Biocatalysis

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Redox Self-Sufficient Biocatalyst Network for the Amination of Primary Alcohols**

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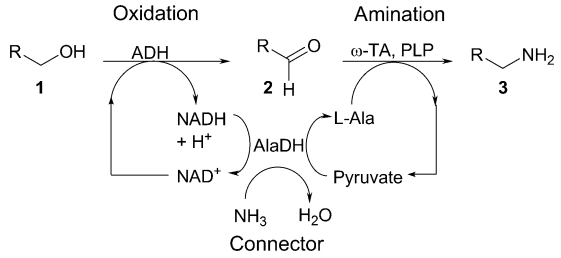
Amines are essential building blocks in the chemical industry, for instance in the large-scale production of polymers and dyes. Furthermore, amines are key intermediates for the synthesis of a plethora of bioactive compounds for the pharmaceutical, agrochemical, and chemical industry.[1] For their preparation carbonyl compounds are frequently reductively aminated.[2] Instead of using carbonyl compounds (aldehydes or ketones) as substrate it was recently shown that also alcohols can serve as alternative starting material employing metal catalysts[3,4] or in the established Mitsunobu reaction.[5] Alcohols are transformed to the corresponding amines by various metal catalysts through 1) an initial catalytic dehydrogenation of the alcohol to give the corresponding carbonyl compound and hydrogen, 2) subsequent formation of the imine, and 3) final hydrogenation leads to the desired amination product. Since the hydrogen required for the final hydrogenation step is generated by dehydrogenation of the alcohol in the first step, this approach was named "borrowing-hydrogen" methodology[6] also known as "hydrogen auto-transfer" reaction.[7] Hence, there is no need for additional hydrogen gas.

Although the transformation of alcohols to amines is vividly investigated employing metal catalysts, no comparable process has been reported for (primary) alcohols employing biocatalytic methods.[8] One reason being that no single enzyme is known for the interconversion of alcohols to amines.

Our aim was to construct an artificial multi-enzyme cascade for the transformation of primary alcohols to the corresponding amines: Similar to the metal-catalyzed reaction sequence for alcohols, the first step was designed as an oxidation step catalyzed by an alcohol dehydrogenase (ADH)[9] consuming NAD^+ leading to the formation of the aldehyde and NADH (Scheme 1). In the second sequential step, an ω-transaminase (ω-TA)[10,11] should aminate the intermediate aldehyde requiring an amine donor. L-Alanine was chosen as amine donor, since it can be recycled in situ from pyruvate, the co-product of the transamination. Other commonly employed amine donors such as 2-propylamine, benzylamine, 1-phenylethylamine cannot be recycled simultaneously by enzymes. For the regeneration of L-alanine from pyruvate an L-alanine dehydogenase (AlaDH)[12] was chosen, which consumes ammonia and NADH. The latter was provided from the oxidation step where NADH was liberated. Thus, the AlaDH connected the oxidation step with the reductive amination step by transferring the hydride from NADH—the by-product of the oxidation—to the amination step by regenerating the amine donor alanine from pyruvate. Consequently, only an ADH can be used in the oxidation step and not an alcohol oxidase, which consumes molecular O_2 leading to hydrogen peroxide as a side product.



Scheme 1. Artificial redox-neutral multi-enzyme network for the bioamination of primary alcohols. ADH: alcohol dehydrogenase, ω-TA: ω-transaminase, AlaDH: L-alanine dehydrogenase, and PLP: 5′-pyridoxal phosphate.

Overall, this designed artificial pathway to transform primary alcohols to amines represents a redox-neutral cascade[13,14] thus no external oxidation or reduction equivalents are consumed.

In an initial study suitable NAD^+-dependent ADHs for the oxidation of primary alcohols were selected whereby the ADH from horse liver[15] (HL-ADH, E-isoenzyme; NP_001075997.1) and the thermostable ADH from *Bacillus stearothermophilus* (ADH-hT; P42328.1)[16] turned out to be best. ADH-hT was used for further studies because of its simpler overexpression in *E. coli*. For the amination two ω-TAs were identified as suitable, namely one from *Chromobacterium violaceum*[17] (CV-ωTA) and a variant of an (*S*)-selective ω-TA from *Arthrobacter citreus* (ArS-ωTA).[18] The AlaDH originated from *Bacillus subtilis*.[19]

Testing 1-hexanol as substrate at a concentration of 50 mM in the presence of all three enzymes (ADH, ω-TA, and

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AlaDH) led to full conversion to 1-hexylamine in the cascade demonstrating that the transformation of a primary alcohol to the corresponding amine is feasible (Table 1, entry 1). Elongating the chain length led to lower conversion (entries 2, 4), which could be partly improved by the addition of a cosolvent (entries 3, 5). From various organic solvents tested,[20] 1,2-dimethoxyethane turned out to be best suitable. Alcohols bearing an aromatic moiety like benzyl alcohol, cinnamyl alcohol, or 3-phenyl-1-propanol were rather well converted to the corresponding amine with conversions from 70% up to >99% (entries 7–9).

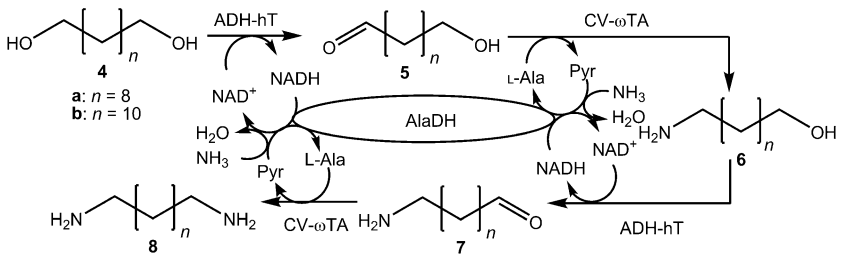
Table 1: Amination of primary alcohols through a redox-neutral cascade (Scheme 1).[a]

No.	Substrate **1**	Conversion [%]	Aldehyde **2** [%]	Amine **3** [%]
1	1-hexanol **1a**	>99	<1	>99
2	1-octanol **1b**	50	<1	50
3	1-octanol **1b**	57[b]	<1	57
4	1-decanol **1c**	2	<1	2
5	1-decanol **1c**	25[b]	<1	25
6	1-dodecanol **1d**	10[b]	<1	10
7	benzyl alcohol **1e**	>99	13	87
8	cinnamyl alcohol **1f**	>99	30	70
9	3-phenyl-1-propanol **1g**	>99	<1	>99

[a] Reaction conditions: substrate (50 mM), CV-ωTA (1 mg, 0.2 U) and ADH-hT (1 mg, 0.25 U), AlaDH (0.04 mg, 0.25 U), PLP (0.35 mM), NAD^+ (0.75 mM), ammonium chloride (275 mM), L-alanine (250 mM), pH 8.5, 24 h, 20°C. [b] 1,2-Dimethoxyethane (10 v%) was added as cosolvent.

Aromatic[21] and aliphatic diamines, especially hexamethylenediamine, are common building blocks for polyamides (e.g. nylon).[22] In a current effort to identify novel bifunctional building blocks for amide polymers possessing new properties and originating from renewable resources,[3a,23] fatty acids represent a promising source for buildings blocks, which can be converted to ω-hydroxy acids.[24]

Unfortunately nature furnishes mainly access to hydroxy-functionalized compounds.[25] Therefore, amination of the corresponding reduced 1,ω-diols would be an interesting option to access novel 1,ω-diamine building blocks for polymers. Obviously in this case two redox-neutral oxidation–amination sequences had to take place in tandem, thus overall four sequential simultaneous steps were required to get to the diamine (Scheme 2).



Scheme 2. Double bioamination of long-chain *n*-alkane-1,ω-diols.

Testing first 1,8-octanediol **4a** as substrate led to high amounts of amino alcohol formation **6a** and low amounts of the diamine **8a** (Table 2, entry 1) employing ArS-ωTA and methyl *tert*-butyl ether (MTBE) as cosolvent. Switching to the transaminase CV-ωTA boosted the conversion to 98% with 46% diamine **8a** formation and 52% of amino alcohol **6a** (entry 2). To increase the availability of the barely soluble diol **4a**, the water miscible solvent 1,2-dimethoxyethane was tested. Careful optimization of temperature and amount of cosolvent 1,2-dimethoxyethane allowed finally to achieve 99% formation of the diamines **8a** and **8b** (entries 9 and 10). Aldehyde-functionalized intermediates **5** and **7** were never detected in significant amounts in any experiment nor any traces of the corresponding acids.

Table 2: Biocatalytic diamination of 1,ω-diols (Scheme 2).[a]

No.	Sub.	Solv. (v%)	*T* [°C]	Conversion [%]	Amount of **6** [%]	Amount of **8** [%]
1	**4a**	MTBE (30)	35[b]	52	49	3
2	**4a**	MTBE (30)	25	98	52	46
3	**4a**	DME (40)	25	95	80	15
4	**4a**	DME (30)	25	>99	18	82
5	**4a**	DME (20)	25	99	16	83
6	**4a**	DME (10)	25	99	1	98
7	**4a**	DME (10)	20	>99	<1	>99
8	**4b**	DME (20)	25	99	6	93
9	**4b**	DME (20)	20	>99	2	98
10	**4b**	DME (10)	20	>99	1	99

[a] General reaction conditions: Substrate (50 mM; Sub.), CV-ωTA (1 mg, 0.25 U) and ADH-hT (1 mg, 0.2 U), AlaDH (0.1 mg, 0.7 U), PLP (0.35 mM), NAD^+ (0.75 mM), ammonium chloride (275 mM), L-alanine (250 mM), pH 8.5, 20 h. [b] ArS-ωTA used instead of CV-ωTA.

The diamination of 1,10-decanediol was finally also performed on a preparative scale (174 mg of substrate) with the optimized conditions leading to 94% conversion and 70% isolated yield.

The advantage of this artificial metabolism results from its self-sufficiency concerning redox equivalents, thus no external hydride source such as glucose or formate was required, thus, the overall process was redox neutral. The only stoichiometric reagent required is ammonium as the amine source. To minimize waste of salt, no common buffer salts like Tris (Tris = tris(hydroxymethyl)aminomethane) or phosphate were used. Therefore this process represents an environmentally benign concept yielding valuable building blocks for the polymer industry, otherwise only accessible through routes demanding harsh conditions.[26]

Summarizing, we have presented the first bioamination of primary alcohols employing a synthetic redox-self-sufficient cascade. By setting up this "artificial metabolic" pathway, a green method for the selective amination of alcohols by a highly atom-efficient one-pot transformation is available, thereby expanding the toolbox for biocatalytic transformations.[27]

Experimental Section

Representative procedure exemplified for the diamination of 1,10-decanediol **4b**: Substrate **4b** (174.2 mg, 1 mmol) was dissolved in DME (2 mL, 10 v%; DME = 1,2-dimethoxyethane) in a round bottom flask (50 mL) and L-alanine (445 mg, 5 mmol) dissolved in 4 mL H_2O was added as well as NH_4Cl (320 mg, 6 mmol in 1.5 mL H_2O). The pH was adjusted to pH 8.5 by addition of 80 μL of a 6 M NaOH solution. NAD^+ (10 mg, 12 μmol) and PLP (2 mg, 8 μmol; PLP = pyridoxal 5′-phosphate), each dissolved in 500 μL of H_2O, were added as well as additional 3.12 mL of H_2O, the ADH (4 mL, 5 U), the ω-transaminase (4 mL, 4 U) and the alanine dehydrogenase (300 μL, 5 U). After shaking at 20 °C, 120 rpm (orbital shaker, Infors Unitron) for 22 h the product was separated from the reaction mixture and purified through a weak acid cation exchanger. Finally, 173 mg (0.70 mmol, 70 % yield) of the product **8b** were obtained. For details see the Supporting Information.

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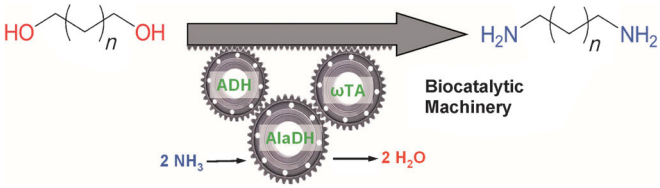
Communications

Biocatalysis

J. H. Sattler, M. Fuchs, K. Tauber, F. G. Mutti, K. Faber, J. Pfeffer, T. Haas, W. Kroutil* _____ ■■■■–■■■■

Redox Self-Sufficient Biocatalyst Network for the Amination of Primary Alcohols



Driving the machinery: A biocatalytic redox-neutral cascade for the preparation of terminal primary amines from primary alcohols at the expense of ammonia has been established in a one-pot one-step method (see picture). Applying this artificial biocatalyst network, long-chain 1,ω-alkanediols were converted to diamines, which are building blocks for polymers, in up to 99% conversion.