932-935.
5. von Kiedrowski G: **Templates, autocatalysis and molecular replication.** *Pure Appl Chem* 1996, **68**:2145-2152.
6. Sievers D, von Kiedrowski G: **Self-replication of complementary nucleotide-based oligomers.** *Nature* 1994, **369**:221-224.
7. Patzke V, von Kiedrowski G: **Self-replicating systems.** *ARKIVOC* 2007, **5**:293-310.
8. Ludlow RF, Otto S: **Systems Chemistry.** *Chem Soc Rev* 2008, **37**:101-108.
9. Peyrelans JJP, Otto S: **Recent highlights in systems chemistry.** *Curr Opin Chem Biol* 2009, **13**:705-713.
10. Tjivikua T, Ballester P, Rebek J Jr: **Small molecule self-replication.** *J Am Chem Soc* 1990, **112**:1249-1250.
11. Nowick JS, Feng Q, Tjivikua T, Ballester P, Rebek J Jr: **Kinetic studies and modeling of a self-replicating system.** *J Am Chem Soc* 1991, **113**:8831-8839.
12. Menger FM, Eliseev AV, Khanjin NA: **"A self-replicating system": new experimental data and a new mechanistic interpretation.** *J Am Chem Soc* 1994, **116**:3613-3614.
13. Menger FM, Eliseev AV, Khanjin NA, Sherrod MJ: **Evidence for an alternative mechanism to a previously proposed self-replicating system.** *J Org Chem* 1995, **60**:2870-2878.
14. Reinhoudt DN, Rudkevich DM, de Jong F: **Kinetic analysis of the Rebek self-replicating system: is there a controversy?** *J Am Chem Soc* 1996, **118**:6880-6889.
15. Lee DH, Granja JR, Martinez JA, Severin K, Ghadiri MR: **A self-replicating peptide.** *Nature* 1996, **382**:525-528.
16. Quayle J, Slawin A, Philp D: **A structurally simple minimal self-replicating system.** *Tetrahedron Lett* 2002, **43**:7229-7233.
17. Rubinov B, Wagner N, Rapaport H, Askhenasi G: **Self-replicating amphiphilic β-sheet peptides.** *Angew Chem Int Ed* 2009, **48**:6683-6686.
18. Li T, Nicolaou KC: **Chemical self-replication of palindromic duplex DNA.** *Nature* 1994, **369**:218-221.
19. Alberts AH, Wynberg H: **The role of the product in carbon-carbon bond formation: stoichiometric and catalytic enantioselective autoinduction.** *J Am Chem Soc* 1989, **111**:7265-7266.
20. Soai K, Niwa S, Hori H: **Asymmetric self-catalytic reaction. Self-production of chiral 1-(3-pyridyl)alkanols as chiral self-catalysts in the enantioselective addition of dialkylzinc reagents to pyridine-3-carbaldehyde.** *J Chem Soc Chem Commun* 1990, 982-983.

21. Soai K, Shibata T, Morioka H, Choji K: **Asymmetric autocatalysis and amplification of enantiomeric excess of a chiral molecule.** *Nature* 1995, **378**:767-768.
22. Shibata T, Morioka H, Hayase T, Choji K, Soai K: **Highly enantioselective catalytic asymmetric automultiplication of chiral pyrimidyl alcohol.** *J Am Chem Soc* 1996, **118**:471-472.
23. Soai K, Shibata T, Sato I: **Enantioselective automultiplication of chiral molecules by asymmetric autocatalysis.** *Acc Chem Res* 2000, **33**:382-390.
24. Mislow K: **Absolute asymmetric synthesis: A commentary.** *Collect Czech Chem Commun* 2003, **68**:849-863.
25. Puchot C, Samuel O, Dunach E, Zhao S, Agami C: **Nonlinear Effects in Asymmetric Synthesis.** *J Am Chem Soc* 1986, **108**:2353-2357.
26. Blackmond DG, McMillan CR, Ramdeehul S, Schrom A, Brown JM: **Origins of asymmetric amplification in autocatalytic alkylzinc additions.** *J Am Chem Soc* 2001, **123**:10103-10104.
27. Buono FG, Blackmond DG: **Kinetic evidence for a tetrameric transition state in the asymmetric autocatalytic alkylation of pyrimidyl aldehydes.** *J Am Chem Soc* 2003, **125**:8978-8979.
28. Schiaffino L, Ercolani G: **Amplification of chirality and Enantioselectivity in the asymmetric autocatalytic Soai reaction.** *ChemPhysChem* 2009, **10**:2508-2515.
29. Mauksch M, Tsogoeva SB, Martynova IM, Wei S: **Evidence of Asymmetric Autocatalysis in Organocatalytic Reactions.** *Angew Chem Int Ed* 2007, **46**:393-396.
30. Mauksch M, Tsogoeva SB, Martynova IM, Wei S: **Demonstration of spontaneous chiral symmetry breaking in asymmetric Mannich and aldol reactions.** *Chirality* 2007, **19**:816-825.
31. Mauksch M, Wei S, Freund M, Zamfir A, Tsogoeva SB: **Spontaneous mirror symmetry breaking in the aldol reaction and its potential relevance in prebiotic chemistry.** *Orig Life Evol Biosp* 2010, **40**:79-91.
32. Etzenbach-Effers K, Berkessel A: **Noncovalent Organocatalysis Based on Hydrogen Bonding: Elucidation of Reaction Paths by Computational Methods.** *Topics Curr Chem* 2009, **291**:1-27.
33. Prins LJ, Reinhoudt DN, Timmerman P: **Noncovalent Synthesis Using Hydrogen Bonding.** *Angew Chem Int Ed* 2001, **40**:2382-2426.
34. Hochstim AR: **Nonlinear mathematical models for the origin of asymmetry in biological molecules.** *Orig Life Evol Biosph* 1975, **6**:317-366.
35. Crusats J, Hochberg D, Moyano A, Ribó JM: **Frank model and spontaneous emergence of chirality in closed systems.** *ChemPhysChem* 2009, **10**:2123-2131.
36. Frank CF: **On spontaneous asymmetric synthesis.** *Biochim Biophys Acta* 1953, **11**:459-463.
37. Mauksch M, Tsogoeva SB: **Spontaneous emergence of homochirality via coherently coupled antagonistic and reversible reaction cycles.** *ChemPhysChem* 2008, **9**:2359-2372.
38. Qian H: **Open-System Nonequilibrium Steady State: Statistical Thermodynamics, Fluctuations, and Chemical Oscillations.** *J Phys Chem B* 2006, **110**:15063-15074.
39. Plasson R, Bersini H, Commeyras A: **Recycling Frank: Spontaneous emergence of homochirality in noncatalytic systems.** *Proc Natl Acad Sci* 2004, **101**:16733-16738.
40. Plasson R: **Energetic and entropic analysis of mirror symmetry breaking processes in recycled microreversible chemical systems.** *J Phys Chem B* 2009, **113**:3477-3490.
41. Amedjkouh M, Brandberg M: **Asymmetric autocatalytic Mannich reaction in the presence of water and its implication in prebiotic chemistry.** *Chem Commun* 2008, 3043-3045.
42. Wang X, Zhang Y, Tan H, Wang Y, Han P, Wang DZ: **Enantioselective Organocatalytic Mannich Reactions with Autocatalysts and Their Mimics.** *J Org Chem* 2010, **75**:2403-2406.

doi:10.1186/1759-2208-1-8
Cite this article as: Tsogoeva: Organoautocatalysis: Challenges for experiment and theory. *Journal of Systems Chemistry* 2010 **1**:8.