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Asymmetric Autocatalysis

Evidence of Asymmetric Autocatalysis in Organocatalytic Reactions**

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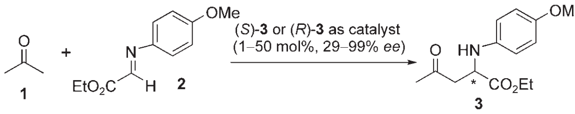
Dedicated to Professor Lutz F. Tietze on the occasion of his 65th birthday

Asymmetric autocatalysis is the process of automultiplication of a chiral compound in which the chiral product acts as a chiral catalyst for its own formation.[1] Such reactions offer striking advantages as the chiral product does not need to be separated from the chiral catalyst and as no other chiral catalyst than the product itself is involved. Several examples are known, all of which involve organometallic reagents and are hence restricted to certain reaction types;[1–3] the most prominent of these is the Soai reaction for its ability to amplify a tiny initial enantiomeric excess of a chiral pyrimidyl alkanol in the presence of $i\mathrm{Pr}_2\mathrm{Zn}$ to almost enantiomeric purity.[3c] A catalytic asymmetric autoinductive aldol reaction in the presence of $\mathrm{Ti^{IV}}$(binol) complexes was described by Szlosek and Figadère.[4] Whereas a purely organic specimen of product catalysis is known, such as the autocatalytic aldol reaction,[5] asymmetric examples of such reactions have not yet been reported.

However, Sievers and von Kiedrowski described a template-based mechanism of autocatalytic self-replication of (naturally asymmetric) oligonucleotide strands.[6] Moreover, Bolm and co-workers cited a fully organocatalytic example of enantioselective autoinduction in the production of a chiral cyanhydrine, catalyzed by a cyclic dipeptide. The product and the external catalyst together form here a more efficient catalytic species, which resulted in higher *ee* values and yields.[7]

These results led us to pose the question of whether the product alone could in principle act as an inductor of chirality and in any asymmetric organic reaction. Reversible reactions appear to be badly suited for such an undertaking, as racemization might occur by the reverse reaction. Additionally, if the reaction-accelerating feature of the product is poorly developed, competition with the "uncatalyzed" reaction further limits the achievable enantiomeric excesses.

Herein, we demonstrate for the first time that even in quite ordinary (and reversible) asymmetric organic reactions (as opposed to reactions involving organometallic species) the chiral product alone could act as a catalyst with high stereoselectivity. As an example, we chose the asymmetric Mannich reaction[8] [Eq. (1)] under various reaction conditions. The choice fell on an example that allows for specific product–substrate interactions through hydrogen-bonded complexes of the product molecules with the prochiral substrate.



(1)

First, we prepared the product catalyst with L-proline as external catalyst in 98 % *ee* (*S*) and with D-proline in 99 % *ee* (*R*) enantiomeric purity.[8,9] Experiments carried out under various conditions (different concentrations of educt; different solvents; different *ee* values, absolute configuration, and loadings of catalyst; variable temperatures and reaction times; see Table 1) revealed to our surprise that the product is formed in nearly the same enantiomeric purity as that of the initially added product catalyst at 15 mol % (Table 1, entries 1–4, 9–12).[10] Higher effective *ee* values of up to 96 % were obtained with very high catalyst loadings (Table 1,

Table 1: Mannich reaction catalyzed by product **3** [Eq. (1)].

Entry	Catalyst **3** Loading [mol %]	*ee* [%] (config.)	*T* [°C]	Reaction time [days]	Product **3** Yield [%][a]	*ee* [%] (red. *ee*)[b]
1[c,d]	15	98 (*S*)	25	2	20	87 (79, *S*)
2[c,d,e]	15	98 (*S*)	25	4	48	85 (81, *S*)
3[c,d]	15	98 (*S*)	25	6	45	91 (89, *S*)
4[c,f]	15	98 (*S*)	25	4	53	86 (83, *S*)
5[c,d]	5	98 (*S*)	25	4	38	28 (19, *S*)
6[c,d]	5	98 (*S*)	25	6	32	23 (11, *S*)
7[c,d]	1	98 (*S*)	25	4	33	29 (27, *S*)
8[c,d]	1	98 (*S*)	25	6	32	23 (20, *S*)
9[d,g]	15	29 (*S*)	0	4	25	25 (22, *S*)
10[d,g]	15	55 (*S*)	0	4	27	56 (57, *S*)
11[d,g]	15	75 (*S*)	0	4	27	69 (66, *S*)
12[c,d]	15	99 (*R*)	25	4	42	94 (92, *R*)
13[c,d]	30	99 (*R*)	25	4	40	96 (94, *R*)
14[c,d]	50	99 (*R*)	25	4	38	95 (90, *R*)
15[c,d]	30	98 (*S*)	25	4	39	94 (90, *S*)
16[c,d]	50	98 (*S*)	25	4	41	95 (91, *S*)

[a] Yields after subtraction of the initially added product catalyst. [b] Enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak OD) in comparison with authentic racemic material. Reduced *ee* values are given in parentheses (see Ref. [10]). [c] Educt concentration: 0.25 mol L^{-1}. [d] Acetone as solvent. [e] A repetition of experiment 2 with a different substrate batch produced a yield of 59 % with 93 % *ee*. [f] DMSO as solvent. [g] Educt concentration: 0.5 mol L^{-1}.

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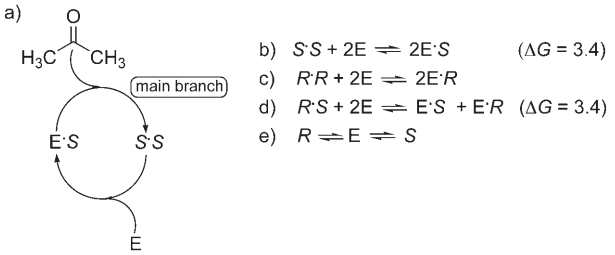
entries 13–16). These results resemble those of Soai et al. for a special metal-containing system.[2a] The use of dimethyl sulfoxide (DMSO) as solvent produces only slightly better results in terms of both *ee* values and yields than acetone (Table 1, entry 2 vs 4).[11]

To see whether the product acts as a catalyst or is merely stoichiometric, we carried out some experiments with lower initial concentrations of product catalyst (Table 1, entries 5–8). A comparison of these results with varying catalyst loadings (1–15 mol%) of a Mannich product catalyst with 98% *ee* (Table 1, entries 2–8) shows that the yield does not depend very strongly on the amount of the catalyst added or the reaction time.[12] However, the impact on enantioselectivities is high. We suppose therefore that asymmetric autocatalysis is in operation here, also because of the still sizeable *ee* values observed even for very low initial concentrations of product catalyst. Intriguingly, better yields were obtained when the reaction was halted after 4 days (Table 1, compare entries 2 vs 3; 5 vs 6; and 7 vs 8). A comparison of experiments that are stopped after 6 days with those that are halted after 4 days shows a tendency for decrease in product *ee* values for longer reaction times, indicating the involvement of racemization, either due to the reversibility of the reaction or to an enantiomerization of the product (Table 1, compare entries 5 vs 6; and 7 vs 8).[13]

Next, we studied the influence of the reaction temperature and the initial *ee* value of the catalyst on the investigated reaction. Carrying out the reaction at 0 °C (Table 1, entries 9–11) with an educt concentration of 0.5 mol L^{-1} in acetone and with catalyst *ee* values of 29%, 55%, and 75% gave the Mannich product in around 25–27% yield with 25%, 56%, and 69% *ee*, respectively. Hence, yields are more strongly influenced here by reaction temperature than by catalyst *ee* values (Table 1, entry 2 vs 9–11). We expected from the inspection of the Gibbs–Helmholtz equation that the resulting *ee* values would be higher at a lower temperature. However, the values achieved relative to the initial values are not higher than in some of the experiments carried out at room temperature.

The catalyst showed a high efficiency in transferring chirality from itself onto the chemically identical product (Table 1). The transfer of chirality appears less than optimal, apparently because of the competing uncatalyzed reaction which can account for significant contributions to the achievable yields. To explain the fairly good induction of chirality, we propose a catalytic cycle (Scheme 1) which involves hydrogen-bonded pre-complexes between the substrate (E) and product and which could be attacked by the enol tautomer of acetone.

In principle, this Mannich reaction might also proceed by an aminocatalytic mechanism that involves the formation of an enamine from the product and acetone.[14] However, the evidence from the ESI mass spectra was somewhat inconclusive.[15] The observation that even the aldol reaction between acetone and *p*-nitrobenzaldehyde gave *ee* values of the isolated product of 71–75% (3–27% yield, 6 days) when the product with 76% *ee* was initially added in various amounts led us to the conclusion that the enamine mechanism probably does not explain the results reported here.



b) $S{\cdot}S + 2E \rightleftharpoons 2E{\cdot}S \quad (\Delta G = 3.4)$

c) $R{\cdot}R + 2E \rightleftharpoons 2E{\cdot}R$

d) $R{\cdot}S + 2E \rightleftharpoons E{\cdot}S + E{\cdot}R \quad (\Delta G = 3.4)$

e) $R \rightleftharpoons E \rightleftharpoons S$

Scheme 1. a) Proposed general catalytic cycle and b–e) pre-complex equilibria with educt (E), *R*, and *S* product dimers. Free enthalpies of reaction for the Mannich reaction (ΔG [kcal mol^{-1}]) are based on computations (see text).

To elucidate further the existence and role of the species involved and to possibly corroborate our intuitive mechanistic proposal (Scheme 1), we carried out density functional theory (DFT) calculations (Table 2) with the B3LYP functional and the 6-31G basis set with the Gaussian 03[16] quantum chemistry package. Full optimizations were carried out for minima and transition-state structures of the Mannich reaction involving the *S*-configured product catalyst (Figure 1). Frequency computations had been done to include zero-point energy (ZPE) and thermal corrections.

Table 2: Computed species at B3LYP/6-31G level for the Mannich reaction [Eq. (1)].

Entry	Species	E_{abs} [Hartree]	E_{rel} [kcal mol^{-1}][a] (NIMAG)[b]
1	*cis*-**2**	−707.18136014	6.0 (0)
2	*trans*-**2**	−707.18968948	0.0 (0)
3	(*S*)-**3**	−900.31395423	0.0 (0)
4	(*S*)-**3**·(*R*)-**3**	−1800.64298375	3.0 (0)[c]
5	(*S*)-**3**·(*S*)-**3**	−1800.64201430	3.0 (0)[c]
6	(*S*)-**3**·*cis*-**2** (I)	−1607.50385835	9.1 (0)
7	(*S*)-**3**·*cis*-**2** (II)	−1607.50605890	9.4 (0)
8	(*S*)-**3**·*trans*-**2** (I)	−1607.51274783	3.8 (0)
9	(*S*)-**3**·*trans*-**2** (II)	−1607.51796910	0.0 (0)
10	TS for (*R*)-**3**[d]	−1800.58622694	31.3 (1)[e]
11	TS for (*S*)-**3**[d]	−1800.59027031	29.5 (1)[f]
12	TS for (*R*,*S*)-**3**[g]	−900.25703468	32.2 (1)[h]

[a] Inclusive ZPE and thermal corrections. [b] Number of imaginary frequencies. [c] With respect to two monomeric (*S*)-**3** molecules. [d] For catalyzed reaction with acetone based on the structure (*S*)-**3**·*trans*-**2** (II) (Figure 1). [e] Relative to entry 4. [f] Relative to entry 5. [g] For uncatalyzed reaction of acetone with *trans*-**2** without product catalyst. [h] Relative to entry 3.

We found that both hetero- (*R*,*S*) and homochiral (*S*,*S*) product dimers are less stable with respect to the monomers, with almost equal energies (Table 2, entry 3 vs 4 and 5). The formation of dimer competes with the complexation of the product with the substrate, which is disfavored by only 3.2 kcal mol^{-1} with respect to the separate educt and product molecules. The latter energy lies a mere 0.3 kcal mol^{-1} higher than either dimerization energy.

It is implicated that the product is formed from the *trans*-educt/*S*-product complex (Table 2, entry 9). The resulting

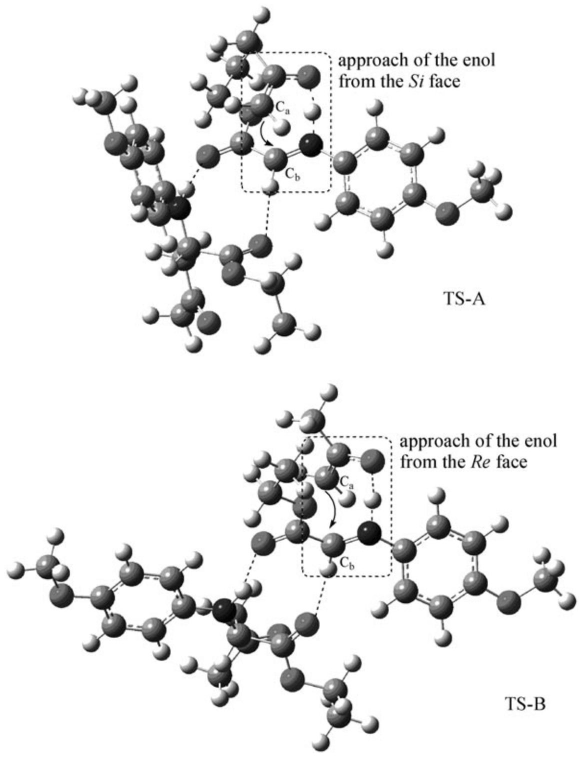


Figure 1. Transition-state structures for the formation of *S* (TS-A) and *R* (TS-B) enantiomers of the Mannich product.

product dimer is most probably homochiral (Scheme 1 a, main branch) because the transition-state structure for the formation of *S*-configured product (entry 11, Table 2) is 1.8 kcal mol^{-1} lower in energy with respect to the respective transition state for the formation of *R*-configured product. Heterochiral dimers might result from the reaction when the absolute configurations of product and product catalyst are not matching (i.e. less than 100 % stereospecificity; side branch not shown). The regeneration of educt–product complexes from free substrate molecules and product dimers is disfavored by 3.4 kcal mol^{-1} (Scheme 1 b). Heterochiral complexes are in equilibrium with a racemic mixture of educt–product complexes (Scheme 1 d). Homochiral dimers and monomers of product are most likely not directly involved in the catalytic step. Entropy-favored racemization can occur by the uncatalyzed back reaction (Scheme 1 e).

Hydrogen transfer from the enol oxygen to the nitrogen of the Schiff base initiates the approach of the methylene carbon (C_a) from the enol towards the carbon (C_b) of the aldimine (Figure 1). The reaction coordinate is represented by a six-membered transition state with a C_a–C_b distance of 2.845 Å (TS-A, Figure 1) to 2.847 Å (TS-B, Figure 1). The respective computed dipole moments of transition-state structures for the formation of *S* and *R* enantiomers (3.97 and 3.12 Db, respectively) offer a possible explanation for the influence of solvent polarity (Table 1, entry 2 vs 4).

Product dimers are in equilibrium with a small amount of educt–product pre-complexes (Scheme 1 b, c; Table 2, entry 9), from which either more product could form, for example, via transition states TS-A or TS-B (Table 2, entries 10 and 11; Figure 1), or, alternatively, that could (thermodynamically favored; Scheme 1 d) "annihilate" to release the substrate and give more inactive meso product dimers.

The amount of enantiomeric excess is limited by the stereospecificity of the product catalyst (i.e. the branching ratio, Scheme 1) and the extent of the racemizing, slightly disfavored "uncatalyzed" reaction (Table 2, entry 12). The mechanism we anticipate here is fully general and, in our opinion, not restricted to the organic reaction discussed herein.

In conclusion, we have demonstrated here for the first time that the product alone might play an important role for yields and achievable enantiomeric excesses in asymmetric organocatalysis. For the Mannich reaction under various reaction conditions, we have shown that the product can be a promising catalyst for its own formation.

Our results pose challenging questions, particularly for organic chemists: What is the role of the product on the yields and *ee* values in those enantioselective organocatalytic reactions reported in the literature? Could the product itself indeed be an effective catalyst in organocatalytic reactions? If so, then it would remove the necessity to separate the product from the catalyst, which could save costs in commercial applications. In principle, it might involve the condition that the catalyst could be self-multiplied to any extent. What remains is to find the proper conditions for higher *ee* values and yields. Extensions of the concept to other reactions with active product catalysis are presently being carried out in our laboratory.

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[9] We cannot preclude that the product may have played a role during its formation in the presence of proline as well.

[10] To assess the effect of asymmetric induction, we have also included the “reduced” *ee* values of the product (ee_p) after deduction of the effect of the initial catalyst on the *ee* values of the isolated product: $ee_p = (n_1/(n_1 - n_o)) \cdot (ee_p' - (n_o \cdot ee_o/n_1))$, with $ee_o = ee$ value of the initially added product catalyst, $ee_p' =$ observed *ee* value of isolated product, $n_o =$ product initially added [mol], $n_1 =$ total isolated product [mol].

[11] We employed also CH_2Cl_2 and toluene as solvents. While the reaction in toluene gave only traces of product, the yield in methylene chloride was 4–6% with an *ee* value of the isolated product close to that of the initially added product (98% *ee*).

[12] Traces of *p*-methoxyaniline have been detected after workup. Unused starting material could be retrieved in all experiments, that is, the reaction does not proceed to completion.

[13] After keeping the product **3** for one month at −21 °C, we observed a decrease in enantiomeric purity from 98% *ee* to 53% *ee*. However, no loss of enantiomeric purity was observed after 4 days at room temperature.

[14] For reviews on asymmetric aminocatalysis, see: a) B. List, *Synlett* **2001**, 1675; b) B. List, *Chem. Commun.* **2006**, 819.

[15] A small ion peak at m/z 329.3 $[M+Na+H]^+$ could be interpreted as originating from the enamine, while another peak at m/z 473.5 $[M+H]^+$ may indicate the formation of a product–substrate complex.

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