Organocatalysis

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Direction of Kinetically versus Thermodynamically Controlled Organocatalysis and Its Application in Chemoenzymatic Synthesis**

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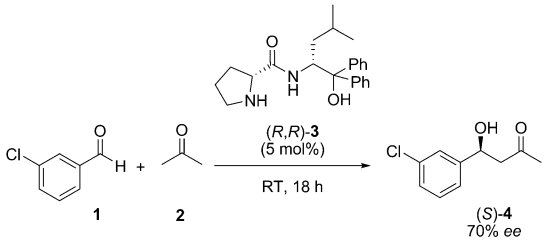
Recent developments in the field of (enantioselective) organocatalysis have established it as a broadly applicable and efficient synthetic tool for the preparation of many types of enantiomerically enriched and enantiomerically pure molecules.[1] In these syntheses, organocatalysts are typically used in amounts of 1 to 20 mol%.[1,2] In general it is assumed that the enantioselective reactions proceed under kinetic control when the amount of catalyst used is within this range. Accordingly, the applied amount of catalyst indicates the degree of catalyst activity, and the catalyst amount can be adjusted in order to optimize the reaction rate and the overall conversion. Although organocatalytic reactions are in general assumed to be kinetically controlled within this range of catalyst loadings, it is in principle possible to switch from a kinetically controlled to a thermodynamically controlled regime even within this narrow range of catalyst loadings and within typical reaction times. Herein we report such an example in which the switch from kinetic to thermodynamic control occurs through a variation of catalyst loading in a narrow range between 0.5 and 10 mol%. Since the transformations reported here can be carried out in water, this also allows new efficient applications for chemoenzymatic one-pot multistep syntheses in aqueous reaction media.[3]

As a model reaction we chose the aldol reaction of acetone (**2**) with 3-chlorobenzaldehyde (**1**) in the presence of the organocatalyst **3**, which was developed by Singh et al.[4] In previous work, we conducted such reactions at room temperature as we had aimed at a combination with enzymatic syntheses, and in this connection we used a loading of 5 mol% of the organocatalyst **3**.[5] Under these reaction conditions the aldol reaction of **2** (9 equiv) with **1** proceeded with an enantioselectivity of 70% *ee* (Scheme 1).[6]



Scheme 1. Organocatalytic aldol reaction in an organic reaction medium.

With a view toward chemoenzymatic one-pot syntheses in aqueous medium we also have been interested in conducting the aldol reaction in this reaction medium. Accordingly we tested this transformation in aqueous NaCl. We observed that with the same catalyst amount (5 mol%), the reaction gave significantly lower enantioselectivity after 48 h, leading to the formation of the desired product (*S*)-**4** with only 47% *ee* (Figure 1). An even more surprising result was obtained in an experiment with 10 mol% of the organocatalyst (*R*,*R*)-**3**, which led to a complete loss of enantioselectivity (0% *ee*). To determine the reasons for this drastic decrease of enantioselectivity, we first studied the effect of lower catalyst amounts. Interestingly, when the catalyst amount was lowered to 1.0 mol%, the enantioselectivity of the reaction continuously improved (Figure 1). For example, in the presence of 1.0 mol% of the catalyst a high, greatly improved enantioselectivity of 91% *ee* was achieved at a product-based conversion of 90% (95% overall conversion). A further increase of the enantioselectivity up to 93% *ee* at a product-based conversion of 92% (95% overall conversion) was obtained upon further decrease of the catalyst amount to 0.5 mol%.

The surprising significant negative influence of increased catalyst amounts of 5 and 10 mol% on the enantioselectivity of the organocatalytic aldol reaction at a reaction time of 48 h is interesting,[7] since many organocatalytic reactions with related catalyst systems are carried out with similar or even higher amounts of catalyst. Thus, reducing the catalyst loading (which also would be advantageous from an economic perspective) might be an option for the optimization and improvement of enantioselectivity of such organocatalytic

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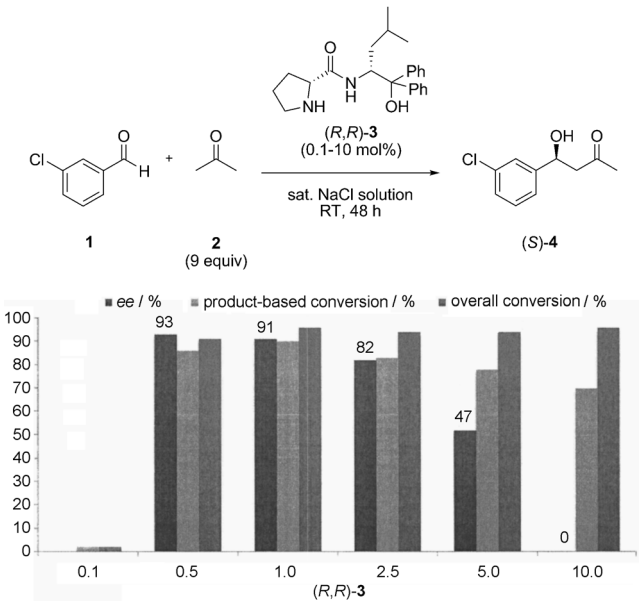


Figure 1. Effect of catalyst loading on the selectivity and conversion of the organocatalytic aldol reaction in an aqueous reaction medium.

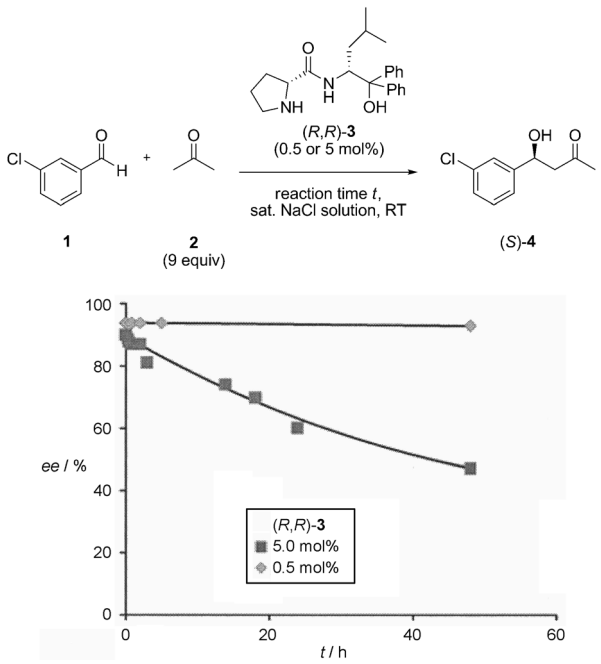


Figure 2. Dependence of the enantioselectivity of the aldol reaction on the reaction time.

reactions, which so far proceed with low to moderate enantioselectivity.

In our search for an explanation of this phenomenon we considered and evaluated the following three conceivable possibilities: 1) catalyst impurities, which effect a nonselective aldol reaction and which play a more significant role at higher catalyst amounts; 2) concentration dependence of the catalytic effects, such that dimeric or oligomeric complexes of **3** act as the catalytic species; 3) thermodynamic rather than kinetic control of the organocatalytic aldol reaction, which results from the rapidly reached reaction equilibrium.

In order to scrutinize explanation option (1), we synthesized the organocatalyst (*S*,*S*)-**3** by two different routes. Since we obtained comparable results with both catalyst samples (which additionally show different degrees of purity), this explanation was discarded (for details, see the Supporting Information).[8] The plausibility of explanation options (2) and (3) was evaluated by investigating the rate of the formation of product (*S*)-**4** and the change in its enantiomeric excess as a function of the reaction time. In the case of explanation option (2), the enantioselectivity should be independent of the reaction time, whereas in case of explanation option (3) the enantiomeric excess of product (*S*)-**4** should be depleted as a result of an initial kinetically controlled reaction and subsequent formation of the thermodynamic equilibrium induced by the catalyst. Interestingly, exactly this result was found when we used a high catalyst amount of 5 mol%: the enantioselectivity decreased significantly from 90% *ee* after 2 min to 47% *ee* after 48 h (Figure 2). In contrast, the enantiomeric excess remained nearly unchanged over a period of 48 h when a low catalyst amount of 0.5 mol% was used. This indicates kinetic control of the reaction within this reaction time.

This change from a kinetically controlled reaction at 0.5 mol% of (*R*,*R*)-**3** to a (predominantly) thermodynamically controlled reaction at an increased catalyst amount of 5 mol% according to explanation option (3) was also confirmed by the observed reaction rates (Figure 3). Whereas in the presence of 0.5 mol% of (*R*,*R*)-**3** the formation of the product (*S*)-**4** proceeded with a reaction course typical of kinetically controlled reactions, the reaction in the presence of 5 mol% of (*R*,*R*)-**3** was so rapid that significant product formation was observed even after a short reaction time (<30 min) with, for example, 58% product-based conversion (61% overall conversion) after 2 min. This goes along with the expectation that thermodynamic control of the reaction is reached relatively rapidly. A further, major advantage from the perspective of process technology when this reaction is conducted with lower amounts of catalyst is the slowing down of side-product formation (caused, for example, by elimination of water from the aldol adduct). In our case, side products accounted for a proportion of 16% after 48 h when 5 mol% of catalyst (*R*,*R*)-**3** was used (Figure 3). Accordingly, in the presence of 0.5 mol% of the catalyst (*R*,*R*)-**3**, the product-based conversion could be enhanced up to 92%, at a decreased side-product proportion of < 5%.

Carrying out the aldol reaction in water under kinetic control with low amounts of the catalyst also offers interesting perspectives for its combination with biotransformations in one-pot multistep processes in an aqueous reaction medium. As a "proof of concept" for such a process, we linked the organocatalytic aldol reaction described above with a subsequent enzymatic reduction of the formed aldol adduct (*R*)-**4** (Scheme 2). After addition of *R*- or *S*-enantioselective alcohol dehydrogenases (ADH), the respective 1,3-diols of type **5** were obtained with excellent diastereoselectivities and enantioselectivities. For the chemoenzymatic one-pot synthesis of the *anti* diastereomer (1*R*,3*S*)-**5** in the presence of the

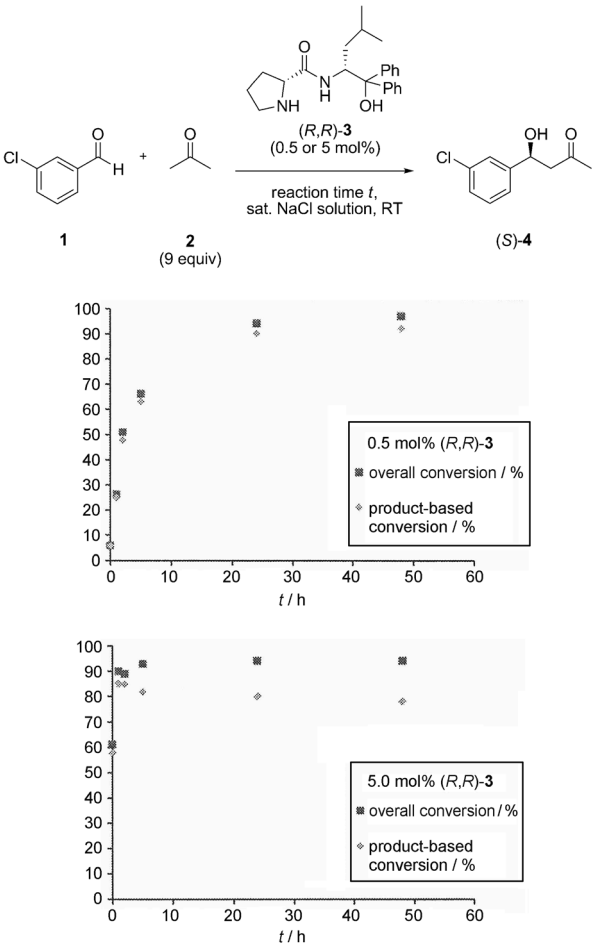
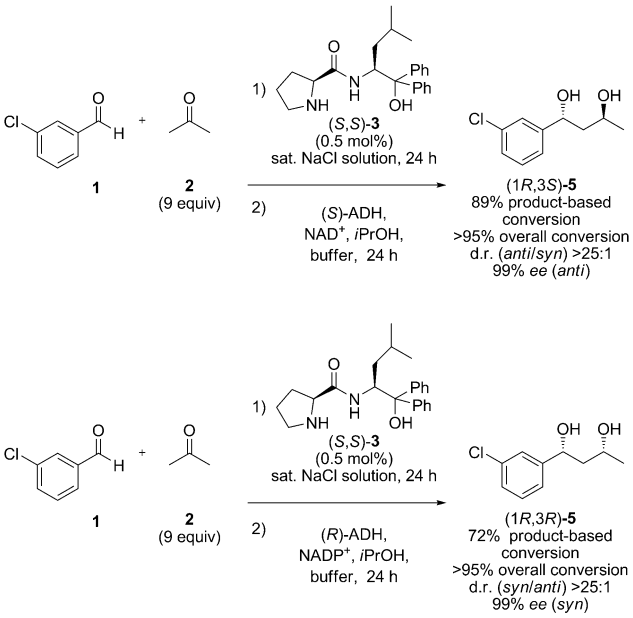


Figure 3. Dependence of the conversion of the aldol reaction on the reaction time.

organocatalyst (*S*,*S*)-**3** and the *S*-alcohol dehydrogenase from *Rhodococcus* sp., a product-based conversion of 89% (>95% overall conversion) at a diastereomeric ratio of >25:1 (*anti*/*syn*) and an enantioselectivity of 99% *ee* was achieved (Scheme 2). The corresponding *syn* diastereomer (1*R*,3*R*)-**5** was obtained in a one-pot synthesis in the presence of organocatalyst (*S*,*S*)-**3** and the *R*-alcohol dehydrogenase from *Lactobacillus kefir* with a product-based conversion of 72% (>95% overall conversion) at a diastereomeric ratio of >25:1 (*syn*/*anti*) and with an enantioselectivity of 99% *ee*. To the best of our knowledge, these are the first examples of a combination of an enantioselective organocatalytic reaction with a subsequent biotransformation, which proceed as one-pot syntheses and completely in aqueous reaction medium (Scheme 2).[9]

In conclusion, we report an enantioselective organocatalytic transformation in which kinetic versus thermodynamic control has been directed through variation of the catalyst amount in a range of 0.5 to 10 mol%. Notably, high enantioselectivities were obtained when low catalyst amounts were used. Although the change from kinetic control to thermodynamic control with increasing amounts of catalyst is well known, it is, however, noteworthy that this change has been observed in a very significant fashion within such a



Scheme 2. Combination of organocatalysis and biocatalysis in a one-pot synthesis in an aqueous reaction medium.

narrow, synthetically widely used range of catalyst amounts. Since such syntheses can furthermore be carried out in water, applications to chemoenzymatic one-pot multistep synthesis in aqueous reaction medium are possible. By means of such a combination with a stereoselective biocatalytic reduction, a one-pot synthesis of 1,3-diols of type **5** has been realized with diastereomeric ratios of >25:1 and excellent enantioselectivities of 99% *ee*.

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[6] With respect to expanding the substrate range, in this work we used 3-chlorobenzaldehyde (**1**) as an aldehyde component instead of 4-chlorobenzaldehyde which was used in our previous work (see Ref. [5]).

[7] This result is in accordance with the work of Singh et al. (see Ref. [4]), who reported higher enantioselectivities at a decreased amount of 0.5 mol % of organocatalyst (*S*,*S*)-**3**, although such a significant discrepancy in the enantioselectivities was not observed (e.g., for the aldol reaction with 3-chlorobenzaldehyde at room temperature: 0.5 mol %: 97 % *ee* after 5 h; 10 mol %: 86 % *ee* after 2 h). An influence of the thermodynamic control on the asymmetric amplification of a proline-catalyzed aldol reaction has been additionally reported in: M. Klussmann, H. Iwamura, S. P. Mathew, D. H. Wells, U. Pandya, A. Armstrong, D. G. Blackmond, *Nature* **2006**, *441*, 621 – 623.

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