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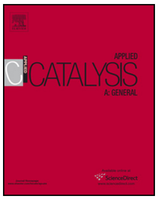

Two sides of the same amino acid—development of a tandem aldol condensation/epoxidation by using the synergy of different catalytic centres in amino acids

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A new tandem catalysis was set up after intensive investigations regarding the amino catalysed aldol condensation and epoxidation. 20 proteinogenic amino acids were investigated as organocatalysts in the epoxidation of an α-branched α,β-unsaturated aldehyde. The most active amino acids were chosen for the optimization of the reaction conditions obtaining excellent yields in the epoxidation. With these insights the first tandem aldol condensation/epoxidation was developed gaining very good yields of the epoxy aldehyde, which was obtained directly from butanal without any purification or isolation of the intermediate. Applying butanal as substrate, which is produced on a large industrial scale, opens up new horizons for novel useful and reactive products. Furthermore, the beneficial influence of lysine and arginine was proven and it was revealed that these amino acids bear two different catalytic centres, which have impact on the synergy in this new tandem catalysis being active within two different reaction mechanisms. The α-amino function catalyses the aldol condensation and the corresponding side chain group is responsible for the catalytically conversion in the epoxidation.

1. Introduction

Tandem catalyses describe the merge of different catalytic reactions in one vessel. Therefore, the resulting intermediate is immediately converted into the desired product, without any isolation or purification steps [1]. Thereby, resources can be saved consuming less solvents, energy and time during the whole process. These are important requirements for developing reactions, which fit in the concept of green chemistry besides e.g. the application of benign reagents [2].

The development of new tandem catalyses is quite challenging, since the compatibility between different catalyses is not given automatically. An intermediate with reactive functionalities is often the key in developing new tandem catalyses. Hence, probably the most developed tandem catalyses contain a hydroformylation step resulting in aldehydes as reactive intermediates, which are easily converted in an organocatalysis [3].

The organocatalysed conversion of aldehydes in homo aldol condensations yields α,β-unsaturated aldehydes, which can be catalysed with benign and natural occurring organocatalysts, e.g. amino acids [4].

In general, α,β-unsaturated aldehydes represent reactive intermediates, which can be functionalised in α-/ β-/ or γ-position by enamine, iminium or dienamine catalysis [5]. The epoxidation of α,β-unsaturated aldehydes as one example is described by iminium catalysis. In 2005, the first organocatalysed epoxidation of α,β-unsaturated aldehydes was developed yielding epoxy aldehydes [6].

Since then, different synthetic organocatalysts were applied in the epoxidation of α,β-unsaturated aldehydes and ketones with a main focus on reaching high enantioselectivities [7].

The use of amino acids as organocatalysts in epoxidations is only described once [7b]. Therein, 30 mol% proline is not active in the epoxidation of cinnamic aldehyde, if applied solely. The further addition of 80 mol% triethylamine yields 79% desired epoxy aldehyde.

The homo aldol condensation of propionaldehyde and higher aldehydes (with longer carbon chains), leads to α,β-unsaturated aldehydes with an α-branching. Only scattered examples are dealing with the epoxidation of these bulky substrates, [7e,8] including the epoxidation of trisubstituted double bonds [9].

Recently, we investigated the amino acid (AS) catalysed homo aldol condensation of aldehydes obtaining α,β-unsaturated aldehydes in a simple reaction system with excellent yields within short reaction times [10]. This reaction system consisted of three substances: the aldehyde, the amino acid and a solvent. We achieved

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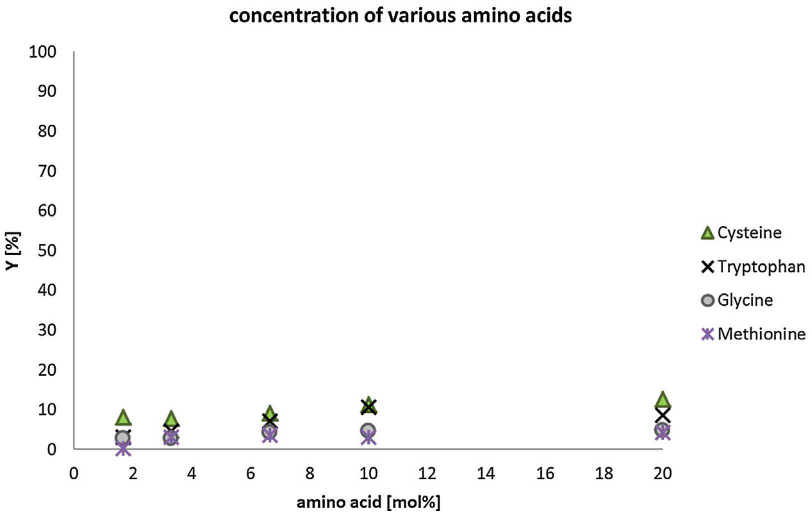
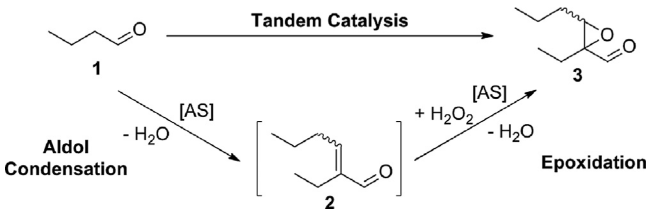


Fig. 1. Yield over catalyst concentration plot of cysteine, tryptophan, glycine and methionine; Conditions: Conditions: 3 mmol **2**, amino acid, 1.1 eq H_2O_2 (35% in water), 1 mL EtOH, r.t., 16 h.



Scheme 1. Tandem aldol condensation/epoxidation catalysed by proteinogenic amino acids.

high yields (up to 99%) with low catalyst amounts (3.33–6.67 mol%) in short reaction times (1–3 h).

In this publication, we apply the aldol condensation product of butanal, which bears a branching at the α-carbon atom, as starting material for the epoxidation with amino acids. Then, we use our gained experiences regarding the aldol condensation [10] and the epoxidation for the development of a new tandem aldol condensation/epoxidation which is catalysed by amino acids using an aqueous hydrogen peroxide solution. This tandem catalysis leads from the aldehyde **1** over the α,β-unsaturated aldehyde **2** as intermediate directly to the epoxy aldehyde **3**. Both reaction steps are catalysed with only one catalyst without isolation or purification of the intermediate (Scheme 1). In this way, reactive intermediates can be synthesized in one tandem catalysis, which are easily accessible directly from aldehydes such as butanal (**1**) with water as the only by product.

2. Experimental

Detailed experimental procedures are available in the Supporting information.

3. Results & discussion

First, we set our focus on the epoxidation of the commercially available 2-ethylhex-2-enal (**2**) with proteinogenic amino acids (AS) as organocatalysts (Scheme 2). This α,β-unsaturated aldehyde has a worldwide production of 3.3 million tons per year and can be easily synthesized by the homo aldol condensation of butanal (**1**), wherefore we chose this unsaturated aldehyde as model substrate, being attractive for the synthesis of the reactive epoxy aldehyde **3**. These epoxidation investigations enable the application of the gained experience from our previous investiga-

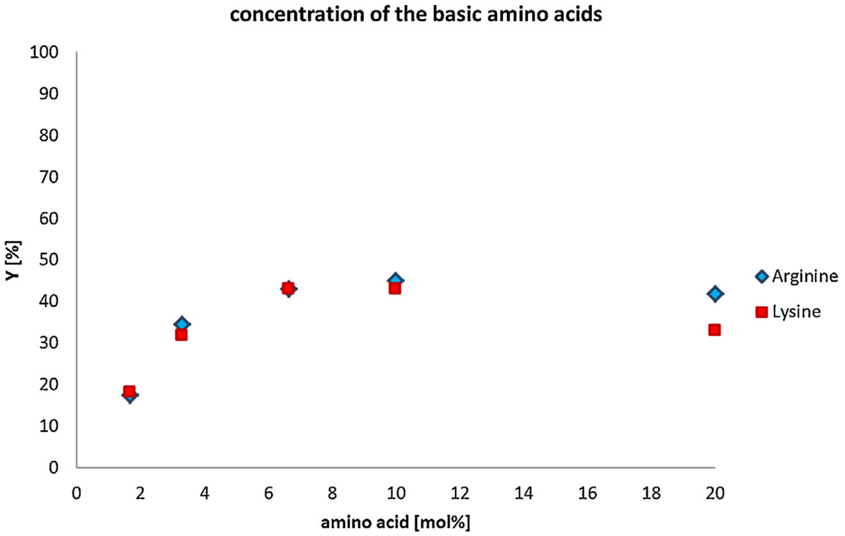


Fig. 2. Yield over catalyst concentration plot of basic amino acids; Conditions: 3 mmol **2**, amino acid, 1.1 eq H_2O_2 (35% in water), 1 mL EtOH, r.t., 16 h.